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THE RELATIONSHIP BETWEEN EXERCISE AND COGNITION
IN DIABETES MELLITUS

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09th January 2015

A thesis submitted to the Faculty of Health Sciences at the University of Sydney in
Fulfilment of the degree:
Doctor of Philosophy (Exercise Health and Performance)
SUPERVISOR’S STATEMENT

I certify that the thesis entitled "The Relationship between Exercise and Cognition in Diabetes Mellitus", submitted by Ren Ru Zhao in fulfilment of the degree of Doctor of Philosophy (Exercise Health and Performance), is ready for submission.

Prof. Maria Fiatarone Singh

09th January, 2015
DECLARATION

I hereby declare that this thesis is my own work, and that to the best of my knowledge and belief, that it contains no material from any other source, except where due acknowledgement is made. The thesis was completed for the Doctor of Philosophy (Exercise Health and Performance) and has not been submitted for a higher degree or diploma in any other University or academic institution.

__________________________
Ren Ru Zhao

09th January, 2015
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CHAPTER 1: INTRODUCTION
1.1 DIABETES: OVERVIEW

1.1.1 CLASSIFICATION, DIAGNOSIS, AND ETIOLOGY OF DIABETES

According to the American Diabetes Association, diabetes mellitus is a common and serious metabolic condition that is characterised by deficiency in insulin secretion or resistance to insulin action or both, resulting in hyperglycaemia.\(^1\) The vast majority of cases of diabetes can be categorised as type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM): T1DM which accounts for 5–10% of all diabetes mellitus, is an absolute deficiency of the insulin secretion resulting from autoimmune destruction of the insulin producing cells in the pancreas.\(^1\) It usually occurs in childhood or adolescence, but can occur at any age and patients require lifelong insulin injections in order to control the levels of glucose in their blood for survival. Patients with uncontrolled T1DM may lead to acute and severe hyperglycaemia with ketoacidosis or coma.

In the other, much more prevalent category, T2DM, which represents 90% - 95% of diabetes cases worldwide, is a resistance to insulin action and an inadequate compensation in the secretion of insulin.\(^1\) It usually occurs in adults, but is increasingly seen in children and adolescents concordant with the obesity epidemic. The pancreas generally retains some ability to produce insulin, but this is insufficient due to resistance to the actions of insulin in target tissues, including skeletal muscle, adipocytes, blood vessels and liver. Autoimmune destruction of pancreatic β-cells does not occur and ketoacidosis is rare, thus insulin therapy may not be required. A chronic elevation of inflammatory biomarkers or abnormal cortisol control is also observed in patients with T2DM. In patients with T2DM, treatment initially consists of a diet to assist with weight loss and increased physical activity.
Less common forms of diabetes include gestational diabetes mellitus (GDM), a condition which poses an increased risk for developing T2DM in the next 5–10 years.\textsuperscript{2} Prediabetes is defined as a condition that occurs when a person’s blood glucose levels are above normal, thus greatly increasing his or her risk for T2DM.\textsuperscript{1} In addition, pancreatic disease, surgery, infections, and drugs or chemicals can predispose to diabetes.\textsuperscript{1}

Diabetes mellitus is diagnosed by individuals demonstrating any one of the following criteria: a fasting plasma glucose $\geq 7.0$ mmol/l (126 mg/dl), or 2-h plasma glucose concentration $\geq 11.1$ mmol/l (200 mg/dl) during an oral glucose tolerance test using 75 g of glucose, or symptoms of hyperglycaemia and casual plasma glucose $\geq 11.1$ mmol/l (200 mg/dl) or higher.\textsuperscript{1} Glycated haemoglobin (HbA1c) concentration $\geq 6.5\%$ is recommended as the cut-off point for diagnosing diabetes. However, a HbA1c value $\leq 6.5\%$ does not exclude the diagnosis of diabetes using plasma glucose concentrations described above.\textsuperscript{3} Prediabetes mellitus is diagnosed by the presence of a HbA1c of 5.7 – 6.4\%, fasting plasma glucose of 5.6 – 6.9 mmol/l, or 2-h post load glucose of 7.8 – 11.0 mmol/l.\textsuperscript{1} Notably, despite diagnosed diabetes reaching epidemic levels globally, diabetes remains underdiagnosed, in part because often people do not realize they have it until they develop complications. Once diagnosed, an individual’s condition can be monitored through self-monitoring plasma glucose concentration, or through routine blood tests carried out by his or her medical practitioner. It is recommended that individuals with diabetes achieve a fasting plasma glucose concentration as close to normal as possible (5.5 mmol/L), thus a target HbA1c of $< 7.0\%$ is commonly set, and indicates very good long term control of plasma glucose concentrations.\textsuperscript{4}
It is well recognized that in people with diabetes, cardiovascular disease (CVD) is the primary cause of morbidity and mortality. Ninety percent of people with T2DM are obese or overweight; 80% have metabolic syndrome (hypertension, dyslipidaemia, visceral obesity and insulin resistance). Visceral adipose tissue is the center of the pathogenesis of prediabetes and T2DM, thus the global epidemic of obesity contributes to the rising prevalence of T2DM. Visceral adipose tissue produces adipokines/cytokines, including tumor necrosis factor-α that can directly contribute to insulin resistance in muscles, adipocytes, liver, and endothelial cells. Excessive sedentary behaviour/low physical activity level, leading to increased visceral adiposity, may also contribute to the pathogenesis of insulin resistance and ultimately the development of T2DM.

Many of these adipokines are considered to be pro-inflammatory, resulting in a state of chronic low-grade systemic inflammation within this cohort, which is linked to both insufficient physical activity and visceral obesity. Systemic inflammation is an independent predictor of all-cause mortality, metabolic syndrome, endothelial dysfunction, myopathy, and even depressive symptoms and cognitive dysfunction in older adults with diabetes.

1.1.2 Prevalence of Diabetes Mellitus

The increasing prevalence and incidence of T2DM has been referred to as a global epidemic. In 2007-2008, almost 898,800 Australians had diabetes, with 87% of those diagnosed with T2DM. Among those with diabetes, 56% were men and 44% were women. It is estimated that 3.5 million Australians will have diabetes by 2025. The global burden of diabetes was 110 million in 1994 and is estimated to have more than doubled to 239 million by 2015, with 592 million adults...
projected to have diabetes worldwide by 2035.\textsuperscript{16}

The ageing of the population is also related to the diabetes epidemic. The rate of diabetes increases with age from 0.3\% among those aged 0–34 years to 15.8\% of 65–69 year olds.\textsuperscript{5} This is similar to recent data from the American Diabetes Association report where it was estimated that in 2012, 12 million, or 21\% of Americans over the age of 60 have diabetes (including T1DM), representing 54\% of the total cases of diabetes amongst all adults within the US.\textsuperscript{17}

Race/ethnicity/geography is related to diabetes mellitus risk. According to a Diabetes Australia report, 12\% of Indigenous Australians are affected by diabetes, compared to 4.1\% non-Indigenous Australians.\textsuperscript{18} In the USA, nearly 14\% of Hispanics and 12\% of African Americans are affected by diabetes compared with 7\% of non-Hispanic whites.\textsuperscript{19} It is becoming increasingly common in the developing world as well. In many countries in Asia, the Middle East, and the Caribbean, diabetes affects 12-20\% of the population, compared to 6-10\% of Caucasians in North America, Australia or Europe.\textsuperscript{20}

1.1.3 The Impact of Diabetes Mellitus

Chronic diabetes, particularly if control is sub-optimal, leads to an increased risk of a myriad of complications, as summarised below:

Diabetic retinopathy

Individuals with diabetes are at increased risk of developing eye disease, and diabetes is the leading cause of blindness in the developed world. Diabetic retinopathy is a condition affecting the blood
vessels of the eye, which is reported to affect greater than 15% of individuals with diabetes.21

**Diabetic nephropathy**

Chronically, diabetes damages the blood-filtering capillaries in the kidneys. Diabetic nephropathy presents initially as asymptomatic leakage of protein into the urine (microalbuminuria, requiring dialysis or organ transplant). The prevalence of microalbuminuria and macroalbuminuria may affect 21.0% and 4.3% of those with diabetes, respectively.22

**Peripheral neuropathy and peripheral vascular disease**

Peripheral neuropathy results from damage to the peripheral nerve (sensory nerves of the lower limbs) in combination with atherosclerosis or calcification of small blood vessels (peripheral arterial disease) in the lower limbs, can lead to the development of ulcers and infections of the lower limb, which in extreme cases can lead to amputation. Diabetes is the leading cause of non-traumatic lower limb amputation.22 Nerve damage affects the legs and feet of approximately 13% of Australians with known diabetes, while the prevalence of poor circulation in the legs and feet is almost 14% in those with known diabetes.21

**Cardiovascular and cerebrovascular disease and mortality**

Cardiovascular disease is a common and often severe complication of diabetes, and is the primary cause of death. Cardiovascular problems include conditions such as coronary heart disease (myocardial ischemia), heart failure, hypertension, and cerebrovascular disease (stroke).23 Major cardiovascular events include myocardial infarction and cerebrovascular accidents (stroke). Almost 58% of people with known mellitus diabetes had cardiovascular disease in the Australia
National Health Survey. People with known diabetes and undiagnosed diabetes had an increased risk of cardiovascular disease mortality (3 times and 1.6 times than those with prediabetes, respectively). Among all cardiovascular disease deaths within the 5-year follow-up period, diabetes and prediabetes contributed to approximately 65% of deaths.23

**Psychosocial problems**

Approximately 40% of people with diabetes also report poor psychological well-being with reports of anxiety, stress, depression and feeling burned-out from coping with their diabetes.24

**Cognitive impairment**

There is a link between cognitive deficits, dementia prevalence and diabetes. Individuals with diabetes have a 1.2- to 1.5-fold greater rate of decline in cognitive function compared to those without diabetes.25

Thus, effective target strategies are required to reduce the severity, or prevent the onset of these complications within this cohort in order to reduce the substantial societal and personal financial burden of comorbidities linked to T2DM. Total annual cost for T2DM is estimated to be 14.6 billion within Australian alone.26 The average annual cost of T2DM for a person without complications is $4,025; while this rises to $9645 annually per person if both micro- and macro-vascular complications are present.16 Elevated glycaemic levels increase the risk of developing these complications in diabetes and are associated with comorbidity. Data from The United Kingdom Prospective Diabetes Study (UKPDS) showed that improvement of glucose control can
greatly reduce the risk of myocardial infarction and stroke. Reducing HbA1c from 8%, to the target of 7% reduced the risk of end stage kidney disease by 40%, macrovascular complications by 37%, amputations by 20% and future myocardial infarction risk by 15%. Thus, there is evidence that modification of diabetic complications and long-term morbidity is possible with more intensive treatment strategies.

As noted above, cognitive impairment and dementia are more common in older patients with T2DM than in older adults without diabetes. As one of the growing list of diabetic comorbidities, cognitive impairment and dementia in patients with T2DM has generated a great deal of interest. An understanding of the mechanisms of cognitive decline and potential treatment modalities in this specific population requires further study. The background information that underlies this emerging field is reviewed briefly below.

1.2 COGNITIVE AGEING IN T2DM

Diabetes mellitus (DM) is a chronic metabolic condition, and a major contributor to cardiovascular disease, comorbidity and mortality. It has become increasingly evident that DM also affects the central nervous system in several ways, a complication sometimes referred to as diabetic encephalopathy resulting in cognitive impairment and hippocampal neural loss.\textsuperscript{27,28} Recently, it has been reported that diabetes is associated with mild to moderate impairments of cognitive functioning, with lowered performance on tests of speed of information processing, episodic memory and, although less consistently, on tests of mental flexibility.\textsuperscript{29} Epidemiological evidence consistently links diabetes with cognitive impairment, higher risk for dementia, and increased pathological changes in the central nervous system.\textsuperscript{30} A recent meta-analysis including
patients with neurodegenerative diseases found that diabetes was associated with an increased risk of developing dementia.\textsuperscript{31} A randomised controlled trial (RCT) found that lower levels of HbA1c were associated with an decreased risk of developing cognitive impairment in older adults with diabetes.\textsuperscript{32} In addition, a number of common diabetic comorbidities, such as depression, cardiovascular, cerebrovascular disease, and chronic inflammation are also risk factors for cognitive deficits.\textsuperscript{33} Furthermore, obesity, which is present in 90\% of older adults with T2DM, has been associated with cognitive dysfunction.\textsuperscript{34} Lower muscle mass is also present in both diabetes and Alzheimer disease.\textsuperscript{35} Moreover, prospective cohort studies have shown that higher levels of physical activity are associated with lower rates of cognitive decline in women with T2DM.\textsuperscript{36} Notably, some previous studies did not use age as an independent predictor, and the largest effect of T2DM on cognitive function were seen in studies in which patients were older.\textsuperscript{37} As they age, people with T2DM develop other related pathologies such as hypertension, atherosclerosis, and macrovascular and microvascular disease that produce further cognitive deficits, which become most apparent in later life. For this reason, prevention of cognitive impairment in older adults with T2DM will be one of the most important medical challenges in diabetes-related cognitive treatment in the future. Many mechanisms have been considered to underlie the association between diabetes and cognitive dysfunction. This chapter provides a focused discussion of potential causative factors linking T2DM with cognitive aging: insulin resistance, glucose homeostasis, pro-inflammation and anti-inflammation, central adiposity, and sarcopenia. Indeed, emerging data suggest that all these factors may be significantly associated with various forms of cognitive impairment.\textsuperscript{38}
1.2.1 Insulin Action and Brain and Cognition of Individuals with Diabetes Mellitus

Hyperglycaemia in diabetes is due to the insufficient action of insulin, and cognitive impairment is not only closely associated with hyperglycaemia, but also with the action of insulin. Insulin enters the brain through the blood–brain barrier where it binds with insulin receptors. In the brain, insulin is involved in various neurological processes. There are a particularly large number of insulin receptors in the hippocampus and cerebral cortex, which play a central role in memory. Insulin induces the release of β-amyloid peptide (Aβ) in cells to the cell exterior, and also promotes the expression of insulin degrading enzyme (IDE). As IDE also degrades Aβ, if there is lack of insulin or resistance to its action, Aβ will accumulate.39, 40

There is evidence that high levels of amyloid are present in Alzheimer’s disease (AD) and are associated with cognitive decline in a dose-dependent fashion. When hyperinsulinaemia or insulin-resistance is present, there is a decrease in insulin receptors in the brain and thus less insulin is bound to these sites due to down regulation. Also, as insulin is degraded by IDE, in the hyperinsulinaemic state, IDE is consumed and its amount decreases, thus resulting in an increase in Aβ. Therefore, hyperinsulinaemia due to insulin resistance can potentially cause cognitive impairment to progress. In support of this, a cohort study in middle-aged adults reported an association between hyperinsulinaemia and cognitive decline.41 Also, in the Hisayama study, autopsy findings showed that hyperinsulinaemia and hyperglycaemia as a result of insulin resistance were associated with enhanced neritic plaque formation.42 Furthermore, Ronnemaa et al.43 reported that a reduction in insulin secretion, not in insulin sensitivity, was associated with the onset of AD, suggesting that improvement in both pancreatic function and insulin resistance may potentially mitigate the overall cognitive risk in individuals with T2DM. Thus, insulin
seems to be definitely connected with AD pathology via amyloid accumulation. In addition to this amyloid pathway linked to cognitive decline, insulin resistance is a risk factor for vascular dementia, as it is associated with atherosclerosis throughout the circulation, manifesting itself as cerebrovascular disease, coronary artery disease, and peripheral vascular disease.

1.2.2 Glucose Homeostasis and Cognition of Individuals with T2DM

There is strong evidence from many cross-sectional studies that patients with hyperglycaemia have cognitive impairment compared to normoglycaemic individuals. One prospective longitudinal study observed a 0.14-point lower Mini-mental State Examination (MMS) score for each 1% higher HbA1c, and reported that hyperglycaemia impaired aspects of cognitive function such as psychomotor speed (Digital Symbol Substitution Test [DSST]), memory (Rey Auditory Verbal Learning Test) and executive function (Stroop test), suggesting a significant negative association between HbA1c level and cognitive function.\(^{44}\) In another study of elderly patients with diabetes, baseline HbA1c level was independently related to cognitive impairment as indicated by DSST, Stroop test and word recall performance.\(^{45}\) One potential mechanistic link between hyperglycaemia and cognitive impairment is advanced products of glycosylation (AGE). Elevated AGE levels are present in those with T2DM due to insulin resistance, which reduces the ability of the glucose transport system to effectively transport glucose into the cells of the liver and muscle, resulting in a high concentration of AGE. In a hyperglycaemic environment, tissues contain increased AGE and up-regulation of its receptor (RAGE) in animal and human with diabetes.\(^{46, 47}\) AGE is known to be related to the traditional microvascular complications of T2D.\(^{48}\) Increased expression of RAGE is also observed in later stages of AD,\(^{49}\) and expression of RAGE is enhanced in blood vessels near Aβ deposits in advanced AD brains.\(^{50}\)
Data from the Informatics in Diabetes Education and Telemedicine Study (IDEATel), a randomised trial of telemedicine vs. usual care in 2169 elderly persons with T2DM, showed that persons in the intervention group, (who had better T2D control parameters compared to usual care), had less global cognitive decline during a maximum of 6 years of follow-up. This study suggested that metabolic control might have beneficial effects on cognitive function. Yanagawa et al. found that after 3 months of treatment with exercise, patients experienced a decrease in HbA1c and performed significantly better on tests of verbal memory. Furthermore, a mediation analysis demonstrated that better HbA1c, (which is an AGE), was the main mediator for the association between improved control and cognitive performance, providing further evidence for the proposed mechanism.

1.2.3 Adiposity and Cognition of Individuals with T2DM

The centre of the pathogenesis of prediabetes and T2DM is obesity, and in particular, the accumulation of central, or visceral adipose tissue. The prevalence of T2DM was found to be three times higher amongst obese Australians than those of normal weight. There is growing evidence that obesity, may be an independent predictor of poor neurocognitive outcomes. It has been estimated that if obesity prevalence were reduced by 10% in midlife, the incidence of AD would decrease by 25%. As obesity is linked in part to behaviours including diet, physical activity and sedentary time, there are potentially lifestyle modifications possible which could mitigate this risk.

There are three commonly proposed mechanistic links between excess adiposity and cognitive impairment. First, an increased production of adipokines/cytokines, including tumour necrosis
factor-α (TNF- α), may directly contribute to cognitive decline. Second, the sustained exposure of the liver to an increased flux of free fatty acids via the portal circulation from visceral adipose tissue may be antecedent to the disturbances in glucose and lipid metabolism. Given that HbA1c, fasting hyperglycaemia, and dyslipidaemia have also been shown to predict cognitive decline, reduction in these metabolic parameters may potentially mitigate the overall cognitive risk in individuals with T2DM. Third, deposition of ectopic fat may promote peripheral insulin resistance. This deposition occurs predominantly in the liver, but can also be present within skeletal muscle, the largest reservoir for glucose disposal, disrupting insulin-mediated glucose transport and exacerbating hyperglycaemia. Figure 1.1 provides a model of how excessive sedentary behaviour/low physical activity level, leading to increased visceral adiposity could result in the pathogenesis of insulin resistance and the development of T2DM. Cytokines secreted from visceral adipose tissue (adipokines) have been causally linked to the development of insulin resistance within skeletal muscle, adipocytes, hepatocytes, and endothelial cells\(^44,55,56\) and diabetic comorbidities including hypertension, cardiovascular disease and metabolic syndrome,\(^57\) which are all known to have important roles in cognitive decline. Adipokines have both proinflammatory and antiinflammatory properties including adiponectin, leptin, resistin, as well as pro-inflammatory cytokines like TNFα and Interlukin-6 (IL-6).\(^58\) Higher adiponectin levels have been associated with better cognitive performance in older individuals.\(^38\)

Pro-inflammatory cytokines result in a state of chronic low-grade systemic inflammation.\(^12,59\) Systemic inflammation is thought to be an independent predictor of cognitive impairment, AD, and vascular dementia. However, it has a causal link to cerebrovascular disease in older adults, as well as to insulin resistance,\(^60-62\) which suggests it may be partially involved in the cerebral
atherosclerosis brain neuropathology, as well as accelerating its progression, thus worsening cognitive function.\textsuperscript{63} Higher levels of C-reactive protein (CRP), a marker of low-grade systemic inflammation, have been shown to predict cardiovascular disease and insulin resistance in individuals with or without T2DM.\textsuperscript{61} Patients with T2DM with elevated levels of systemic inflammatory markers, like CRP, are more likely to exhibit cognitive dysfunction.\textsuperscript{64} Longitudinal studies have shown that elevated baseline CRP levels are associated with decreased cognition and executive function over time.\textsuperscript{65} In a prospective study of individuals with T2DM, those with a high concentration of CRP (>3mg/L) had a higher relative risk of cognitive decline and developing cardiovascular disease compared to those with a low concentration of CRP (≤3mg/L) over 7 years.\textsuperscript{61, 64} Importantly, CRP concentration has been shown to predict cognitive impairment and CVD mortality independently from diabetes and insulin resistance.\textsuperscript{66} Given that HbA1c\textsuperscript{66} and fasting hyperglycaemia\textsuperscript{67} have also been shown to predict cognition and CVD mortality within this cohort, reduction in both inflammation and glycaemic parameters may potentially mitigate the overall cardiovascular risk and cognitive function in individuals with T2DM. In light of the adverse effects of excessive and visceral deposition of adipose tissue on insulin resistance and systemic inflammation, effective treatment strategies that reduce adiposity may potentially reduce cognitive impairment risk within this vulnerable cohort. Such an improvement in risk factor profile would be predicted to reduce cognitive decline, dementia incidence, other comorbidity, and mortality itself, although this hypothesis requires confirmation in long term, prospective trials of high-risk individuals.

One of the most important anti-inflammatory adipokines is adiponectin. Adiponectin is a hormone, almost exclusively secreted by adipose tissue, which regulates insulin sensitivity,
glucose homeostasis, fatty acid catabolism, the immune system, and has potent anti-inflammatory properties effects by inhibiting the expression of IL-6 or TNFα.\textsuperscript{68, 69} Reduction in circulating adiponectin levels has been implicated in the development of insulin resistance syndrome, visceral obesity, and elevated levels of TNF-a and IL-6.\textsuperscript{69-73} In addition, adiponectin also has important roles in obesity-related insulin resistance, cardiovascular disease, T2DM, and also neurodegenerative disorders.\textsuperscript{74}

It has been suggested that there is a link between adiponectin and cognition, such that if adiponectin were increased, cognitive function would be improved. In a small clinical sample of patients with AD, mild cognitive impairment (MCI) and controls, low adiponectin levels were significantly associated with cognitive impairment in individuals with MCI and AD as compared to elderly controls.\textsuperscript{38} In a population-based study, higher levels of adiponectin in dementia-free individuals were an independent predictor of the risk of all-cause dementia and AD, particularly in older adults.\textsuperscript{75} Animal studies have also shown that higher adiponectin expression is another mechanism of neuroprotection against amyloid-beta neurotoxicity in AD.\textsuperscript{76} Adiponectin modulates amyloid β in AD and so improves cognition. Previous studies demonstrate that the insulin sensitizing action of adiponectin may be another mechanism of neuroprotection in AD.\textsuperscript{77-79} Thus, adiponectin may be a promising therapeutic target to alleviate neurodegenerative pathways related to neurotoxicity or insulin resistance in the brain.

\textbf{1.2.4 Skeletal Muscle Mass and Cognition of Individuals with T2DM}

Both sarcopenia and T2DM have been identified as important risk factors for poor cognitive function among older adults. White matter lesions and cerebral atrophy have been found to be
more common in adults with T2DM, and hyperglycaemia and insulin resistance have been shown to predict poor performance on executive function and memory. It has also been reported that low muscle mass may be linked to cognitive performance. One study found an association between low muscle mass and poorer cognition. Other studies have also reported loss of muscle quality (higher intramuscular lipid) is independently associated with worse cognitive function. Additionally, higher muscle mass is associated with a 43% decreased risk of AD. Given the increased prevalence of T2DM amongst older adults, it is important to consider the role of sarcopenia in the development and progression of T2DM with age. Skeletal muscle is responsible for 85% of glucose uptake during a hyperinsulinaemic/euglycaemic clamp, and as such, is the largest depot for glucose storage available. Given that HbA1c and fasting hyperglycaemia have also been shown to predict cognitive decline and dementia within this cohort, increase in muscle mass may potentially mitigate the overall cognitive risk mediated through these metabolic parameters in individuals with T2DM via increased capacity for glucose disposal. Ageing is associated with a loss of skeletal muscle, potentially contributing to the risk for T2DM, separate from that attributable to obesity. Sarcopenia, defined by some investigators as having skeletal muscle mass 2.5 standard deviations below that of a healthy, gender-matched cohort, has been shown to be independently associated with insulin resistance in individuals with and without T2DM.

In addition to the age-related loss of skeletal muscle mass, it has been suggested that systemic inflammation may accelerate this process, while insulin resistance within skeletal muscle has also been proposed to contribute to anabolic resistance within skeletal muscle. Thus, the presence of T2DM can accelerate the age-related loss of skeletal muscle mass. Not only can this
reduction in skeletal muscle mass result in reduced capacity for storage of glucose, reductions in skeletal muscle mass can impose physical limitations, further reducing physical activity levels, contributing to frailty and mobility impairment, all of which will ultimately decrease energy expenditure and thereby increase adiposity. This excess adiposity may lead to further cytokine-mediated muscle wasting, disrupt endothelial functioning, and impact atherosclerosis. Insulin resistance with obesity may prompt an increase in β-amyloid in the brain, which is considered one of the earliest detectable signs of AD and is associated with cognitive decline, neurodegeneration, and synaptic dysfunction. Thus, the development of a vicious cycle of body composition shifts contributing to diabetes onset and progression can be observed. Breaking of this vicious cycle is necessary to appropriately address all components contributing to cognitive decline in older adults with T2DM.

1.2.5 Vascular Disease and Cognition of Individuals with T2DM

A large number of studies have shown that macrovascular risk factors, such as elevated total and low-density lipoprotein cholesterol, hypertension, and atherosclerosis, are associated with cognitive impairment and risk of dementia. Moreover, there are also a large number of prospective studies showing that macrovascular risk factors, such as atherosclerosis, hyperlipidemia, and hypertension, are associated specifically with development of AD. There is also evidence supporting a role of microvascular disease, such as retinal microvascular abnormalities, on risk of cognitive impairment and dementia. As patients with diabetes are more likely to have atherosclerosis, stroke, hyperlipidemia, hypertension, and retinopathy, individuals with diabetes is plausible that in patients with diabetes both of these sets of risk factors play a role in the development of dementia, with a resultant increased incidence of dementia in
diabetes.

Diabetes alters cerebral microvascular structure in a number of ways. Findings from animal models suggest that in uncontrolled diabetes, there are focal changes in the thickness of vascular basement membranes and calcium deposits in the microvessel walls.\(^\text{107}\) Several lines of evidence indicate that cerebral microvascular disease increases the risk of AD,\(^\text{108}\) and findings from pathology studies indicate that cerebral microcirculation and microvessel are affected in AD.\(^\text{109}\) More specifically, AD involves cerebral arteriolar narrowing, endothelial cell dysfunction, capillary microaneurysms, and breakdown of the blood-brain barrier.\(^\text{110}\) Although several studies have found associations between cerebrovascular risk factors and cognitive functioning,\(^\text{111}\) only one study has examined microvascular risk factors and cognitive functioning. Also, an association between cognitive impairment and retinal microvascular abnormalities or chronic kidney disease has been reported in patients without diabetes,\(^\text{108}\) and it primarily involved cerebral small vessel disease. More specifically, retinal and cerebral small vessels are considered to have a similar embryological origin and structures, and share common physiological characteristics, and it is thought that damage to retinal and cerebral small vessels as a result of ischemia and so on leads to decline in a cognitive function. In middle-aged adults, those with retinopathy or kidney disease, including microaneurysms, retinal haemorrhage, and had significantly lower mean cognitive scores as well as a greater risk of cognitive impairment.\(^\text{106}\) Furthermore, the vascular bed of the kidney and cerebral small vessels are structurally similar, and disorders of blood flow or shear stress as a result of hypertension and so on cause damage to both the brain and kidney, showing the brain and the kidney connection.\(^\text{110}\) Therefore, in cognitive impairment occurring when there are retinal abnormalities and kidney disease, there is more likely to be impairment of executive function and processing speed, which stem from cerebrovascular disorders, than memory.
Regarding neuropathy, it is thought that nerve sheaths in the brain are damaged by a similar mechanism to the one for peripheral neuropathy, and that this leads to a decline in cognitive function. In this connection, it has been suggested that increased activity of the polyol pathway and abnormal myo-inositol metabolism, which are closely associated with the development of diabetic neuropathy, could alter glucose metabolism in the frontal lobe, as mentioned previously, resulting in cognitive impairment.\textsuperscript{112,113} Regarding decline in cognitive function, it is important to consider the association with cerebral small vessel disease. Types of cerebral small vessel disease usually seen on brain MRI are silent brain infarction, white matter lesions and microbleeds, and all of them are reportedly related to cognitive dysfunction.\textsuperscript{114} Among these, silent brain infarction has been found to be more prevalent in diabetes than in non-diabetes.\textsuperscript{115} Other research has shown that the presence, severity and progression of cerebral small vessel disease were associated with cognitive impairment in elderly patients with diabetes.\textsuperscript{116} An association was observed between cerebral small vessel disease and frontal lobe impairment, the latter assumed to be a result of damage to the prefrontal loop caused by silent brain infarction in the thalamus, and deep and periventricular white matter lesions. Patients with diabetes have a high incidence of silent brain infarction in the thalamus and basal ganglia.\textsuperscript{117}

In general, hypertension plays a major role in the onset of cerebral small vessel disease, but hyperglycaemia is also considered aetiologic. Hyperglycaemia damages the endothelium of brain microvessel, resulting in disruption of the blood–brain barrier, which in turn leads to cerebral small vessel disease.\textsuperscript{116} An association between vascular endothelial function and cerebral small vessel disease, white matter lesion, and silent brain infarction has been reported, as well as an association between a rise in serum levels of intercellular adhesion molecule-1 and a decline in cognition.\textsuperscript{118}
1.2.6 **Physical Performance and Cognitive Function of Individuals with T2DM**

It has been reported that poorer physical performance is related to cognition among community-dwelling older adults. Many studies have shown that physical performance, such as 6-minute walk distance, muscle strength, balance, habitual gait velocity, and chair stand capacity, are associated with cognitive function.\textsuperscript{35, 119-124} Moreover, there are also a large number of prospective studies showing that physical performance, such as balance, mobility, and muscle strength, are associated with cognitive impairment and development of AD.\textsuperscript{121, 122, 125, 126} In addition, several previous studies have indicated that aspects of physical performance, such as gait dysfunction,\textsuperscript{119,120} reduced postural stability,\textsuperscript{121} and decline in cardiorespiratory fitness,\textsuperscript{127} are related to structural changes of the brain (e.g., leukoaraiosis, medial temporal lobe atrophy,\textsuperscript{128} and whole-brain volume decline\textsuperscript{127} in older people. In addition, a prospective, observational cohort study indicated that muscle weakness was associated with an increased risk of developing AD and MCI.\textsuperscript{35, 129}

Diabetes and its common complication, peripheral neuropathy, may result in balance impairment, reduced mobility capacity, and alternations in gait characteristics. Patients with diabetes and peripheral neuropathy have lower gait velocity, decreased cadence, shorter stride length, increased stance time and higher step to step variability compared to healthy individuals in controls.\textsuperscript{130, 131} One study found that among younger healthy subjects with T2DM, balance was a predictor of global cognitive function and executive function.\textsuperscript{132} A higher six minute walk distance and gait speed have been shown to be an independent predictors of cognition.\textsuperscript{124} It has been argued that a higher gait speed and exercise capacity increases the cerebral blood flow especially in the
prefrontal cortex, a brain region that plays a crucial role in executive functions. In addition, high physical fitness has been shown to be an independent predictor of cognitive and physical performance. These factors could explain why cognition has been related to habitual gait speed, six minute walk distance, and balance.

1.2.7 CLINICAL IMPLICATIONS

A growing body of research indicates that diabetes-related risk factors pose substantial threats to physical health. Insulin resistance, hyperglycemia, inflammation, obesity, physical inactivity, depression, loss of skeletal muscle mass, and worse physical performance may increase risk for cognitive decline as well as other comorbidities in older adults with T2DM. Although advancing age is still the most prominent risk factor for cognitive decline and dementia, the escalating prevalence of obesity, insulin resistance (including frank diabetes), inflammation, sarcopenia and functional problems could create a scenario in which the burden of late-life cognitive disorders would actually be far greater than that which would be anticipated by virtue of the demographic shifts alone. Fortunately, these diabetes-related risk factors are potentially modifiable. Regular physical activity and healthy diet promote insulin sensitivity; reduce hyperinsulinaemia, and lower levels of inflammatory markers. Finally, a more healthful body composition profile has been reported to reduce insulin resistance and inflammation. Thus, a strategy of decreasing adiposity and increasing muscle mass in middle-aged and older adults should be considered the cornerstone of diabetes prevention.

Critical to these prevention strategies is the development of a theoretically-grounded exercise
intervention that targets the diabetes-related biology outlined above, and thereby potentially offers either enhancement or protection of late-life cognitive function in this cohort.

1.3 PHYSICAL ACTIVITY AND T2DM

Prevention is the best approach to the global epidemic of T2DM. A healthy lifestyle is encouraged to address the issue of obesity, metabolism, and inactivity, and thus reduce or delay the incidence of T2DM. Dietary modifications to reduce total calorie intake and lower glycemic load, and increase in physical activity and decrease in sedentary behavior will help to improve energy balance, glucose control, as well as weight loss and maintenance. Many systematic reviews and meta-analyses reporting lifestyle interventions and prevention of diabetes have been published. Diabetes prevention programs have been implemented around the world with marked success. For example, the Diabetes Prevention Program, the Finnish Diabetes Prevention Study, the Indian Diabetes Prevention Programme, the Da Qing study in China, the Vasterbotten Intervention Programme, the Asti Diabetes Prevention Program, and the Japanese Diabetes Prevention Programme, all significantly reduced the incidence of T2DM in high risk cohorts through lifestyle modification. These lifestyles enhanced insulin sensitivity and reduced blood levels of inflammatory markers, such as CRP and IL-6, in persons at high risk for the development of T2DM. In particular, one study using lifestyle modification showed that persons with prediabetes were able to restore normal glucose homeostasis without medication. However, in addition to prevention of T2DM, lifestyle modification is required to improve glucose control of individuals with T2DM, in order to lower the incidence and severity of diabetes complications. When medications such as oral hypoglycemia or insulin are used to control T2DM, lifestyle improvements should always be continued as complementary treatment.
In support of this, physical activity has been shown to improve glycaemic control, improve insulin sensitivity, decrease adiposity, reduce inflammation, reduce blood pressure, reduce blood lipids,\textsuperscript{146} and increase muscle mass and functional performance when added to usual pharmacotherapies in T2DM. Numerous systematic reviews document the significant role of physical activity on improvements in glycaemic control.\textsuperscript{147, 148} Glycaemic benefits are of the same order of magnitude as oral hypoglycaemic drugs, as long as the physical activity interventions have been prescribed under supervision.\textsuperscript{149} Furthermore, physical activity has a clinically important effect on other chronic diseases in older adults such as depression,\textsuperscript{150, 151} cognitive function,\textsuperscript{152} osteoarthritis,\textsuperscript{153} osteopenia/osteoporosis,\textsuperscript{154} physical frailty,\textsuperscript{155} etc. Each one of these conditions is associated with increased blood levels of inflammatory markers and imposes its own limitations to exercise capacity and habitual levels of physical activity. Thus, the use of physical activity in the treatment of obesity and T2DM is multi-factorial in both its rationale and clinical utility.\textsuperscript{156, 157} The appropriate prescriptions for physical activity can improve body composition and metabolic health, as well as diabetes-related complications associated with ageing, making it a much more potent therapy than any medication alone. Thus, these health outcomes of physical activity emerge as a key component in the management of T2DM, a view that has been supported by many professional bodies, including position stands from the Exercise Sport Science Australia (ESSA),\textsuperscript{158} and American College of Sports Medicine (ACSM) and the American Diabetes Association,\textsuperscript{159} among others.

1.4 GENERAL GUIDELINES FOR PHYSICAL ACTIVITY IN T2DM

For many years, aerobic exercise has been considered a cornerstone of diabetes management, along with progressive resistance training, as a means to improve glucose control, and thus minimise
diabetic complications, morbidity and mortality. A summary of these exercise guidelines can be found in Table 1.1. The ACSM/ADA guidelines suggest a minimum 150 min of moderate-intensity aerobic activity, ideally 3 days of the week at a moderate intensity (40-60% of VO\textsubscript{2}\text{max}). Individuals with T2DM are also recommended to participate in progressive resistance training (PRT) on 2 or 3 non-consecutive days per week. A moderate to high intensity is suggested from 50% or 80% of the one repetition maximum (1RM). Each training session should minimally include 5–10 exercises involving the major muscle groups (in the upper body, lower body, and core) and involve completion of 10–15 repetitions to near fatigue per set early in training. Both aerobic and resistance training improve insulin action, at least acutely, and can assist with the management of glucose levels. Current guidelines, however, do not yet focus on the potential role of exercise for the prevention or treatment of cognitive decline in this cohort. Given the major risk for cognitive decline imposed by diabetes (as reviewed above), this is an area requiring further empirical study and clinical application. The rationale for the use of exercise to improve cognition in this cohort is outlined in the sections that follow.

1.5 THE COGNITIVE ADAPTATION TO EXERCISE

1.5.1 ANIMAL STUDIES

Research using animal models of exercise training have demonstrated clear beneficial effects on cognitive function. Daily wheel (voluntary) running and forced graded increased exercise improved memory performance in mice. Rats participating in mentally and physically stimulating activities had greater effects on memory compared to either physical or cognitive activity alone or sedentary controls rats. Furthermore, aerobic training has been shown to counteract age-related cognitive decline on tasks involving memory and learning compared to
Sedentary control rats. Similar improvements in memory performance occurred after 5 days of wheel running and 4 weeks of treadmill running in mice. Chronic aerobic exercise maintained cognitive function in mice exposed to stress induced by cortisone administration or immobilisation. Finally, animal trials indicated that exercise may improve brain function directly through the induction and regulation of neurotrophins, transmitters, vasculature, and/or indirectly via the modulation of systemic inflammation.

1.5.2 Human Studies

Many cross-sectional studies in humans suggest that more physically active individuals have decreased cognitive impairment and risk of dementia prevalence and/or incidence. For example, individuals participating in light exercise interventions had a reduced odds ratio for all-cause and AD compared to those reporting no activity. Cognitive decline was more prevalent in those reporting no activity versus moderate and high physical exercise in a community-based study of persons over 55 years. Moreover, higher self-reported activity levels at mid- and late-life were associated with a reduced odds ratio for mild cognitive impairment (MCI) in late life, and physical activity levels at various points across the lifespan (teenage, age 30, age 50, and age >65) were associated with reduced risk of cognitive impairment in older adults. Self-reported history of high-intensity exercise was associated with better cognitive performance in those over 80 years, but worse cognitive performance in postmenopausal women. Moderate activity levels, however, were correlated with better cognitive performance in postmenopausal women. Older (>60 years) marathon runners and bicyclists performed better than inactive controls on one cognitive task—the Five Point Test—of the Vienna Neurophysiological and CERAD Test Batteries. A recent meta-analysis of 16 prospective studies including patients
with neurodegenerative diseases found that higher physical activity was associated with a 28% reduction in incident dementia.\textsuperscript{178} Frequent exercisers (>3/week) have been reported to exhibit stable or improved cognitive health over 5 years.\textsuperscript{179} It has been estimated from prospective cohort studies such as these that reducing inactivity by 25% would prevent 1 million cases of dementia worldwide.\textsuperscript{180}

Experimental trials also indicate that increased physical activity may be associated with better cognitive performance, although the average effect size (ES) observed is generally small and there is a wide range of ESs for individual studies. Exercise interventions of as little as one week of aerobic exercise can result in improved memory, attention, and reaction time.\textsuperscript{181} Sustained improvements, particularly in executive function, have been shown after aerobic training (ES = 0.41), combined aerobic and resistance training (ES = 0.59), and resistance training alone (ES = 0.53), even after exercise was withdrawn in some cases.\textsuperscript{182}

The consistency of the epidemiological literature is not matched by the outcomes of clinical trials of exercise and cognition. This may be explained in part by unmeasured factors differentiating physically active and inactive individuals which may underlie some of the cognitive differences observed.\textsuperscript{183} Moreover, one area of difficulty in this literature is the lack of consistency in outcome variables measured (i.e., cognitive performance, dementia development, AD risk or mortality) and measurement techniques (e.g., cognitive test battery used, criteria for dementia or cognitive impairment). Such differences make it difficult to compare studies and draw firm conclusions. In addition, rigorous clinical trials investigating the central and peripheral synergistic benefits of exercise for improved cognitive function in older obese individuals with
T2DM or hyperglycaemia or insulin resistance are lacking. Existing data will be reviewed in Chapter 3. Unfortunately the largest and longest trial of lifestyle modification in T2DM to date the LOOKAHEAD Study did not measure cognitive function at baseline, and did not find differences in cognition cross-sectionally at follow-up.

1.6 PROGRESSIVE RESISTANCE TRAINING: AN INTERVENTION POTENTIALLY BENEFICIAL FOR BOTH T2DM AND COGNITIVE DECLINE

Progressive resistance training (PRT) is a unique approach to the treatment of T2DM and metabolic syndrome. This is an anabolic form of exercise, differing substantially from aerobic exercise in its ability to induce muscle hypertrophy and associated metabolic and functional changes. Resistance training directly targets the underlying pathophysiology of metabolic syndrome: visceral obesity and insufficient skeletal muscle activity, thus dually enhancing insulin sensitivity. Given the role of insulin in the brain, disturbances in insulin could negatively affect cognitive function. It has been shown in randomised controlled trials to improve insulin sensitivity, glucose homeostasis, blood pressure, dyslipidaemia, markers of inflammation, adiponectin, and catabolism, and visceral obesity, thus addressing all of the components of metabolic syndrome in T2DM, those of which when compromised may threaten cognitive integrity. Resistance training also improves aerobic capacity, disability, depression, functional status, and gait and balance impairments, thus addressing a large spectrum disorders which may all potentially translate into better cognitive function in older T2DM. Resistance training also specifically targets type II muscle fibres associated with age-related sarcopenia, and increases neural recruitment, a high priority in the context of the negative impact of diabetes on peripheral and autonomic nerves, as well as cognitive function. This theoretical benefit of PRT on cognition
has been studied empirically, although not nearly as extensively as aerobic training. Resistance training has been shown to positively influence executive function, and particularly inhibitory capacity.\textsuperscript{199} Similarly, other studies found that PRT contributed to better cognitive function, using the Trail Making Test measure of cognition, in community-dwelling cohorts of older adults.\textsuperscript{200, 201} A systematic review indicated that PRT was effective in improving cognition in older adults.\textsuperscript{202} A higher intensity and longer intervention duration of resistance training appeared most beneficial, but these, along with training frequency, were parameters that required further investigation in specifically-designed dose-response trials.\textsuperscript{202} Notably, high intensity PRT is often feasible even when robust aerobic exercise is difficult or impossible due to osteoarthritis, making it particularly suitable for the obese elderly individual with diabetes.\textsuperscript{157} Increasing evidence indicates that PRT is a safe and effective intervention that promotes positive effects on metabolic and vascular health in T2DM.\textsuperscript{157} Given the multiple pathways by which PRT may potentially benefit brain metabolism and function, there is a need for robust research on the effect of PRT on cognition in older adults with T2DM. Importantly, investigation into the relationships between potential mediators (improved body composition, metabolic health, systemic inflammation, adiponectin, exercise capacity, and functional performance), and changes in cognitive function following PRT in individuals with T2DM is warranted.

\section*{1.7 RATIONALE FOR THIS THESIS}

There is strong evidence for a PRT intervention for prevention and management of T2DM; however, to date, only two randomised controlled trials investigating the efficacy of PRT exclusively within older adults (>60 years) have been published.\textsuperscript{189, 190} Other published investigations, while including older adults, also included middle-aged adults.\textsuperscript{187-189} The benefits
documented in these PRT trials have included improved glycaemic control and insulin resistance, systematic inflammation, visceral adiposity, adiponectin, muscle mass, functional performance, quality of life, and depressive symptoms.\textsuperscript{147, 149, 186-190, 192, 203-206} Much less consideration has been given to alterations in cognition after exercise, or factors which may underlie cognitive benefits. Thus, investigations in older adults into the role of PRT on cognition itself, as well as in the relationships between modifications in body composition (increases in skeletal muscle mass and reductions in adipose tissue), insulin resistance, glycaemic control, systemic inflammation, adiponectin, exercise capacity, functional performance, quality of life, depressive symptoms, and the effects of these modifications on cognition are warranted.

Among the above exercise-related adaptations, a reduction in visceral adipose tissue (as opposed to overall adiposity) has now become a primary target in the management of T2DM. Such an adaptation, which has been thought to underlie much of the improvement in insulin resistance, glycaemic control and systemic inflammation after PRT, would theoretically improve cognition as well. Furthermore, increases in skeletal muscle mass after PRT has been shown to improve insulin resistance, glycaemic control, systemic inflammation and oxidative stress,\textsuperscript{96, 129, 207} which are all important abnormalities in T2DM that have been associated with a risk of cognitive decline.\textsuperscript{208, 209} As noted earlier, other cross-sectional reports have confirmed that increased the muscle mass is associated with a decreased risk of developing AD.\textsuperscript{35} Thus, PRT has the potential to address both of the body composition factors linked to cognition (obesity and sarcopenia), making it unique among exercise modalities in this regard.

Diabetes increases the risk of disability and accelerates decline in both physical and cognitive
function. While epidemiologic data suggest that changing these variables can influence health and function achieved via lifestyle intervention, experimental data also strongly suggest that increased physical activity may contribute to the observed cognitive benefits even when weight loss did not occur. The long-term effects of PRT alone on cognitive function have never been evaluated for an at-risk group of older adults with diabetes mellitus, hyperglycaemia or insulin resistance. Also there is no data available within a single cohort on PRT-related modifications in body composition (increases in skeletal muscle mass and reductions in adipose tissue), insulin resistance, glycaemic control, systemic inflammation, and adiponectin, allowing simultaneous exploration of multiple putative mechanisms linking PRT with changes in cognitive function. Finally, there is no prior study that has investigated a specific variant of PRT called power training (high velocity, high intensity PRT) for its effects on metabolic health, body composition and cognition. Theoretically, power training (POWER) best addresses the selective loss of Type II fast twitch fibres that typify skeletal muscle ageing and the profound loss of muscle power observed in older adults.\textsuperscript{97, 210} This loss of muscle power has been linked to functional impairment to an even greater extent than losses of muscle strength,\textsuperscript{211} thus underscoring its potential utility of power training in this cohort which is at high risk for functional decline from both physical and cognitive deficits.

Given the high prevalence of obesity and diabetes in older adults, there is a clear public health imperative to understand the cognitive implications of treatment of this cohort via physical exercise. Our Graded Resistance Exercise And Type 2 Diabetes in Older adults (GREAT2DO) study randomized 103 participants with T2DM (men and women, over 60 years old). The intervention group performed high intensity power training (high velocity, high intensity resistance
training) 3 times/week for 12 months, and the control group performed low intensity, non-progressive resistance training (SHAM exercise) for the same duration and frequency. The aims of this GREAT2DO sub-study were to identify cognitive adaptations to exercise training in adults with T2DM or impaired glucose tolerance, and to assess the relationship cognition and insulin resistance, glucose control, systematic inflammation, adiponectin, abdominal adiposity, and muscle mass, and capacity and function following a 12-month high intensity power training in older adults with T2DM.

1.8 OUTLINE OF THESIS

The present chapter provides an introduction to the diagnosis, aetiology, prevalence, and clinical presentation of T2DM, as a background to the current problem of increased risk for cognitive impairment in patients with T2DM. It discusses the current intervention treatment guidelines for T2DM, potential mechanisms of cognitive impairment in T2DM, role of exercise in both diabetes and cognition, and presents the specific rationale for a particular kind of exercise, power training, which targets many of the putative pathways elevating the risk of cognitive impairment in T2DM. The notable gap in the literature with respect to the evidence that PRT or POWER training will benefit cognition in T2DM, and if so, what mechanisms underlie this benefit, is outlined. Chapters Two to Three are systematic reviews of literature that were undertaken at the commencement of this project in order to establish an understanding of the current evidence for any exercise modality for cognitive function in both animal models and human subjects with diabetes. The first review, Chapter Two is a review of RCTs and NRCTs that have examined the effect of any exercise modality on cerebral morphology, biochemistry, and function in animal models with diabetes, IGT or insulin resistance. This review using animal models investigates
whether improvements in cognitive function following exercise interventions were related to concomitant changes in brain structure and biochemistry to provide insight into the possible cellular and molecular mechanisms that underlie the effects of physical activity on cognitive function for our own studies.

Chapter Three is a review of RCTs, NRCTs and observational studies that have investigated the effect of any form of exercise on cognitive function in older adults with T2DM, IGT or insulin resistance. This review compared the evidence for current aerobic exercise treatment guidelines to the evidence for alternative modes of exercise for cognitive improvements in this cohort, and identified gaps in existing literature, and defines the context within which to view our results.

Chapter Four presents the rationale and methodology of our RCT of POWER training designed as treatment for metabolic health and comorbidities including cognitive function entitled GREAT2DO. Cognitive function was one of the pre-specified secondary outcomes of this trial. Our methodology is presented for the investigations of the baseline body composition, metabolism, systemic inflammation, adiponectin, exercise capacity, functional performance, quality of life, depressive symptoms, and cognitive function, as well as adaptations of these characteristics to a 12-month exercise intervention in the older adults with T2DM enrolled in our clinical trial GREAT2DO.

Chapter Five presents baseline characteristics of the cohort, as well as analyses of the relationships among body composition, the metabolism, exercise capacity, physical performance, and cognitive function of older adults with T2DM.
Chapter Six presents the 12-month outcomes of the SHAM-exercise controlled RCT on cognitive function in our cohort with T2DM. Additionally, relationships between physiological adaptations and cognitive outcomes are explored to attempt to delineate mechanisms underlying any cognitive improvements observed.

Chapter Seven discusses the results of thesis, and places it in context of existing literature. The role of body composition, metabolic health, inflammation, adiponectin, exercise capacity and physical performance of older adults with T2DM in relation to their cognitive performance is presented. An assessment of the efficacy of power training for cognition in this trial is presented, as well as its ability to beneficially modify body composition, metabolic health and physical performance in relation to cognitive health outcomes, in this vulnerable cohort. Finally, future directions for research will also be explored, which will focus on identifying possible mechanistic links that require additional investigation, among power training, body composition, metabolic health, and cognition of older adults with T2DM. An emphasis will be placed on the potential clinical significance of the results from this thesis, and whether these results can be translated into the clinical setting.

1.9 OUTLINE OF THE PROJECT

1.9.1 AIM

This thesis aims to first synthesise the evidence base supporting the rationale and utility of current exercise treatment guidelines for T2DM, and secondly to provide the rationale and first evidence of efficacy of a more novel form of exercise, power training, for cognitive function in this cohort. This will be accomplished by 1) systematically reviewing the animal and human literature for
current evidence of aerobic exercise as well as various modes and intensities of exercise as alternatives to aerobic exercise for improving cognition in this cohort; 2) exploring the relationship of cognition to metabolic health and other characteristics in older adults with T2DM at baseline; 3) investigating the effect of POWER training on cognition in this cohort by conducting a RCT over one year to test the efficacy of high intensity POWER versus low intensity non-progressive resistance training (SHAM control) in older adults with T2DM; 4) determining possible underlying mechanisms as to how exercise may improve cognition in this cohort. Adaptation to PRT is known to be intensity-dependent for many outcomes. However, to date, there has not been one trial to report changes in cognition in response to PRT of any intensity or velocity, in older adults with T2DM, nor have there been dose-response relationships described between PRT intensity and cognitive adaptation. Thus, both the efficacy and preferred PRT intensity and velocity for cognitive benefit in T2DM is unknown, and requires explicit investigation, which is the primary aim of this part of our trial.

The following hypotheses were investigated over the course of this thesis

The primary hypotheses for this sub-study of the GREAT2DO Trial was that 12 months of supervised high intensity power training would improve cognitive outcomes in individuals with T2DM compared to supervised low intensity non-progressive resistance training (SHAM exercise).

Secondary hypotheses were:

1. Better baseline cognitive function will be related to better metabolic health, higher muscle mass and lower adiposity.

2. Increases in skeletal muscle mass (mid-thigh cross-sectional area) in response to high intensity
power training will be directly related to improvements in cognitive function.

3. Decreases in abdominal adipose tissue (computerised tomography and anthropometric indices) in response to high intensity power training will be inversely associated with improvements in cognitive function.

4. Improvement in glycaemic control and insulin resistance in response to high intensity power training will be directly related to improvements in cognitive function.

5. Favourable changes in adiponectin and inflammatory markers in response to high intensity power training will be directly related to improvements in cognitive function.

6. Improvements in functional mobility/exercise capacity in response to high intensity power training will be directly related to improvements in cognitive function.

7. Improvements in quality of life and depressive symptoms in response to high intensity power training will be directly related to improvements in cognitive function.
1.10 REFERENCES


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FIGURE 1.1 POTENTIAL MECHANISMS LINKAGE BETWEEN T2DM, SARCOPENIA, AGE, AND COGNITIVE IMPAIRMENT

- **Ageing**
  - **Sarcopenia**
    - **Physical Activity/Excessive Energy Intake**
      - **Visceral Obesity**
        - **Insulin Resistance**
          - **Inflammation**
            - **Effects**
              - **Muscle**
                - Impaired glucose Intake
              - **Liver**
                - No inhibition of Hepatic Gluconeogenesis
              - **Endothelium**
                - Impaired Smooth Muscle relax
              - **Adipose Tissue**
                - Increased Plasma Triglycerides

- **Systemic Anabolic and Inflammatory Abnormalities**
  - Insulin Resistance
  - Total Brain Volume

- **Type 2 Diabetes Mellitus**
  - Hypoinsulinaemia
  - Hyperglycaemia
  - Hypertension
  - Dyslipidaemia

- **End-Organ Damage**
  - **Cognitive Impairment**

- **Metabolic Factors**
  - White Matter Lesions
  - Total Brain Volume
  - Blood Brain Barrier Disturbance
  - Cerebrovascular Disease and Stoke
FIGURE 1.2 THEORETICAL MODEL OF MECHANISMS LINKAGE PROGRESSIVE RESISTANCE TRAINING AND COGNITIVE AND FUNCTIONAL OUTCOMES

Progressive Resistance Training and Aerobic Exercise

Systemic Mechanism
- Increased brain-derived neural growth factor
- Increased cerebral blood flow
- Increased IGF-1 uptake in brain
- Improved Body composition (decreased fat, increased muscle)
- Insulin sensitivity, glucose use energy metabolism, lipid–cholesterol balance
- Reduced hypertension
- Decreased inflammation cortisol response to stress
- Increase social integration complexity
- Improved self-efficacy

Brain Morphology and Biochemistry
- Increased brain-derived neural growth factor
- Increased neurogenesis
- Increased synaptic complexity
- Angiogenesis
- Increased cortical thickness
- Alternated functional connectivity
- Increased phosphocreatine metabolism

IMPROVED COGNITIVE FUNCTION

REDUCED DEMENTIA INCIDENCE
IMPROVED FUNCTIONAL INDEPENDENCE
<table>
<thead>
<tr>
<th>Year</th>
<th>Governing Body</th>
<th>Aerobic Training</th>
<th>Guidelines PRT Guidelines</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>2012</td>
<td>ESSA&lt;sup&gt;154&lt;/sup&gt;</td>
<td><strong>Moderate intensity</strong>&lt;br&gt;40-59% of VO2R or HRR&lt;br&gt;55-69% HRmax&lt;br&gt;Minimum of 150min/week&lt;br&gt;Repetition 12-13</td>
<td>Minimum of 60 min/week,&lt;br&gt;to be performed on-top of&lt;br&gt;aerobic exercise</td>
<td>To be performed with no more than 2 consecutive days without exercise</td>
</tr>
<tr>
<td>2010</td>
<td>ACSM/ADA&lt;sup&gt;155&lt;/sup&gt;</td>
<td>Minimum least 150 min /week of&lt;br&gt;Moderate (40-60% VO&lt;sub&gt;2&lt;/sub&gt;max)&lt;br&gt;Vigorous &gt;60% VO&lt;sub&gt;2&lt;/sub&gt;max) aerobic exercise</td>
<td>To be performed in addition</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Vigorous Intensity</strong>&lt;br&gt;60-84% of VO2R or HRR&lt;br&gt;70-89% HRmax&lt;br&gt;Minimum of 65 min/week&lt;br&gt;RPE 14-16</td>
<td>8-10 exercises&lt;br&gt;2-4 sets&lt;br&gt;70-84% 1RM–equivalent to 8-10RM&lt;br&gt;1-2 minute rest intervals&lt;br&gt;Complete 2 or more times per week</td>
<td></td>
</tr>
</tbody>
</table>
HRmax: Maximum heart rate. Can be determined by the maximum heart rate achieved during a graded exercise test to exhaustion, or via estimation using the formula HRmax = 220 – age (years).

HRR: Heart rate reserve. Can be calculated using the following formula; HRR = HRmax (bpm) – Resting heart rate (bpm).

VO₂: The rate at which oxygen can be consumed by the body in either litres / minute (absolute; l / min) or millilitres / kilogram/minute (relative; m/kg/min)

VO₂max: The maximum rate at which oxygen can be consumed by the body. It can be determined using indirect calorimetry during a graded exercise test to exhaustion, or through estimation using a submaximal exercise test with at least 3 grades.

RM: Repetition maximum. This refers to the maximum weight that can be lifted for a given exercise. In the case of a 1RM, this is the maximum weight that can be lifted once.

ESSA: Exercise and Sports Science Australia

ACSM: American College of Sports Medicine

ADA: American Diabetes Association

RPE: Rating of perceived exertion

PRT: Progressive resistance training
CHAPTER 2

SYSTEMATIC REVIEW OF EXERCISE AND CENTRAL NERVOUS SYSTEM FUNCTION, BIOCHEMISTRY AND MORPHOLOGY IN ANIMAL MODELS OF DIABETES MELLITUS, INSULIN RESISTANCE OR HYPERGLYCAEMIA
2.1 ABSTRACT

**Objectives** - The purpose of this review was to systematically investigate the current knowledge on the effects of exercise on morphology, biochemistry, and function in animal models with diabetes or insulin resistance or hyperglycemia.

**Methods** - A systematic and critical literature search was completed from earliest record until February 2014 using computerized databases. Articles were considered for inclusion in the review if they were animal studies, assessed brain morphology, biochemistry, or cognitive function, as long as they included an exercise intervention, were conducted in any age animal with diabetes or insulin resistance or hyperglycemia. Seven randomized controlled trials and eight non-randomized controlled trials were analyzed.

**Results** - There were 15 voluntary or forced exercise (thirteen running and two swimming) trials conducted for 6 to 84 days in which exercising animal were compared to control animals with diabetes. Seventy-three percent of the studies were in animals with a model of type 1 diabetes mellitus (T1DM) and 27% of the studies were in animals with a model of type 2 diabetes mellitus (T2DM) or insulin resistance. Overall, 14/15 trials showed significant improvement in at least one cerebral morphological, biochemical, or cognitive process after aerobic exercise compared to control animals. Beneficial adaptations to exercise were seen primarily in cell proliferation, cFos, long term potential, pre-synaptic plasticity, lesion size, insulin level, insulin and leptin signalling, nerve growth factor, brain-derived neurotropic factor, glucocorticoid levels, and memory.

**Conclusions** - Animal studies to date support a role for exercise in beneficial adaptations in central nervous system (CNS) outcomes in animals with diabetes, hyperglycaemia or insulin resistance. More studies are necessary to clarify cellular and molecular mechanisms underlying improvement in memory in response to various modalities and doses of exercise in variations of animal species
with models of T2DM.

**Key words:** Exercise, Diabetes or Hyperglycaemia or Insulin Resistance, CNS Outcomes, Animals
2.2 INTRODUCTION

The prevalence of diabetes is increasing, with estimates that it will affect 435 million adults by 2030, and it is a leading contributor to premature mortality and morbidity globally.\textsuperscript{1,2} Diabetes is characterised by deficiency in insulin secretion or resistance to insulin action or both,\textsuperscript{3} and is often accompanied by widespread biochemical, morphological and functional abnormalities which may affect central and peripheral nervous systems, cardiovascular and renal function, hepatic function, physical performance, and muscle mass, among other characteristics. There are a growing number of studies identifying the brain as a site of possible complications in diabetes; indeed, evidence accumulated from animal and human clinical studies suggested a correlation between diabetes and cognitive deficits in memory, information processing speed, attention, and executive function.\textsuperscript{4} In addition, individuals with diabetes have identified alterations in brain structure, including brain atrophy and greater white matter high-intensity lesion volumes, predominantly in the subcortical regions.\textsuperscript{5} Magnetic Resonance Imaging (MRI) has also demonstrated hippocampal and amygdala atrophy relative to control subjects with T2DM.\textsuperscript{6} Hippocampus and amygdala regions have also been found to be atrophied in humans with Alzheimer’s disease.\textsuperscript{7} Furthermore, hippocampal function, synaptic plasticity, and neurogenesis is critical to learning and spatial memory function, and these capacities have been shown to have deteriorated in animals with diabetes as compared to control animals.\textsuperscript{8} A reduced insulin, insulin-like-growth factor-1 (IGF-1), leptin, nerve growth factor, brain derived neutrophic factor signaling, and increased glucocorticoid expression as occurs in diabetes, and is associated with impaired brain functions and with an increased prevalence of Alzheimer’s disease.\textsuperscript{8-10}

There is strong evidence from animal and human cross-sectional and prospective cohort studies
that participation in physical activities is associated with decreased prevalent and incident cognitive impairment\textsuperscript{11-14} Epidemiological evidence consistently links physical exercise with cognitive benefits, lower risk for dementia, and reduced pathological changes\textsuperscript{11, 15, 16} A recent meta-analysis of 16 prospective studies including patients with neurodegenerative diseases found that higher physical activity level was associated with a 28\% reduction in incident dementia.\textsuperscript{17} Frequent exercisers (>3/wk) have been reported to exhibit stable or improved cognitive health over 5 years.\textsuperscript{18} Experimental trials indicate that just one week aerobic training can significantly improve performance in healthy adults on a range of cognitive tasks.\textsuperscript{19} The largest effects on cognitive function were found on motor function, auditory attention and delayed memory functions (effect sizes of 1.17, 0.52, and 0.50, respectively).\textsuperscript{11} In one set of clinical studies, Colcombe and colleagues provided cross-sectional and prospective brain imaging data to suggest that aerobic exercise ameliorates age-related volume loss for older adults, changes that are most striking for brain regions that support executive control processes and memory including the hippocampus.\textsuperscript{20, 21} In addition, aerobic exercise has improved peripheral metabolism and induced up-regulation of hippocampal BDNF, and has also been associated with improvements in cognition and brain structure.\textsuperscript{22-24} Thus, although it has been shown in many studies that exercise can enhance cognitive function, morphology, and biochemistry in animal models and human studies, there is as yet no systematic review of the effects of exercise on CNS adaptations in animal models at high risk of cognitive dysfunction due to diabetes, insulin resistance or hyperglycaemia to our knowledge. The importance of such animal models lies in the ability to explore biochemical and morphological changes in the CNS in response to exercise, and their potential relationship to cognitive performance in ways that are not possible in human investigations.
Therefore, the purpose of this investigation was to systemically review adaptations to exposure to any mode of exercise in the domains of central nervous system function, biochemistry, or morphology in animals with diabetes, insulin resistance or hyperglycaemia, for the purpose of identifying underlying mechanisms which may be targeted in future studies of lifestyle interventions to combat this global epidemic.

2.3 METHODS AND PROCEDURES

2.3.1 LITERATURE SEARCH

A literature review was conducted from the year 1966 to May 2014 using computerised databases performed in Medline (1966-2014), CINAHL (1982-2014), EMBASE (1966-2014), SportDiscus (1967-2014), PsycINFO (1966-2014), Cochrane Controlled Trials Registry (1st Quarter 2014), Cochrane Dementia and Cognitive Improvement Group (1985-issue 1,2014), Cochrane Reviews (1985-issue 1, 2014) with the last search being conducted in Feb 2014. The searches for the following categories were conducted using text words pertaining to cognition, exercise and diabetes. A combination of text-based terms in all fields was used to find records.

a) Intervention: Exercise, or training, or physical activity, or aerobic, or physical capacity, or aerobic capacity, or physical performance, or physical endurance, or motor activity, or resistance, or weight lifting, or strength, or power training, or strength training, or weight-training, or resistance-training, or resistance exercise

b) Animals: Any animal species/strains with diabetes, insulin resistance, hyperinsulinemia, or hyperglycaemia

c) Outcome: Cognition, or cognitive or mental or mental process, or memory, or brain, or neuropsychology, or neurological
Searches a, b, and c were combined with ‘AND’ to produce the initial set of retrieved references. Reference lists in all eligible papers and review articles were hand-searched for any additional papers. (Figure 1)

2.3.2 INCLUSION AND EXCLUSION CRITERIA

Studies were included if they met all of the following criteria:

1. They included animals with diabetes, insulin resistance or hyperglycaemia were diagnosed on blood glucose level (≥280mg/dl or ≥14–35 mmol/L) or fasting glucose level (≥6.5-6.6mM).

2. They included an intervention of any form of exercise training (defined as planned, structured, and repetitive physical activity which has as a final or intermediate objective, the improvement or maintenance of physical fitness), where clear prescriptive parameters were provided, whether supervised (forced) or unsupervised (voluntary), and conducted in a laboratory setting.

3. Animals were exposed to chronic exercise. A minimum of one week of exercise was used as the definition for chronic exposure. This was to exclude studies of known acute bout effects on attention span and focus on chronic adaptations within the CNS or periphery affecting cognition.

4. Any validated test of cognition, brain morphology, or biochemistry reported at follow-up.

5. The design of the study must have been set up so that the independent effects of exercise could be seen in animals with diabetes, insulin resistance or hyperglycaemia. Enriched environment or dietary co-interventions were allowed, only if the exercise effect could be isolated from the dietary effect.

6. The study was a randomised controlled trial (RCT) and non-randomised controlled trial (NRCT).
The study was a full-length article published in a peer-reviewed English language journal. Trials were excluded if they met any of the following criteria:

1. Studies included human beings with diabetes, insulin resistance or hyperglycaemia.
2. No validated test of cognitive function, brain morphology or biochemistry was reported as an outcome.
3. Studies were non-English language articles or unpublished papers; or the articles were reviews or abstracts.

2.3.3 Study Selection and Data Extraction

One author (RRZ) conducted the search and extracted all data. After eliminating duplicates, all papers identified by the search strategy were screened by the author, first by title and then by abstract using the above eligibility criteria. Two authors (RZ and MFS) screened papers accepted for inclusion in the review. Quality assessment of all eligible papers was undertaken separately by these two authors using a modified Physiotherapy Evidence Database (PEDro)\textsuperscript{25} for assessing the quality of animal RCTs and NRCTs. Five additional items (“Exercise supervised, animal strain reported, age and weight reported: yes/no; and exercise paradigm reported: voluntary/forced”) were included to identify these important components of exercise studies relevant to animals, providing a final possible score of 14. Points were only awarded if the criterion was clearly satisfied. Any disputes were resolved by consensus, or by a third author (AOS) if necessary. Data were extracted regarding study methodology, animal cohort characteristics, exercise intervention paradigms, outcomes of cognition, morphology, and biochemistry, and any concomitant relationships between changes in cerebral biochemistry or cerebral morphology and cognition. If data were only presented graphically, attempts were made
to obtain data from authors; if this was not available, values were measured from the published graphs.

2.3.4 Data Analysis

Due to the heterogeneity of exercise prescriptions, outcomes assessed and measurement tools used, a systematic review was conducted rather than a meta-analytic approach. Trials were split into the following groups: 1) RCTs and 2) NRCTs. Studies were considered to employ control groups if one group was assigned an exercise intervention, and the other group was assigned to non-exercise control, SHAM exercise control, or an alternate form of exercise intervention. Study characteristics were summarised as mean (SD) or median (range) as appropriate for normal or non-normally distributed data respectively. Data that were reported as mean ± SEM were converted to mean ± SD. Relative Effect Size (ES) (mean change Treatment – mean change Control) ÷ SD Pooled baseline was calculated for controlled trials relevant data were available. Effect sizes were interpreted according to Cohen’s scale of ‘trivial’ (<0.20), ‘small’ (0.20 to <0.50), ‘moderate’ (0.50 to <0.80), and ‘large’ (>0.80). ESs and 95% CIs were graphed as forest plots. Statistical significance level was assumed if p < 0.05, and/or ES 95% CIs were not inclusive of zero. Finally, results of statistical associations between any of the cognitive, cerebral morphological, or biochemical outcomes were extracted, where such relationships were available.

2.4 Results

2.4.1 Studies Retrieved

Figure 2.1 displays the search results. The combined search yielded 5578 studies, while hand
searching identified a further 3 studies. After the removal of duplicates, 4435 studies remained. Titles and abstracts were examined, and studies not meeting the eligibility criteria were excluded. The whole text of 97 studies was examined, and 15 trials were found to meet the criteria for review. This included 7 RCTs\textsuperscript{28-34} (one trial with swimming, four with treadmill, and two with wheel running) and 8 NRCTs\textsuperscript{35-42} (8 with treadmill exercise). Three of the 15 studies assessed cognitive function.\textsuperscript{30, 38, 39} Eight out of 15 studies had measures of cerebral morphology,\textsuperscript{28, 30, 31, 35, 37, 39, 40, 42} and 8 had measures of biochemistry.\textsuperscript{29, 32-34, 36, 39-41}

2.4.2 \textit{Study Quality Assessment}

Study quality on the basis of a modified version of the Physiotherapy Evidence Database (PEDro) is summarised in Table 2.1. Overall, the quality of the RCT trials\textsuperscript{28-34} included in this review was moderate, with most receiving a score of 7 out of 14, and only one study scoring 10 out of 14. Common limitations in quality were: lack of concealed allocation,\textsuperscript{28-34} lack of blinded assessors in 7 trials,\textsuperscript{28-34} lack of interventionists blinded to hypotheses in 6 trials,\textsuperscript{28, 29, 31-34} absence of intention-to-treat analysis in 7 trials,\textsuperscript{28-34} and insufficient available information regarding baseline matching between groups in 7 trials.\textsuperscript{28-34} Exercise interventions were fully supervised in all RCTs\textsuperscript{28-34} and key outcomes were obtained in greater than 85\% of animals enrolled in each trial. Quality of the included NRCTs was also only moderate, with, on average, 6 of 14 quality criteria being met (mean 6.4 ± 1.4, range 5-8/14). It is recognised that some quality elements such as concealment of allocation are minimally relevant to animal models as opposed to human trials for which PEDro scale was designed.
2.4.3 Animal Characteristics

A variety of animal models were used in the 15 studies (see Table 2.2). One study reported a model of intracerebral hemorrhage. Total samples (mean n=15, range: 10 to 20), were divided into intervention and control groups varying between 5 and 10 animals in 7 RCTs (Sprague Dawley rats, Wistar rats, and Zucker fatty rats with diabetes) with the larger groups (Wistar rats) participating in swimming programs, while 108 animals (Sprague Dawley rats, Wistar rats, and db/db mouse) were included in 8 NRCT. The average age of animals across all trial trials was 61 days, with age ranging from 30 to 161 days (Weanling: 21-35 days, preadolescent: 35-63 days, adults: 63-180 days). Thirteen of 15 publications reported the weight of animals (mean 198±53 grams) and two publications did not report this variable. Sex breakdown was provided in all studies. Overall, 13 trials included male only, while the remaining 2 trials were comprised of mixed male and female animals.

2.4.4 Diagnostic Criteria

Only 5 out of 15 trials reported diagnostic criteria for T2DM or insulin resistance as either fasting glucose > 300mg/dl or fed glucose 6.5-6.6mM or 30.9±1.7mmol/l. While the remaining 10 trials reported diagnostic criteria for T1DM or hyperglycemia as either fasting glucose >300mg/dl or blood glucose level (BGL) 14–35 mmol/l.

2.4.5 Type of Diabetes

We also identified four different types/aetiologies of diabetes: 10 out of 15 trials reported medication treatment to induce a metabolic state similar to T1DM. The most common medications used for this purpose were Streptozotocin and Alloxan. The remaining five
trials did not employ a diabetes inducing injection agent. Instead, they utilised animal strains bred (Zucker fatty rats with diabetes and db/db mice) for obesity and development of insulin resistance/T2DM or pancreatectomy (Wistar rats) to induce models of insulin resistance and/or T2DM.

2.4.6 MEASURES OF GLUCOSE LEVEL AND INSULIN SENSITIVITY

Postprandial blood glucose was used in 4 out of 15 trials as a measure of glucose level of diabetes, while the fasting and random glucose levels were measured in one trial, respectively. Only 1 trial used an oral glucose tolerance test to assess insulin sensitivity. A blood glucose concentration was used in 9 trials as a measure of diabetes.

2.4.7 THE TIME POINT OF ASSESSMENT FOR COGNITIVE FUNCTION AND BRAIN STRUCTURE AND BIOCHEMISTRY

Assessment of time interval between the last bout exercise session and cognitive function, brain structure, and brain biochemical markers. The majority of studies reported the immediate measures for cognitive function, cerebral tissue, and cerebral biochemistry, and four studies were between 0.5-48 hours after exercise while no report was found in one study.

2.4.8 MEASURES OF CEREBRAL MORPHOLOGY

Cell proliferation in the hippocampus was most commonly measured (4 publications) via immunohistochemistry; Plasticity of the dentate gyrus was measured by using a
concentric bipolar stimulating electrode and a DAM80 differential amplifier to determine extracellular field potentials amplified (100×) and filtered (1 Hz to 3 kHz band pass) in two publications.\textsuperscript{37,42} One trial utilised the Image-Pro Plus computer-assisted image analysis system (Media Cyber-betics Inc., Sliver Spring, MD, USA) to detect change in cFos as a measure of neurogenesis.\textsuperscript{30} One trial acquired images for analysis of dendritic spine density.\textsuperscript{40} Nissl staining was employed in 1 trial to specifically determine lesion volume in a study of cerebral haemorrhage and exercise exposure.\textsuperscript{28}

2.4.9 MEASURES OF CEREBRAL BIOCHEMISTRY

Two trials measured insulin levels using radioimmunoassay.\textsuperscript{29,32} One utilized radioimmunoassay and biochemical measurement to calculate insulin growth factor 1 (IGF-1) and glycogen.\textsuperscript{32} One trial utilised immunoblotting analysis to determine insulin and leptin signaling.\textsuperscript{36} Two trials used immunohistochemical staining to detect hyperglucocorticoidemia receptors.\textsuperscript{33,34} A Kodak Image Station for protein determination of nerve growth factor was measured in one trial.\textsuperscript{39} One trial examined BDNF levels using an enzyme-linked immunosorbent assay.\textsuperscript{40} One trial used chromatography and fluorescence detection to calculate gamma-aminobutyric acid and glutamate.\textsuperscript{41}

2.4.10 MEASURES OF COGNITIVE FUNCTION

Relatively few trials (only 3/15) measured cognitive function in comparison to the central morphology and biochemistry measures outlined above. Amongst animal cognitive ability assessments, spatial learning and memory performance,\textsuperscript{38} while one trial utilised radial arm maze task measures to test memory, from which memory was assessed by spatial acquisition, and spatial
A passive avoidance test apparatus was used in one trial to specifically test memory retention. A summary of the training protocols can be seen in Table 2.3.

Exercise modality

All studies investigated the effects of the aerobic training. Among the RCTs, 5 trials utilised forced treadmill running compared to non-exercise control groups. Two examined effects of forced swimming compared to non-exercise control groups. The remaining trial used a voluntary wheel running compared to a non-exercise control group. The 7 NRCTs compared the effects of forced treadmill training to non-exercise control groups.

Volume of exercise and duration of trial

Exercise volume varied from 30 to 60 minutes per session, mean 40.8±12.4 minutes. Seven sessions per week was the most common training prescription, utilised in 7/15 trials; but it was as low as four to five sessions per week in the remaining 5 trials. Trial duration ranged from 1 to 12 weeks, mean 7.7±4.6 weeks; the majority of studies were between 5-12 weeks, and three studies were between 1-4 weeks.

Intensity and progression

Despite all trials utilising a mode of aerobic training, there was a large variation in the protocols used to conduct the exercise intervention. Aerobic exercise intensity in Kim (2003) and Lee
(2005) were prescribed at 2 metres per minute for 5 minutes, 7 times per week, which progressed from 5 to 8 m/min and the duration increased from 5 to 20 minutes over 1 week exercise.\textsuperscript{28, 35} Reishi report workload 5 meter / minute for 10 minutes, which increased 17 metres /minute for 40 minutes in week 1, workload set 17 meters / minutes for 40 minutes starting from week 2 to week 12.\textsuperscript{37, 38, 41, 42} In Park et al (2005),\textsuperscript{36} aerobic exercise was prescribed at 20 metres per minute for 30 minutes, 4 times per week. Aerobic intensity was set at speed of 12 metres/minute for 60 minutes in daily (5 days a week), for 7 weeks, which speed increased from 1 metre/minute per week and the duration was 60 minutes over the course of 5 days from week 1 to week 12.\textsuperscript{34} You et al (2003)\textsuperscript{30} set the duration of aerobic exercise at 75 minutes/session, 7 times per week for 6 weeks, and the exercise intensity consisted of running for 5 minutes at a constant speed of 4000 metres/hour, followed by running for 5 minutes at 5000 metres/hour, and then running for 20 minutes at 7000 metres/hour. In Yi et al (2009)\textsuperscript{31}, aerobic exercise was prescribed at 5 to 17 metres / min for 15 minutes in week 1, which gradually progressed to 22 metres per minute for 45 minutes, while duration increased from 10 to 40 minutes from week 2 to week 5. Campbell et al (2010)\textsuperscript{33} set the average daily running distances for the exercising animals began at 3.4 ± 0.2 km/day during week 1, peaked at 6.5 ± 0.5 km/day during week 6, and then slowly declined to 4.5 ± 0.7 km/day during week 10. Finally, the speed and duration of the treadmill exercise in Chae et al (2007)\textsuperscript{39} were gradually increased from 10 metres/minute for 10 minute (grade 0%) in the 1st week to 10 m/min for 20 minutes in the 2\textsuperscript{nd} week, 14–15 metres/minute for 20 minutes (grade 0%) in the 3\textsuperscript{rd} week, 14–15 metres/minute for 30 minutes in the 4\textsuperscript{th} week, and 17–18 metres/minute for 30 minutes from the 5\textsuperscript{th} week. Swimming exercise was set a 5% body weight for 60 minutes.\textsuperscript{29} Similarly, one aerobic exercise included three swimming sessions and set 4%, 5%, and 6% body weight, swimming workload is 4% body competed with 90% the maximal lactate steady state from
25 to 60 minutes in two week, which is gradually increased workload from 5% to 6% body weight interval week.\textsuperscript{32}

Overall, aerobic training intensity was considered to be low in 8 studies,\textsuperscript{28, 31, 34, 35, 37-39, 41, 42} moderate in 2 studies,\textsuperscript{36} and high in 3 studies\textsuperscript{29, 30, 32} of the 13 studies where prescriptive elements were reported. However, no intensity (speed) were reported in two studies.\textsuperscript{33, 40} All but two trials\textsuperscript{28-31, 34-38, 40-42} were fully forced, supervised treadmill exercise without any inclination, while two studies utilised voluntary unsupervised wheel running exercise.\textsuperscript{32, 33}

2.4.12 Outcome Measures

2.4.12.1 Morphological Outcomes

Results are reported in Table 2.4. Eight trials investigated the effects of forced treadmill running on cell proliferation\textsuperscript{28, 31, 35, 39} and synaptic plasticity.\textsuperscript{30, 37, 40, 42} Improved cell proliferation and synaptic plasticity were the most consistent positive adaptations observed, and in general, the effect sizes were large and moderate.

Neuronal cell proliferation

Four studies measured neuronal cell proliferation in the hippocampus.\textsuperscript{28, 31, 35, 39} Compared to control groups, neuronal cell proliferation significantly improved in two trials of low and moderate intensity exercise, with very large ESs calculated [(ES: 4.64; 95\% CI: 2.76, 6.52)\textsuperscript{35} and (ES: 6.28; 95\% CI: 4.15, 8.42)].\textsuperscript{39} Aerobic training significantly increased Ki67 positive nuclei assessed using immunohistochemistry (a marker of cell proliferation) and doublecortin (DCX) immunoreactivity (a marker of progenitors differentiating into neurons measured by Western Blot
analysis) in one trial of low intensity running, again with very large ESs [(Ki67 ES: 5.99; 95% CI: 3.70, 8.29), (DCX in the dentate gyrus ES: 2.20; 95% CI: 0.96, 3.44), (DCX with tertiary dendrites ES: 17.81; 95% CI: 11.56, 24.08), and DCX without tertiary dendrites ES: 4.97; 95% CI: 2.99, 6.95)], respectively. In another trial of low intensity exercise in animals with hyperglycaemic complication of cerebral haemorrhage, (60 minutes/session, five session/per week ± 5 weeks), increases in cell proliferation were seen following early or later aerobic training [(Early exercise ES: 2.50; 95% CI: 0.99, 4.01) and (Later exercise ES: 2.31; 95% CI: 0.85, 3.77)], compared to a control group. Compared to the control group, early aerobic training also significantly reduced lesion size and neuronal apoptosis (ES: -1.96; 95% CI: (-3.34, -0.58), while later exercise (ES: -2.87; 95% CI: -4.48, -1.26) failed to produce such an effect in this trial.

Synaptic plasticity

Four studies measured the effects of forced treadmill running on synaptic plasticity in the hippocampus. In two studies, paired pulse index [short-term forms of synaptic plasticity; (ES: -3.09; 95% CI: -4.77, -1.42)] and field excitatory post-synaptic potential (ES: -3.36; 95% CI: 5.12, -1.60)] as well as long term potential-population spike [a form of activity-dependent synaptic plasticity; (ES: 3.02; 95% CI: 1.36, 4.67] and long term potential-field excitatory post-synaptic potential slope (ES: 1.94; 95% CI: 0.57, 3.31), were enhanced in the hippocampus from running rats as compared controls. Mixed results were reported in another study, in which aerobic exercise (low intensity voluntary wheel running for 12 weeks) had no effect on dendritic spine length using Golgi impregnation and analysis, (ES: 0.40; 95% CI: -0.74,1.55) although a significant increase was observed in dendritic spine density (ES: 2.11; 95% CI: 0.70, 3.52) In another trial aerobic exercise significantly improved hippocampal cFos expression [neuronal
immediate-early gene (IEG) cFos expression], which is associated with regulated synaptic activity (ES: 0.96; 95% CI: 0.67, 1.25) using the Image-Pro® Plus computer-assisted image analysis system, compared to the control group.\textsuperscript{30} Two trials\textsuperscript{30, 39} reported that the increased cFos and neuronal cell proliferation and enhancement in memory observed after low or high intensity running, respectively. However, no other studies reported whether such relationships existed.

\textbf{2.4.12.2 BIOCHEMISTRY OUTCOMES}

Three NRCTs compared voluntary or forced aerobic training to a non-exercise control group, with aerobic training shown to improve insulin, insulin-like-growth factor-1 insulin signaling, leptin signaling, nerve growth factor signaling, BDNF, glutamate, and glucocorticoid receptor, but not gamma-amino-butyric acid. Voluntary wheel running improved both dendritic spine density and BDNF levels in another trial.\textsuperscript{40} Increased nerve growth factor signaling and increased BDNF and improved memory were observed following aerobic exercise. However, no study reported the relationships between increased nerve growth factor signaling and increased BDNF and memory.

\textit{Insulin/insulin like growth factor 1 (IGF-1)}

When comparing exercise training to a non-exercise control group, one RCT was shown to improve insulin level in one trial for high intensity running (ES: 2.12; 95% CI: (0.89, 3.34)\textsuperscript{29} while no effect was seen on insulin (ES: 0.58; 95% CI: -0.31, 1.47) and insulin-like growth factor 1 (ES: 0.30; 95% CI: -1.18, 0.58) in one RCT trial for high intensity running.\textsuperscript{32}

\textit{Insulin and leptin signaling}

Improvements in brain insulin signaling assessed by tyrosine phosphorylation insulin receptor
substrate 2 (IRS2) and Akt were seen following aerobic training in one trial [IRS2 cortex (ES: 3.59; 95% CI: 2.17, 5.01), (IRS2 hypothalamus ES: 4.21; 95% CI: 2.64, 5.79), (Akt cortex ES: 8.36; 95% CI: 5.62, 11.09), and (Akt hypothalamus ES: 18.87; 95% CI: 12.95, 24.78)]. Aerobic exercise improved leptin signaling measured by STAT3 in one trial [(ES: 3.19; 95% CI: 1.87, 4.51) and (ES: 10.90; 95% CI: 7.41, 14.39)]. One NRCT trial observed a significant increase in glycogen synthesis of the cortex and hypothalamus [(ES: 3.19; 95% CI: 1.87, 4.51) and (ES: 10.90; 95% CI: 7.41, 14.39)], while one RCT trial and one NRCT failed to report such an effect in hippocampus.

**Neurotrophic factor and neurotransmitters**

Three NRCT trials compared voluntary or forced aerobic training to a non-exercise control group, with aerobic training shown to improve nerve growth factor signaling by determined tyrosine kinase receptor A (TrkA) (ES: 3.92; 95% CI: 2.43, 5.43) and extracellular signal-regulated kinase 1/2 (Erk1/2) [(tErk1 ES: 1.85; 95% CI: 0.50, 3.21) and (tErk2 ES: 8.97; 95% CI: 5.21, 12.74)], brain derived neurotrophic factor (ES: 4.77; 95% CI: 2.22, 6.32), and glutamate (ES: 2.37; 95% CI: 0.90, 3.85), but not gamma-aminobutyric acid (ES: 0.34; 95% CI: -0.65, 1.32). Voluntary wheel running improved dendritic spine density with increased brain derived neurotrophic factor levels. However, one study reported spin density and BDNF levels improved with aerobic exercise, a finding that implicates a potential benefit of improved BDNF levels on spine density and cognitive processes.

**Glucocorticoid receptor (GR)**

Two trials measured GR and reported significant change, and ESs were modest or large.
Campbell et al\(^{33}\) reported a net increase ranging from 40.6% and 76.4% in quantification of the relative signal intensity of hippocampal GR and hippocampal GR content and the between group effect sizes for this trial were large. The second trial reported\(^{34}\) a net decrease of 136.8, 98.2 and 48.2 in stratum pyramidal and radiatum, respectively, but not significant changes in stratum orients and dentate gyrus, and the between groups effect size we calculated was non-significant. However, as there are only two trials\(^{33,34}\) investigating glucocorticoid receptor and exercise, further investigation is required to confirm these findings and assess the relevance to enhanced glucocorticoid receptor in different area of hippocampus after exercise.

2.4.12.3 COGNITIVE FUNCTION

A summary of the results can be found in Table 2.6. Three studies measured some aspect of cognitive function (learning and memory)\(^{30,38,39}\), and it was significantly improved in all them. Very large ESs were demonstrated after low to high intensity running, with volumes ranging from 30 to 40 minutes per session, five to seven sessions per week, and duration of interventions ranging from 6 to 12 weeks. For example, exercise improved spatial learning and memory [error number (ES: -2.47; 95% CI: -4.12, -0.83)]\(^{30}\) spatial acquisition [(escape latencies ES: -3.43; 95% CI: -4.97, -1.89); swim distance (ES: -2.13; 95% CI: -3.35, -0.90); swim speed (ES: 2.01; 95% CI: 0.81, 3.21)]; spatial retention [(platform located chance % ES: 1.27; 95% CI: 0.20, 2.35) and crossing number (ES: 1.83; 95% CI: 0.67, 3.00)]\(^{38}\) and retention latency (ES: 1.68; 95% CI: 0.66, 2.70)].\(^{39}\)

2.5 DISCUSSION

This systematic review identified seven RCTs and eight NRCTs of exercise in animal models with diabetes or hyperglycemia or insulin resistance. The quality of this literature was moderate, and
the majority of trials had samples too small for sufficient power to detect small effects. The major finding of this review was that there was a significant improvement in cerebral structure, chemistry in the majority of these trials after exposure to a variety of doses of chronic aerobic exercise, and ESs were generally large to very large. Limited data were available on improvements in cognitive performance itself, but what was reported was significant as well. This review also showed that the elevations in the cell proliferation, cFos expression, and nerve growth factor levels in this rodent model of with diabetes or hyperglycemia or insulin resistance were associated with increased memory ability, although these data come from only two trials which investigated such relationships. Notably, all but two of the 15 trials used forced exercise, which could theoretically have had negative impacts on brain structure and function through elicitation of a stressor response, but this was not evident. As no trials to date have directly compared the benefits of forced and voluntary exercise on cerebral morphology or function, it is not possible to ascertain whether improvements would have been even greater if a voluntary exercise paradigm had been utilised.

The literature search only retrieved two investigation that assessed the effects of voluntary and forced exercise on glucocorticoid receptor in the hippocampus in zucker rats with diabetes, showing different effects. Given the associations between glucocorticoid receptor, and hippocampal degeneration and the emergence of learning and memory deficits, this gap in the literature should be addressed in future trials. A better understanding of the interaction between the glucocorticoid receptor and changes in cognitive function in response to voluntary and forced exercise may lead to the development of mechanisms to beneficially modulate such glucocorticoid receptor and thus provides compelling evidence for the need and augment the effect of exercise in
future trials.

Despite the numerous studies performed measures of cerebral morphology and/or biochemistry, many failed to report whether any relationships existed between the changes in these variables and function, thus making them unable to be conclusion in this particular review. If functional significance related to these variables were able to be reported by future investigations, this would provide a very rich pool of data in which to explore potential relationships.

2.5.1 Brain Morphological Outcomes

This review identified seven trials (3 RCT and 4 NRCTs) that measured brain structure. The modest amount of evidence available suggests that aerobic exercise improves neurogenesis, synaptic plasticity, and intracerebral lesion size. Previous reviews have shown that there is a positive effect of aerobic exercise on brain neuroplasticity within healthy animals.\(^{44,45}\) It is clear from the trials included in this review that significant, large improvements in neurogenesis and neuroplasticity occurred with exercise training in these models of diabetes and insulin resistance as well. Specifically, the results showed that increases in neuronal cell proliferation in the hippocampus.\(^{28,35,39}\) Furthermore, in one randomised controlled trial of aerobic training,\(^{31}\) ki67 and DCX cells, signifying cell proliferation and cell differentiation, respectively, markedly increased in the exercise group in the dentate gyrus. In this trial,\(^{31}\) doublecortin positive cells with or without tertiary dendrites were significant increased. In addition, cFos,\(^{30}\) hippocampal neuronal immediate-early gene, significantly increased after training and there was a significant direct association between enhanced cFos levels and increased memory. Increase in long term potential (34-50%),\(^{42}\) and dendritic spine density (10%)\(^{40}\) as well as reduction in pre-synaptic
plasticity (301-307%)\textsuperscript{37} and reduced lesion size (7.6-20%) and neuronal apoptosis (12-32%)\textsuperscript{28} in animal models with diabetes or insulin resistance was also seen. Given that these cerebral benefits occurred across a wide range of exercise doses and intensities, there does not seem to be an obvious dose-response relationship between exercise exposure and CNS adaptation. However, as there were no studies that directly compared the benefits of different doses, there is a need for future studies to confirm both optimal and minimal exercise exposure for cerebral benefits in diabetes or insulin resistance or hyperglycaemia. There is limited evidence yet that these morphological adaptations result in improved cognitive performance. In the one study to explore this question, increase in synaptic plasticity associated with forced exercise occurred in the hippocampus, which was concomitantly linked to increased memory performance, suggesting that enhancement in new cells and cFos may have a functional role in this process. Additional studies are needed to extend and confirm this finding.

Whether exercise exposure is effective for both prevention and treatment of cerebral pathology in diabetes is an important question that has received little empirical study. In the one trial to examine this question, improvements in CNS hemorrhagic lesion volume was related to early exercise intervention (12 hours), but no significant benefit was observed when exercise was started later (after the lesion).\textsuperscript{28} It was concluded that regardless of mode or intensity of exercise, later intervention was not able to reduce lesion size, nor provide a robust neuroprotective benefit, because neuronal cell apoptosis reached the maximum level 72 h after the hemorrhage.

Thus, the timing of exercise with respect to prevention of diabetes-related pathology in the brain (such as hemorrhage) may be important. The animal review suggested that aerobic exercise, in
an optimal time window, increased proliferation and reduced haemorrhagic lesion size in the brain, and was therefore recommended as a behavioral intervention to promote functional recovery in brain diseases in an animal model with hyperglycaemia. Additionally the finding of beneficial cellular changes in brain structures in animal models, brought about by exercise, provides compelling evidence for the need for further study of stroke in humans. However, it is ischemic stroke in humans, which occurs with higher prevalence in type 2 diabetes patients. Ischemic stroke is the most common type of stroke, accounting for almost 80 percent of all strokes. Therefore, the relevance of these animal data to ischemic stroke in humans with type 2 diabetes is not known at this time, and should be the focus of future epidemiological and experimental investigations.

Aerobic exercise in optimal time window increased proliferation and reduced haemorrhagic lesion size in the brain, and is also recommended as a behavioral intervention to promote functional recovery in brain diseases animal model with hyperglycaemia. Nevertheless, ischemic stroke in human, a severe complication in type 2 diabetes patients, is the most common type of stroke, accounting for almost 80 percent of all strokes. The finding of cellular changes in analogous brain structures in animal models, brought about by exercise, provides compelling evidence for the need for further study of stroke in humans.

Future studies are needed to delineate the optimal time for initiation of exercise in metabolic dysfunction and diabetes for maximum neuroprotection for this and other kinds of pathology (ischemic stroke) related to cognitive impairment. Eight trials (4 RCTs and 4 NRCTs) tested cerebral biochemistry. Some benefits were seen in hippocampal molecular
pathways and metabolites after aerobic exercise training.

2.5.2 Brain Biochemical Outcomes

Neurotrophic factor

BDNF concentrations were elevated significantly in response to aerobic exercise.\textsuperscript{40} This result is in agreement with the findings from healthy animal studies, which have clearly shown that a period of aerobic exercise elevates levels of BDNF mRNA and protein in the hippocampus and other brain regions in healthy males\textsuperscript{46-48} However, the study suffered from the limitations in terms of the small sample size (6 mice in each group). More studies are warranted to determine the adaptation of hippocampal BDNF in response to long-term voluntary and forced exercise training.

One trial reported increases of NGF, TrkA, p-Erk1/2, and p-CREB protein expression,\textsuperscript{39} which has been demonstrated to be low in patients with T1DM compared to control in healthy rats,\textsuperscript{39} and has been reported to increase with aerobic exercise training.\textsuperscript{39} Notably, all positive adaptations above (NGF/TrkA/p-Erk1/2/ p-CREB) are from non-randomised controlled trials. These results can therefore only be considered a weak form of evidence at present, and they require confirmation in randomised controlled trials.

Insulin/IGF-1 and/or leptin signaling

Two RCT studies investigated insulin.\textsuperscript{29,32} In Leme et al (2011), exercise significantly increased in insulin concentration.\textsuperscript{29} In one case, even though no significant changes in insulin level were observed, there is an increase in exercise groups.\textsuperscript{32} These ranged from 2.3 pmol/kg/wet in the
aerobic training group. However, other than exercise modality, there is no obvious explanation for this lack of adaptation for insulin in aerobic training studies.

While radioimmunoassay analysis for IGF-1 was performed in one trial, swimming increased the expression of hippocampal IGF-1 that are decreased in diabetes. Glycogen synthesis increases in the cerebral cortex and hypothalamus were reported in one aerobic training trial, but no significant increases were observed in glycogen in hippocampus. With the limited data available, it is difficult to conclusively determine the specific role of changes in IGF-1 contents and glycogen.

One RCT trial tested some parameters of insulin and leptin signaling. Some beneficial improvements in insulin signaling were seen in the cerebral cortex and hypothalamus after exercise training. One aerobic training trial reported increases of insulin receptor substrate 2, Akt (protein kinase B), glucose transporter type 2, and signal transducer and activator of transcription 3, which result in insulin signaling. Exercise also decreased leptin signaling in the cerebral cortex and increased leptin signaling in the hypothalamus. However, only one trial reported the positive effects of exercise on insulin and leptin signaling, thus more trials is need to confirm other insulin and leptin singling outcomes in the regional brain after exercise.

Glucocorticoid receptor (GR)

Two RCT trials with voluntary and forced aerobic exercise reported significant change in GR. One trial reported increased GR, but another one reported decreased GR. However, no consistent pattern has been demonstrated for other GR synthesis outcomes in the regional brain. Further investigation is required to confirm these findings and assess the relevance to enhanced
glucocorticoid receptor in hippocampus after exercise.

**Neurotransmitters**

Glutamate, the most common neurotransmitter in the brain, is an excitatory neurotransmitter involved in many aspects of brain function, including learning and memory. Animal studies have shown that treadmill running significantly increases glutamate levels during and for a short while following exercise in healthy rats. In rats with diabetes, aerobic training markedly improved glutamate, but not GABA. The changes of glutamate (93%) after exercise training in T1DM rats were similar to those in a healthy control group (82%), it is clear from the trials included in this review that increases in glutamate was observed in aerobic group. There is only one non-randomised controlled trial, thus more trials should be considered if aerobic exercise improves the positive adaptations above in neurotransmitters (glutamate) with various strain and species animal models.

2.5.3 **Cognitive Performance**

In three studies (two NRCTs and one RCT) of forced treadmill training, significant large ESs were reported for learning and memory. In healthy rodents, a previous review reported both voluntary wheel running and forced treadmill training have also been shown to enhance spatial learning using different types of mazes (such as water, radial maze). Running improved memory performance in other hippocampus-dependent tasks in healthy rodents. Thus the adaptations of the current review of animals with diabetes are in accordance with the adaptations observed in healthy animal models, although the extent of the literature is very small at present.
2.5.4 **Functional Significance of Neurogenesis, Neuroplasticity and Neurotrophic Factor**

Data available suggest that improvements in learning and memory may be partially mediated by increases in hippocampal neurogenesis, although the role of neurogenesis in these functions is controversial at present. The results in our review showed increases in cell proliferation with a concomitant improvement (40.5%) in memory (step-through passive avoidance) (Table 2.7).

Physical activity has also been shown to improve neural cell proliferation in the hippocampus in elderly rats with diabetes. There is evidence that exercise stimulated proliferation of the neural progenitor population, increased the number of new neurons, and promotes survival of these new cells. New formed neurons can integrate into a neural network and become functional.

Exercise has also been reported to induce cell proliferation is associated with enhanced synaptic plasticity in key brain areas for learning and memory, such as the hippocampus where synaptic neurotransmitters and their receptor are responsive to exercise. In particular, cFos expression in the hippocampal is believed to play crucial roles in neuroplasticity and neurogenesis associated with spatial learning and memory.

In our review, cell proliferation and cFos expressions were compared in hippocampal slices from running and control rats with diabetes. Increased cell proliferation and cFos were accompanied by memory in running group compared to diabetes control rats. However, there is only two trials included in this review that demonstrated improvements in memory were partially dependent on increases in cell proliferation and cFos in the hippocampal rats with diabetes. Thus, future studies should specifically aim to link cognitive performance with potential underlying adaptations in cerebral structure and metabolism to further understanding of the most important mediators of such functional improvements. Understanding of this pathway may allow development of more
specific exercise interventions designed to maximally stimulate the most relevant components.

Exercise resulted in a greatly increased growth factor in the hippocampus. Increases in growth factors expression may potentially explain changes in cell proliferation, learning and memory (Morris water maze), exercise, and synaptic plasticity. Trophic factors that influenced adult neurogenesis and synaptic plasticity, included nerve growth factor and BDNF in healthy and insulin resistance animal models. Increases in hippocampal BDNF levels are thought to contribute to the upregulation of adult dendritic spine density in hippocampus that is observed aerobic treatment. Indeed, animal studies have shown that hippocampal BDNF levels are decreased in patients with diabetes and exercise intervention can ameliorate this deficit associated with synapse plasticity. On the basis of the extensive literature linking plasticity among spines with synaptic function, and the relationship between spine and synapse plasticity and hippocampus-dependent memory, it is possible that hippocampal BDNF mediates the efficacy of exercise on synapse plasticity hippocampus-dependent memory. Consistent with these previous findings, in one trial, enhanced BDNF level and dendritic spine density were observed after aerobic exercise in the mice hippocampus with T2DM.

Much like BDNF, increases in NGF, TrkA, p-Erk1/2, and p-CREB protein levels may explained a significant portion of the variance in cell proliferation, synaptic plasticity, and memory. Previous results from available animal studies have strongly demonstrated that decreased NGF and TrkA levels are associated with the impaired function of cholinergic neurons. Clinical trials have shown that patients with mild cognitive impairment had low TrkA and NGF levels. Recently animal studies have strongly demonstrated that NGF and TrkA is a crucial mediator of exercise-
induced neuroplasticity and brain function.\textsuperscript{46, 64, 72} In agreement with this idea, this reviewed reported that aerobic exercise as a fitness intervention for the rats with diabetes significantly increases the NGF and TrkA while also increasing cell proliferation and improving memory in hippocampus of rats with insulin resistance / diabetes.\textsuperscript{39}

Meanwhile, many investigators have contribute to an understanding potential relationships between the molecular, cellular, and cognitive behaviour after exercise. Rodents studies performed by Shen et al\textsuperscript{73} has shown that exercise upregulates multiple proteins involved in signal transduction (protein kinase C (PKC), calcium-calmodulin-dependent protein kinase II and IV, and mitogen-activated extracellular-signal-regulated kinases protein kinase (MAPK), transcriptional regulation (cyclic AMP response element binding protein (CREB)), BDNF, and neurotransmitters (increased glutamate level). Current study suggests that the molecular mechanisms by which exercise stimulates cellular regeneration via the upregulation of growth factors (BDNF and NGF) through a calmodulin-dependent protein kinase and CREB. It is thought that a calcium influx in the setting of metabolic demand stimulates the calmodulin-dependent protein kinase, which in return phosphorylates CREB. CREB drives the synthesis of BDNF, providing further activate CREB. Moreover, CREB phosphorylated by MAPK modifies the plasticity of neurons and is involved in controlling the formation of long-term memories.\textsuperscript{74} Impey et al.\textsuperscript{75} and Russo-Neustadt et al.\textsuperscript{76} reported that 1 or 2 days of maximal running increased p-CREB levels in the hippocampus, and that these effects lasted for 7 days. Shen et al. (2001)\textsuperscript{73} observed that MAPK and CREB levels were high in the hippocampus of animals that had exercised for longer periods, extending from 1 week to 1 month. Our review in agreement with our previous study,\textsuperscript{72} in which regular physical exercise activate MAPK/Erk and CREB in the hippocampus, which results in the
increased retrograde transport of NGF. Thus, it is suggested that the improvement of cognitive function by exercise in animal models with diabetes, induces phosphorylated CREB and facilitates NGF signaling by activity MAPK/Erk1/2. It is clear that growth factors and growth factor signaling cascades are central regulatory mechanisms underlying the effects of exercise in the CNS. However, the two concomitant relationships reported in this review do suggest that increases in neurogenesis and synapse plasticity and trophic factors may potentially contribute to the improvements in memory in animals with diabetes exposed to aerobic exercise. Increases in neurogenesis and synapse plasticity involved in dependent-hippocampal memory may be mediated in part by exercise-induced growth factors and growth factor signaling cascades. If reproduced, these results would confirm that physical exercise induces growth neurotropic effects on brain structures and functions at the molecular and structural levels in animal animals with diabetes with diabetes, providing a rationale for exploring these pathways in human trials.

2.5.5 IMPLICATIONS FOR EXERCISE INTERVENTIONS AND FUTURE RESEARCH

The findings from this systematic review support the view that one of the goals of aerobic interventions for brain disease in diabetes should be maximisation of neurogenesis, neuroplasticity, growth factors, and function. Factors which may be relevant maintain progressive overload and adequate intensity, and/or avoiding plateaus in adaptation through varying exercises, which supports cerebral metabolism, neuroplasticity, nerve growth factor, and function. With only 15 trials meeting the criteria for this review, further research is required in order to adequately address the relationship between increases in neurogenesis, neuroplasticity, nerve growth factor, and the improvements in cognitive function on memory in animal models with T2DM. In particular, the current data presented in these trials were performed primarily in animal models of T1DM,
whereas 90% of human diabetes is T2DM. Thus, the relevance of these animal models to the bulk of human diabetes is not known, and future animal trials should focus on models of potentially more relevance to human disease. Additionally, there was not much discussion or exploration of the mechanistic links between morphology, biochemistry, and cognitive performance, which future studies should focus on. There is also evidence from human studies that many forms of exercise (aerobic exercise, resistance training, combinations of resistance and aerobic exercise,) may have a beneficial effect on cognitive impairment and dementia. As all of the animal studies to date have utilised aerobic exercise, exploration of resistance training models is warranted in future animal investigations in this field.

Finally, it is possible that heterogeneous outcomes in the trials reviewed may be due to differences in species, genetics, age, weight, metabolic condition, specific exercise paradigms (modality, voluntary/forced, intensity, dose), and behavioural tasks used, but these influences are poorly understood as of yet. Identifying and addressing the possible reasons why animals are likely to be unresponsive to aerobic exercise may improve aerobic training-induced outcomes within future trials. Future studies specifically designed for the investigation of the direct relationships between improvements in neurogenesis, neuroplasticity, and signaling pathways and cognitive health of animals with models T2DM are particularly warranted.

In conclusion, the limited data available suggest that aerobic exercise improves brain structure, biochemistry, and function in animal models with diabetes or insulin resistance or hyperglycaemia, while there is insufficient evidence exploring any relationship between improvements in hippocampus-dependent memory task and increases of cell proliferation, cFos, and growth factor
in animal models of T1DM or T2DM. Future research in this field should include robust measures of hippocampus structure and biochemistry profile, and explore the species, genetic, clinical and physiological factors that potentially mediate the relationships between these two domains. Such investigations will lead to a better understanding of the mechanisms underlying the exercise-induced cognitive improvements and ultimately to the design of interventions specifically targeting cerebral structure plasticity and biochemistry tailored to the mechanisms identified and to the unique needs of specific individuals or cohorts.
Conflict of interest

The authors declare that they have no conflict of interest.
2.5 REFERENCES


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Notes:

a Forced exercise (supervision) is associated with certain level of stress, involved a slower, more consistent pace for longer periods of time.

b Voluntary exercise (non-supervision) is characterized by rapid pace and short duration, which allows rats/mice to freely use running wheel exercise with recorded distance traveled, average speed and time spent daily by computer system.

c Author added 5 criteria related to animal studies.
<table>
<thead>
<tr>
<th>Citation</th>
<th>Animal type</th>
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<th>Treatments</th>
<th>Inclusion</th>
<th>Group (n)</th>
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<td>STZ</td>
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<td>175-200</td>
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<td>Reisi, 2009&lt;sup&gt;38&lt;/sup&gt;</td>
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TABLE 2.2 ANIMAL CHARACTERISTICS - CONTINUED

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<td>38</td>
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TABLE 2.2 ANIMAL CHARACTERISTICS - CONTINUED

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<td>STZ</td>
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<td>(4 groups) 10 / CO 10 / EX 10 / DC 10 / DE</td>
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<td>Stranahan, 2009&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Mice</td>
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<td>PM</td>
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<td>MM</td>
<td>BGL 6.5-6.6mM</td>
<td>(3 groups)</td>
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Notes:

Data is presented as mean ± SD or Median (range)

% men is represented in percent

Streptozotocin (Streptozocin, STZ, Zanosar®) and alloxan are a naturally occurring chemical that is particularly toxic to destroy the insulin-producing beta cells of the pancreas in mammals. It is used to produce an animal model for T1DM in large dose

Zucker fatty (ZDF) rat with diabetes is considered to be an excellent animal model of T2DM that presents a physiological and metabolic profile similar to those seen in humans, and male ZDF rats develop a phenotype of obesity, insulin resistance, and hyperglycemia

db/db mouse is a model of obesity, diabetes, and dyslipidemia

* represents the blood glucose level estimated from graphics

SD: Sprague Dawley rat

WR: Wistar rat

db/db Mice: C57Bl/6 mice

ZDF: Zucker fatty rat with diabetes
T1DM: Type 1 diabetes mellitus

T2DM: Type 2 diabetes mellitus

IR: Insulin resistance

HG: Hyperglycemia

\( ^1\)DC: Hyperglycemia

\( ^2\)DC: Hyperglycemia - hemorrhage

\( ^3\)DEE: Hyperglycemia – hemorrhage early exercise

\( ^4\)DLE: Hyperglycemia – hemorrhage later exercise

CO: Control

EX: Exercise

DC: Diabetes control

DE: Diabetes exercise

DCR: Diabetes control diet restrict
DER: Diabetes control diet restrict exercise
DCL: Diabetes control- low dexamethasone
DCH: Diabetes control-high dexamethasone
DEL: Diabetes exercise- low dexamethasone
DEH: Diabetes exercise-high dexamethasone
STZ: Streptozotocin
ALL: Alloxan
MM: Missense mutation
PM: Point mutation
NR: Not reported
FBG: Fed glucose level
BGL: Blood glucose level
### TABLE 2.3 INTERVENTION CHARACTERISTICS

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<thead>
<tr>
<th>Citation</th>
<th>Type</th>
<th>Volume (or meter)</th>
<th>Frequency (day/week)</th>
<th>Duration (weeks)</th>
<th>Intensity (minute)</th>
<th>Control treatment</th>
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<td>0 degree of inclination</td>
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<td>2 m / min × 5 min</td>
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</tr>
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<td>8 m / min × 20 min</td>
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<td>Aerobic exercise (Late treadmill) b</td>
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<td>More than one week (later)</td>
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<td>No exercise on treadmill for 30 minutes</td>
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<td>20 m / min × 30 min</td>
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<td>Aerobic exercise (Treadmill)</td>
<td>40</td>
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<td>12</td>
<td>0 degree of inclination</td>
<td>No exercise on treadmill for 40 minutes</td>
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<td></td>
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<td>5-17 m / min × 10 min at initial workload</td>
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<td>17 m / min × 40 min at 2nd week until 12 week</td>
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TABLE 2.3 INTERVENTION CHARACTERISTICS - CONTINUED

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<th>Citation</th>
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<th>Duration (weeks)</th>
<th>Intensity (minute)</th>
<th>Control treatment</th>
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<tbody>
<tr>
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<td>5% of the body weight</td>
<td>No exercise on swimming for 60 minutes</td>
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<td>Aerobic exercise (Treadmill) Forced and supervised</td>
<td>40</td>
<td>7</td>
<td>12</td>
<td>0° inclination (5-17 m) / min × (10-40 min) at initial workload for 5 days 17 m / min × 40 min at second week until 12 weeks</td>
<td>No exercise on treadmill for 40 minutes</td>
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<td>Aerobic exercise (Treadmill) Forced and supervised</td>
<td>30</td>
<td>7</td>
<td>6</td>
<td>0 degree of inclination 4000 m / min for 5 min 5000 m / min for 5 min 7000 m / min for 20 min</td>
<td>No exercise on treadmill for 30 minutes</td>
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<tr>
<td>Yi, 2009³¹</td>
<td>Aerobic exercise (Treadmill) Forced and supervised</td>
<td>60</td>
<td>5</td>
<td>5</td>
<td>0° inclination 15 m / min × 15 min at initial workload for 1st week 22 m / min × 60 min for 2nd week the speeds accelerated 2m / min per-2 week</td>
<td>No exercise on treadmill for 60 minutes</td>
</tr>
<tr>
<td>Citation</td>
<td>Type</td>
<td>Volume (minute or meter)</td>
<td>Frequency (day/week)</td>
<td>Duration (weeks)</td>
<td>Intensity (minute)</td>
<td>Control treatment</td>
</tr>
<tr>
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<tr>
<td>Gomes, 2009&lt;sup&gt;32&lt;/sup&gt;</td>
<td>Aerobic exercise (swimming)</td>
<td>60</td>
<td>5</td>
<td>7</td>
<td>90% MLSS x 60 min in load of 4% of body weight at 2&lt;sup&gt;nd&lt;/sup&gt; week</td>
<td>No swimming exercise for 60 minutes</td>
</tr>
<tr>
<td></td>
<td>Forced and supervised</td>
<td></td>
<td></td>
<td></td>
<td>90% MLSS x 60 min in load of 5% of body weight at 4&lt;sup&gt;th&lt;/sup&gt; week</td>
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<tr>
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<td></td>
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<td></td>
<td>90% MLSS x 60 min in load of 6% of body weight at 6&lt;sup&gt;th&lt;/sup&gt; week</td>
<td></td>
</tr>
<tr>
<td>Chae, 2009&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Aerobic exercise (Treadmill)</td>
<td>30</td>
<td>5</td>
<td>7</td>
<td>0 degree of inclination 10 m / min × 10 min in 1&lt;sup&gt;st&lt;/sup&gt; week</td>
<td>No exercise on treadmill for 30 minutes</td>
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<tr>
<td></td>
<td>Forced and supervised</td>
<td></td>
<td></td>
<td></td>
<td>20 m / min × 20 min in 2&lt;sup&gt;nd&lt;/sup&gt; week</td>
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<td></td>
<td></td>
<td>10-14 m / min × 20 min in 3&lt;sup&gt;rd&lt;/sup&gt; week</td>
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</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>14-15 m / min × 30 min in 4&lt;sup&gt;th&lt;/sup&gt; week</td>
<td></td>
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<tr>
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<td></td>
<td></td>
<td>17-18 m / min × 30 min in 5&lt;sup&gt;th&lt;/sup&gt; week</td>
<td></td>
</tr>
<tr>
<td>Stranahan, 2009&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Aerobic exercise (wheel running) voluntary and nonsupervised</td>
<td>1800 meters</td>
<td>Continuously available</td>
<td>12</td>
<td>NR</td>
<td>No exercise and diet restriction</td>
</tr>
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</table>
### TABLE 2.3 INTERVENTION CHARACTERISTICS - CONTINUED

<table>
<thead>
<tr>
<th>Citation</th>
<th>Type</th>
<th>Volume (minute or meter)</th>
<th>Frequency (day/week)</th>
<th>Duration (weeks)</th>
<th>Intensity (minute)</th>
<th>Control treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reisi, 2009&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Aerobic exercise (Treadmill) Forced and supervised</td>
<td>40</td>
<td>7</td>
<td>12</td>
<td>0 degree of inclination 2 m / min × 5 min 5 m / min × 5 min 8 m / min × 20 min</td>
<td>No exercise on treadmill for 40 minutes</td>
</tr>
<tr>
<td>Reisi, 2009&lt;sup&gt;42&lt;/sup&gt;</td>
<td>Aerobic exercise (Treadmill) Forced and supervised</td>
<td>40</td>
<td>7</td>
<td>12</td>
<td>0 degree of inclination 5-17 m / min × 10 min initial workload until 40 min at 1&lt;sup&gt;st&lt;/sup&gt; week 17 m / min × 40 min at 2&lt;sup&gt;nd&lt;/sup&gt; week until 12 weeks</td>
<td>No exercise on treadmill for 40 minutes</td>
</tr>
<tr>
<td>Campbell, 2010&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Aerobic exercise (Wheel running) Voluntary Non-supervised</td>
<td>3500-6500 meters</td>
<td>Continuously available</td>
<td>10</td>
<td>NR</td>
<td>No exercise</td>
</tr>
<tr>
<td>Hwang, 2011&lt;sup&gt;34&lt;/sup&gt;</td>
<td>Aerobic exercise (Treadmill) Forced and supervised</td>
<td>60</td>
<td>5</td>
<td>7</td>
<td>12 m / min × 60 min initial workload 1&lt;sup&gt;st&lt;/sup&gt; week 13 m / min × 20 min in 3&lt;sup&gt;rd&lt;/sup&gt; week 14 m / min × 30 min in 5&lt;sup&gt;th&lt;/sup&gt; week 15 m / min × 30 min in 7&lt;sup&gt;th&lt;/sup&gt; week</td>
<td>No exercise on treadmill for 60 minutes</td>
</tr>
</tbody>
</table>
Notes:

NR: Not reported

MLSS: Maximal lactate steady state
## TABLE 2.4 ANIMAL BRAIN MORPHOLOGICAL OUTCOMES

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (TSLEB)</th>
<th>Outcomes</th>
<th>Results</th>
<th>Statistics</th>
<th>+/- Change (%)</th>
<th>Effect size (95%, CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Year Reference</td>
<td>Variable</td>
<td>Method</td>
<td>Group</td>
<td>Post-exercise (Mean ± SD)</td>
<td>P value (Inter-group)</td>
<td></td>
</tr>
<tr>
<td><strong>Kim, 2003</strong>&lt;sup&gt;35&lt;/sup&gt;</td>
<td>30 minutes</td>
<td>BrdU-positive cells in dentate gyrus</td>
<td>BrdU Immune-histochemistry</td>
<td>DC DE</td>
<td>40.25 ± 8.20* 83.25 ± 9.10*</td>
<td>&lt;0.05 (DE vs DC)</td>
</tr>
<tr>
<td><strong>Lee, 2005</strong>&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Immediate</td>
<td>Lesion volume in the striatum</td>
<td>Nissal Staining, Image-pro plus image analyzer</td>
<td>DC&lt;sup&gt;a&lt;/sup&gt; DEE DEL</td>
<td>9.90 ± 2.00* 8.26 ± 1.76* 9.20 ± 1.27*</td>
<td>&lt;0.05 (DEE vs DC)</td>
</tr>
<tr>
<td></td>
<td>The number of TUNEL-positive cells</td>
<td>TUNEL staining</td>
<td>DC&lt;sup&gt;a&lt;/sup&gt; DEE DEL</td>
<td>138.9 ± 31.5* 96.7 ± 25.1* 129.1 ± 33.2*</td>
<td>&lt;0.05 (DEE vs DC)</td>
<td>NS (DLE vs DC)</td>
</tr>
<tr>
<td></td>
<td>Cell proliferation in the dentate gyrus</td>
<td>BrdU Immune-histochemistry</td>
<td>DC&lt;sup&gt;a&lt;/sup&gt; DEE DEL</td>
<td>39.64 ± 21.68* 126.42 ± 39.70* 106.57 ± 30.99*</td>
<td>&lt;0.05 (DEE vs DC)</td>
<td>&lt;0.05 (DLE vs DC)</td>
</tr>
<tr>
<td><strong>Reisi, 2008</strong>&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Immediate</td>
<td>Paired pulse index (%)</td>
<td>Electrophysiological recording</td>
<td>DC DE</td>
<td>355.50 ± 45.00* 88.53 ± 24.51*</td>
<td>&lt;0.05 (DE vs DC)</td>
</tr>
<tr>
<td></td>
<td>EPSP slope index (%)</td>
<td>Electrophysiological recording</td>
<td>DC DE</td>
<td>236.72 ± 65.71* 51.33 ± 31.1*</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>-361.1 -3.36 (-5.12, -1.60)</td>
</tr>
<tr>
<td>Citation</td>
<td>Time point (TSLEB)</td>
<td>Outcomes</td>
<td>Results</td>
<td>Statistics</td>
<td>+/- Change (%)</td>
<td>Effect size (95%, CI)</td>
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<tr>
<td><strong>Author, Year Reference</strong></td>
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<tr>
<td>You, 2009&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Immediate</td>
<td>The number of cFos positive cells in the hippocampus</td>
<td>Variable</td>
<td>The Image-Pro® Plus computer-assisted image analysis system</td>
<td>Group</td>
<td>Post-exercise (Mean ± SD)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>DC DE</td>
<td>93.99 ± 82.00*</td>
</tr>
<tr>
<td>Yi, 2009&lt;sup&gt;31&lt;/sup&gt;</td>
<td>NR</td>
<td>Density of cells in the dentate gyrus</td>
<td>Variable</td>
<td>Immunohistochemistry</td>
<td>Group</td>
<td>Post-exercise (Mean ± SD)</td>
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<td></td>
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<td>Ki67 cells</td>
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<td>DC DE</td>
<td>104.72 ± 9.52</td>
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<td>Granule cells</td>
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<td>DC DE</td>
<td>44.00 ± 12.50</td>
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<tr>
<td></td>
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<td>Western Blot Analysis</td>
<td></td>
<td></td>
<td>DC DE</td>
<td>229629±29629</td>
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<tr>
<td></td>
<td></td>
<td>DCX positive cells with tertiary dendrites</td>
<td></td>
<td></td>
<td>DC DE</td>
<td>885.00 ± 142.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DCX positive cells without tertiary dendrites</td>
<td></td>
<td></td>
<td>DC DE</td>
<td>1896.05 ± 172.41</td>
</tr>
<tr>
<td>Citation</td>
<td>Time point (TSLEB)</td>
<td>Outcomes</td>
<td>Results</td>
<td>Statistics</td>
<td>+/- Change (%)</td>
<td>Effect size (95%, CI)</td>
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</tr>
<tr>
<td>Chae, 2009</td>
<td>Immediate</td>
<td>The number of BrdU-labeled cells</td>
<td>DC: 176.40 ± 29.40 DE: 335.51 ± 17.64</td>
<td>&lt;0.01 (DE vs DC)</td>
<td>+90.1</td>
<td>6.28 (4.15, 8.42)</td>
</tr>
<tr>
<td>Stranahan, 2009</td>
<td>Immediate</td>
<td>Dendritic spine density</td>
<td>DC&lt;sup&gt;b&lt;/sup&gt;: 15.00 ± 0.86 DE&lt;sup&gt;c&lt;/sup&gt;: 16.50 ± 0.35</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+11</td>
<td>2.11 (0.70,3.52)</td>
</tr>
<tr>
<td>Reisi, 2009</td>
<td>Immediate</td>
<td>Long term potential - population spike</td>
<td>DC: 237.80 ± 21.60 DE: 319.00 ± 27.70</td>
<td>&lt;0.01 (DE vs DC)</td>
<td>+34.1</td>
<td>3.02 (1.36, 4.67)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Long term potential - field excitatory post-synaptic potential slope</td>
<td>DC: 236.40 ± 63.10 DE: 355.24 ± 48.97</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+50.2</td>
<td>1.94 (0.57, 3.31)</td>
</tr>
</tbody>
</table>
Notes:

Higher BrdU-positive cells in dentate gyrus indicate to increase new nervous cell formation.

Higher cFos expressions indicate better synaptic plasticity.

Higher dendritic spine density indicates better synaptic plasticity.

Higher field excitatory post-synaptic potential (fEPSP) slope and population spike (PS) amplitude indicate better synaptic plasticity.

Higher number of TUNEL-positive cells indicates to decrease new nervous cell formation.

Higher paired puLse and excitatory post-synaptic potential values indicate worse synaptic plasticity.

TUNEL staining detects DNA fragmentation and neurons death.

cFos is immediate early gene, whose expression is considered as a marker for stimuli-induced changes in the metabolic activity of neurons, and cFos upregulation in the hippocampus is known to be associated with enhanced spatial memory capacity.

Ki67 and doublecortin (DCX) immunoreactivity, which is a marker of cell proliferation expressed during cell cycles and a marker of progenitors differentiating into neurons in the subgranular zone of the dentate gyrus, respectively.

+/- represents increase/decrease.
Results reported in Mean +/-SD.

* SEM were converted from SD.

Between group effect size = (mean change in treatment –mean change in control)/pooled baseline SD.\textsuperscript{26}

SD: standard deviation

EPSP: Excitatory post-synaptic potential

Brud: Bromodeoxyuridine.

TUNEL: Terminal deoxynucleotidyl transferase dUTP nick end labeling

TSLEB: Time since last exercise bout

DE: Diabetes exercise

DC: Diabetes control

\textsuperscript{a}DC: Hyperglycemic hemorrhage

\textsuperscript{b}DC: db/db sedentary

\textsuperscript{c}DE: db/db sedentary running
NR: Not reported

NS: Not significant

vs: Versus

CI: confidence interval

UTBC: Unable to be calculated; Data was estimated from graphics
### TABLE 2.5 ANIMAL BRAIN BIOCHEMICAL OUTCOMES

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (TSLEB)</th>
<th>Outcomes</th>
<th>Results</th>
<th>Statistics</th>
<th>+/- Change (%)</th>
<th>Effect size (95%, CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Year Reference</td>
<td>Variable</td>
<td>Method</td>
<td>Group</td>
<td>Post-exercise (Mean ± SD)</td>
<td>P value (Inter-group)</td>
<td></td>
</tr>
<tr>
<td>Park, 2005&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Immediate</td>
<td>Biochemical Measurement</td>
<td>DC</td>
<td>18.15 ± 1.89</td>
<td>NS (DE vs DC)</td>
<td>+4.8</td>
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<tr>
<td></td>
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<td></td>
<td>DE</td>
<td>19.03 ± 1.83</td>
<td>NS (DE vs DC)</td>
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<tr>
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<td>DC</td>
<td>11.30 ± 1.33</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+10.4</td>
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<tr>
<td></td>
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<td>DE</td>
<td>13.30 ± 1.00</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+11.6</td>
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<tr>
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<td>DC</td>
<td>17.00 ± 1.67</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+26.5</td>
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<td>DE</td>
<td>19.70 ± 1.67</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+26.5</td>
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<td>DC</td>
<td>15.80 ± 1.67</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+60.4</td>
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<td>DE</td>
<td>20.00 ± 2.00</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+2.6</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>DC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.86 ± 0.10</td>
<td>NS (DE vs DC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.38 ± 0.19</td>
<td>NS (DE vs DC)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DC&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.90 ± 0.20</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+2.6</td>
</tr>
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<td></td>
<td></td>
<td>DE&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.40 ± 0.26</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+2.6</td>
</tr>
<tr>
<td>Citation</td>
<td>Time point (TSLEB)</td>
<td>Outcomes</td>
<td>Results</td>
<td>Statistics</td>
<td>+/- Change (%)</td>
<td>Effect size (95%, CI)</td>
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</tr>
<tr>
<td>Park, 200536</td>
<td>Immediate</td>
<td>pAkt / Akt (cerebral cortex)</td>
<td>Immunoblot</td>
<td>DCa 0.48 ± 0.10</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+97.9 3.68 (2.16, 5.20)</td>
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<tr>
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<td></td>
<td>IRS2 / ps85 (Hypothalamus)</td>
<td></td>
<td>DEa 0.95 ± 0.14</td>
<td></td>
<td></td>
</tr>
<tr>
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<td></td>
<td>IRS2 / PY20 (Hypothalamus)</td>
<td></td>
<td>DCa 0.48 ± 0.05</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+43.8 1.52 (0.52, 2.52)</td>
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<tr>
<td></td>
<td></td>
<td>pAkt / Akt (Hypothalamus)</td>
<td></td>
<td>DEa 0.69 ± 2.67</td>
<td>&lt;0.05 (DE vs DC)</td>
<td></td>
</tr>
<tr>
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<td>Levels of glucokinase / p85</td>
<td></td>
<td>DCa 1.33 ± 0.14</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+87.9 9.16 (6.03, 12.29)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(cerebral cortex)</td>
<td></td>
<td>DEa 2.50 ± 0.10</td>
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<tr>
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<td></td>
<td>GLUT2 (cerebral cortex)</td>
<td></td>
<td>DCa 0.19 ± 0.05</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+236.8 5.42 (3.42, 7.42)</td>
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<tr>
<td></td>
<td></td>
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<td></td>
<td>DEa 0.64 ± 0.10</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Levels of lucokinase / p85</td>
<td></td>
<td>DCa 0.89 ± 0.08</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+49.4 4.36 (2.66, 6.05)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(Hypothalamus)</td>
<td></td>
<td>DEa 1.33 ± 0.11</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>GLUT2 (Hypothalamus)</td>
<td></td>
<td>DCa 0.25 ± 0.06</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+96.0 5.04 (4.47, 5.60)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>DEa 0.49 ± 0.03</td>
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<tr>
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<td></td>
<td></td>
<td>DCa 0.93 ±0.14</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+50.5 3.37 (1.93, 4.80)</td>
</tr>
<tr>
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<td>DEa 1.50 ± 0.18</td>
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</tr>
<tr>
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<td></td>
<td>DCa 0.35 ±0.14</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+54.3 1.53 (1.22, 1.85)</td>
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<td>DEa 0.54 ±0.17</td>
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<td>Citation</td>
<td>Time point (TSLEB)</td>
<td>Outcomes</td>
<td>Method</td>
<td>Group</td>
<td>Post-exercise (Mean ± SD)</td>
<td>P value (Inter-group)</td>
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<tr>
<td>Leme, 2008&lt;sup&gt;29&lt;/sup&gt;</td>
<td>48 hours</td>
<td>Hippocampus insulin contents</td>
<td>Radioimmuno-assay</td>
<td>DC</td>
<td>1.89 ± 0.89</td>
<td>&lt;0.05 (DE vs DC)</td>
</tr>
<tr>
<td>Gomes, 2009&lt;sup&gt;32&lt;/sup&gt;</td>
<td>48 hours</td>
<td>Hippocampus insulin levels</td>
<td>Radioimmuno-assay</td>
<td>DC</td>
<td>5.20 ± 4.60</td>
<td>NS (DE vs DC)</td>
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<tr>
<td></td>
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<td>Hippocampus glycogen</td>
<td>Colorimetry Immunoradiometric assay</td>
<td>DE</td>
<td>7.60 ± 3.20</td>
<td>NS (DE vs DC)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hippocampus insulin-like growth factor-I levels</td>
<td></td>
<td>DC</td>
<td>0.058 ± 0.030</td>
<td>NS (DE vs DC)</td>
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<tr>
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<td></td>
<td>DE</td>
<td>0.052 ± 0.026</td>
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<td></td>
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<td></td>
<td></td>
<td>DC</td>
<td>0.80 ± 0.27</td>
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<td></td>
<td></td>
<td>DE</td>
<td>0.88 ± 0.27</td>
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<tr>
<td>Chae, 2009&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Immediate</td>
<td>Nerve growth factor TrkA</td>
<td>DC</td>
<td>100.00 ± 6.25</td>
<td>&lt;0.01 (DE vs DC)</td>
<td>+125.0</td>
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<td></td>
<td></td>
<td>P75 receptor protein level t-PI3-K</td>
<td>DE</td>
<td>225.00± 37.50</td>
<td>&lt;0.01 (DE vs DC)</td>
<td>+108.8</td>
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<td></td>
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<td></td>
<td>DC</td>
<td>100.00 ± 0.00</td>
<td>N (DE vs DC)</td>
<td>-4.7</td>
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<tr>
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<td>DE</td>
<td>208.75 ± 37.50</td>
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<td>DC</td>
<td>84.61 ± 7.69</td>
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<td>DE</td>
<td>80.76 ± 3.85</td>
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<td></td>
<td></td>
<td>DC</td>
<td>100.00 ± 2.78</td>
<td></td>
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<td></td>
<td></td>
<td>DE</td>
<td>100.00 ± 1.39</td>
<td></td>
</tr>
<tr>
<td>Citation</td>
<td>Time point (TSLEB)</td>
<td>Outcomes</td>
<td>Results</td>
<td>Statistics</td>
<td>+/- Change (%)</td>
<td>Effect size (95%, CI)</td>
</tr>
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</tr>
<tr>
<td>Chae, 2009</td>
<td>Immediate</td>
<td>p-PI3-K</td>
<td>Chemical test (EDTA, SDS-PAGE, TBST)</td>
<td>DC: 92.00 ± 14.70, DE: 104.00 ± 4.90</td>
<td>NS (DE vs DC)</td>
<td>+13.0 (-0.20, 2.20)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Caspase-3 protein</td>
<td></td>
<td>DC: 123.48 ± 10.80, DE: 111.72 ± 14.40</td>
<td></td>
<td>-10.5 (-0.85, -2.03, 0.33)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t-Erk1 (p44)</td>
<td></td>
<td>DC: 81.39 ± 8.15, DE: 93.70 ± 12.24</td>
<td></td>
<td>+15.1 (0.89, -0.30, 2.07)</td>
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<tr>
<td></td>
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<td>t-Erk2 (p42)</td>
<td></td>
<td>DC: 69.93 ± 20.39, DE: 86.58 ± 24.47</td>
<td></td>
<td>+23.8 (0.68, -0.48, 1.85)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-Erk1 (p44)</td>
<td></td>
<td>DC: 96.57 ± 14.28, DE: 126.54 ± 31.62</td>
<td>&lt;0.001 (DE vs DC)</td>
<td>+31.0 (1.85, 0.50, 3.21)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-Erk2 (p42)</td>
<td></td>
<td>DC: 106.56 ± 6.13, DE: 179.82 ± 8.15</td>
<td>&lt;0.001 (DE vs DC)</td>
<td>+67.8 (8.97, 5.21, 12.74)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>t-CREB</td>
<td></td>
<td>DC: 106.40 ± 1.92, DE: 110.02 ± 3.84</td>
<td>NS (DE vs DC)</td>
<td>+3.0 (1.14, 0.20, 2.09)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>p-CREB</td>
<td></td>
<td>DC: 115.54 ± 5.70, DE: 134.61 ± 7.60</td>
<td>NS (DE vs DC)</td>
<td>+16.5 (3.29, 1.94, 4.63)</td>
</tr>
<tr>
<td>Citation</td>
<td>Time point (TSLEB)</td>
<td>Outcomes</td>
<td>Results</td>
<td>Statistics</td>
<td>+/- Change (%)</td>
<td>Effect size (95%, CI)</td>
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<tr>
<td>Stranahan, 2009&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Immediate</td>
<td>Brain-derived neurotrophic factor</td>
<td>ELISA</td>
<td>DC 3.01 ± 0.15&lt;br&gt;DE 3.65 ± 0.13</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+21.2 (4.27, 2.22, 6.32)</td>
</tr>
<tr>
<td>Reisi, 2009&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Immediate</td>
<td>Glutamate&lt;br&gt;Gamma-Aminobutyric acid</td>
<td>NR&lt;br&gt;NR&lt;br&gt;NR&lt;br&gt;NR DC 3292.69 ± 698.37*&lt;br&gt;DE 1096.25 ± 461.31*&lt;br&gt;DC 1260.11 ± 461.18*&lt;br&gt;DE 1704.54 ± 524.23*</td>
<td>&lt;0.05 (DE vs DC) NS (DE vs DC)</td>
<td>+93.1 (2.37, 0.90, 3.85)</td>
<td>+14.9 (-0.65, 1.32)</td>
</tr>
<tr>
<td>Campbell, 2010&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Six hours</td>
<td>Quantification of the relative signal intensity in hippocampal GR Hippocampal GR content</td>
<td>ICS&lt;br&gt;DC 480.00 ± 67.50*&lt;br&gt;DE 675.00 ± 52.50*</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>+40.6 (1.07, 0.05, 2.08)</td>
<td>1.89 (0.74, 3.03)</td>
</tr>
<tr>
<td>Citation</td>
<td>Time point (TSLEB)</td>
<td>Outcomes</td>
<td>Results</td>
<td>Statistics</td>
<td>+/- Change (%)</td>
<td>Effect size (95%, CI)</td>
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<tr>
<td><strong>Hwang, 2011</strong>³⁴</td>
<td>Immediate</td>
<td>ROD % at CA1 region <strong>Stratum orientes (GR)</strong></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td><strong>Stratum pyramidal</strong></td>
<td>DC</td>
<td>110.02 ± 29.33*</td>
<td>NS (DE vs DC)</td>
<td>-3.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DE</td>
<td>106.12 ± 29.03*</td>
<td></td>
<td>-0.11 (-1.16, 0.94)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>346.15± 122.10*</td>
<td>&lt;0.01(DE vs DC)</td>
<td>-136.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>146.15 ±50.87*</td>
<td></td>
<td>-1.99 (-3.27, -0.71)</td>
</tr>
<tr>
<td></td>
<td></td>
<td><strong>Stratum radiatum</strong></td>
<td>DC</td>
<td>148.00 ± 48.90*</td>
<td>&lt;0.01 (DE vs DC)</td>
<td>-98.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DE</td>
<td>74.67 ± 18.52*</td>
<td></td>
<td>-1.86(-3.12, -0.61)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ROD % at dentate gyrus <strong>Polymorphic layer</strong></td>
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<tr>
<td></td>
<td></td>
<td><strong>Granule cell layer</strong></td>
<td>DC</td>
<td>216.09 ± 58.34*</td>
<td>&lt;0.01 (DE vs DC)</td>
<td>-48.4</td>
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<tr>
<td></td>
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<td></td>
<td>DE</td>
<td>145.53 ± 17.64*</td>
<td></td>
<td>-1.52 (-2.71,-0.33)</td>
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<tr>
<td></td>
<td></td>
<td><strong>Molecular layer</strong></td>
<td>DC</td>
<td>335.16 ± 46.67*</td>
<td>&lt;0.01 (DE vs DC)</td>
<td>-245.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>DE</td>
<td>97.02 ± 23.38*</td>
<td></td>
<td>-6.00 (-8.46, -3.54)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>101.14 ± 35.00*</td>
<td>NS (DE vs D)</td>
<td>-9.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>92.61 ± 23.23*</td>
<td></td>
<td>-0.71 (-1.79, 0.37)</td>
</tr>
</tbody>
</table>
Notes:

*Male Sprague-Dawley rats had 90% of their pancreas removed (Px rats) or received a SHAM pancreatectomy.

Px rats glucose levels of random fed serum should be greater than 9.4 mM after surgery, thus represents the insulin resistance or T2DM.

Relative optical densities (ROD) as % values of GR in the dentate gyrus.

Results reported in Mean +/- SD.

Between group effect size = (mean change in treatment –mean change in control)/pooled baseline SD.²⁶

*SEM were converted from SD.

SD: standard deviation

GR: Glucocorticoid receptor

TSLEB: Time since last exercise bout

IRS2: Insulin receptor substrate 2

Akt is known as protein kinase B (PKB)

STAT: Signal transducer and activator of transcription 3,
GLUT2: Glucose transporter 2

Trk: Transforming tyrosine kinase protein

PI3K: Phosphatidylinositol-4, 5-bisphosphate 3-kinase

p75: Neurotrophin receptor

Erk: Extracellular-signal-regulated kinases

CREB: cAMP response element-binding protein

ICS: Immunohistochemical staining

DE: Diabetes exercise

DC: Diabetes control

NR: Not reported

NS: Not significant

vs: Versus

CI: confidence interval
### TABLE 2.6 ANIMAL BRAIN FUNCTIONAL OUTCOMES

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (TSLEB)</th>
<th>Outcomes</th>
<th>Method</th>
<th>Group</th>
<th>Post-exercise (Mean ± SD)</th>
<th>P value (Inter-group)</th>
<th>Effect size (95%, CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reisi, 2009&lt;sup&gt;38&lt;/sup&gt;</td>
<td>24 hours</td>
<td>Spatial acquisition</td>
<td>Morris water maze</td>
<td>DC</td>
<td>49.98 ± 7.34*</td>
<td>&lt;0.001 (DE vs DC)</td>
<td>-3.43 (-4.97, -1.89)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Escape latencies (sec)</td>
<td></td>
<td>DE</td>
<td>23.36 ± 7.34*</td>
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<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Swim distance (cm)</td>
<td></td>
<td>DC</td>
<td>796.43±138.01*</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>-2.13 (-3.35, -0.90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Swim speed (cm/sec)</td>
<td></td>
<td>DE</td>
<td>485.32±138.01*</td>
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<tr>
<td></td>
<td></td>
<td>Spatial retention</td>
<td></td>
<td>DC</td>
<td>16.06 ± 7.30*</td>
<td>&lt;0.01 (DE vs DC)</td>
<td>2.01 (0.81, 3.21)</td>
</tr>
<tr>
<td></td>
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<td>Time spent (%) in each zone 1</td>
<td></td>
<td>DE</td>
<td>26.20 ± 2.28*</td>
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<tr>
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<td></td>
<td>Time spent (%) in each zone 2</td>
<td></td>
<td>DC</td>
<td>33.36 ± 20.13*</td>
<td>NS (DE vs DC)</td>
<td>0.97(-0.06, 2.01)</td>
</tr>
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<td>Time spent (%) in each zone 3</td>
<td></td>
<td>DE</td>
<td>54.29 ± 20.13*</td>
<td>NS (DE vs DC)</td>
<td>-0.97 (-2.00, 0.07)</td>
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<tr>
<td></td>
<td></td>
<td>Time spent (%) in each zone 4</td>
<td></td>
<td>DC</td>
<td>30.5 ± 10.13*</td>
<td>NS (DE vs DC)</td>
<td>-0.17 (-1.15, 0.81)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Time spent (%) in quadrant zone</td>
<td></td>
<td>DE</td>
<td>20.12 ± 10.13*</td>
<td>NS (DE vs DC)</td>
<td>-0.37(-1.32, 0.65)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>The number of crossing in exact place</td>
<td></td>
<td>DC</td>
<td>16.02 ± 10.06*</td>
<td>NS (DE vs DC)</td>
<td>-0.37(-1.32, 0.65)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>DE</td>
<td>14.24 ± 10.06*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DC</td>
<td>17.8 ± 10.06*</td>
<td>NS (DE vs DC)</td>
<td>1.27 (0.20, 2.35)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>DE</td>
<td>14.24 ± 10.06*</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>DC</td>
<td>25.02 ± 13.69*</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>1.83 (0.67, 3.00)</td>
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<td></td>
<td></td>
<td>DE</td>
<td>54.29 ± 27.54*</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>DC</td>
<td>0.19 ± 0.37*</td>
<td>&lt;0.05 (DE vs DC)</td>
<td>1.83 (0.67, 3.00)</td>
</tr>
<tr>
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<td></td>
<td></td>
<td>DE</td>
<td>1.50 ± 0.88*</td>
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## TABLE 2.6 ANIMAL BRAIN FUNCTIONAL OUTCOMES - CONTINUED

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (TSLEB)</th>
<th>Outcomes</th>
<th>Results (Mean ± SD)</th>
<th>Statistics</th>
<th>Effect size (95%, CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Year Reference</td>
<td></td>
<td></td>
<td>Group</td>
<td>Post-exercise (Mean ± SD)</td>
<td>P value (Inter-group)</td>
</tr>
<tr>
<td>You, 2009&lt;sup&gt;30&lt;/sup&gt;</td>
<td>Immediate</td>
<td>bThe number of errors in the spatial memory</td>
<td>DC</td>
<td>11.00 ± 2.21</td>
<td>&lt;0.05 (DE vs DC)</td>
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<tr>
<td></td>
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<td>Radial arm maze test</td>
<td>DE</td>
<td>6.50 ± 0.71</td>
<td></td>
</tr>
<tr>
<td>Chae, 2009&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Immediate</td>
<td>aRetention latency (cognitive function)</td>
<td>DC</td>
<td>213.5 ± 70.00</td>
<td>&lt;0.05 (DE vs D)</td>
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<tr>
<td></td>
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<td>The passive avoidance test</td>
<td>DE</td>
<td>300.00 ± 0.00</td>
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</tbody>
</table>

### Notes:

- aHigher retention latency represents better memory.
- bThe decreased number of error indicates better the spatial memory.

SD: standard deviation

TSLEB: Time since last exercise bout

DE: Diabetes exercise

DC: Diabetes control
CI: confidence interval

vs: Versus
## TABLE 2.7 CONCOMITANT RELATIONSHIP BETWEEN MORPHOLOGY AND COGNITION

<table>
<thead>
<tr>
<th>Citation</th>
<th>Brain Morphology</th>
<th>Cognition</th>
<th>Change% Morphology/cognition</th>
<th>Relationship</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>You, 2009&lt;sup&gt;30&lt;/sup&gt;</td>
<td>cFos</td>
<td>Memory</td>
<td>93.2 / 69.2</td>
<td>Increase in cFos with concomitant improvements in memory</td>
<td>Aerobic exercise group only</td>
</tr>
<tr>
<td>Chae, 2009&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Cell proliferation</td>
<td>Memory</td>
<td>90.1 / 40.5</td>
<td>Increase in cell proliferation with concomitant improvements in memory</td>
<td>Aerobic exercise group only</td>
</tr>
</tbody>
</table>
FIGURE 2.1 FLOW CHART OF SEARCH STRATEGY

1. **Condition**
2. **Intervention**
3. **Outcome**

**Combined search**
- Hand search: n=3
- Total number of retrieved articles: n=5581
- Records after removal of duplicates: n=5281
- Full text evaluated: n=97
- Removed by title: n=4572
- Removed by abstract: n=612

Ineligible criteria:
- Human studies: n=5
- No exercise intervention: n=12
- No assessment of cognitive outcomes: n=22
- No biochemistry: n=16
- No morphology: n=3
- English: n=1
- Non-diabetes: n=23

**Studies included in systematic review**
- Morphology outcomes: n=8
- Biochemistry outcomes: n=8
- Function outcomes: n=5
- RCTs: n=7
- NRCTs: n=8
RCTs: Randomised Controlled trials

NRCT: Non-randomised Controlled trials
CHAPTER 3

SYSTEMATIC REVIEW OF EXERCISE OR PHYSICAL ACTIVITY AND COGNITIVE FUNCTION IN ADULTS WITH TYPE 2 DIABETES MELLITUS OR INSULIN RESISTANCE OR IMPAIRED GLUCOSE TOLERANCE
3.1 ABSTRACT

Objectives - The purpose of this review was to systematically evaluate the effects of exercise or physical activity on cognitive function in adults with type 2 diabetes mellitus (T2DM) or insulin resistance (IR) or impaired glucose tolerance (IGT).

Methods - A systematic search of studies published from 1966 to the last update in Dec 2014 was conducted using Medline, EMBASE, SportDiscus, CINAHL, PsycINFO, PubMed, and Cochrane Controlled Trials Registry. Any experimental or observational study was included if it evaluated the relationship between exercise or physical activity exposure/intervention on any measure of cognition function in adults with T2DM, IR or IGT.

Results - Six trials including 1767 subjects met the eligibility criteria. Only four of the five studies (80%) reported significant benefits of exercise/physical activity for at least one cognitive outcome. Exercise was associated with improved cognition in these studies, explaining 12% of improvements in delayed memory, 14% of improvements in global cognition, and 30% of improvements in executive function. Overall, only 18% of cognitive outcomes were significantly improved across all trials. Three trials examined any association between insulin, glucose control, and cognitive function. Increased insulin levels were related to worse delayed memory ($r=-0.52$, $p=0.047$). Clinical improvements in HbA1c and glucose fasting control were related to improvements in delayed memory ($r=-0.627$, $p=0.029$) and executive function ($r=0.611$, $p=0.035$), respectively. In addition, higher glucose infusion rate values were correlated with better delayed word list scores ($r=0.614$, $p=0.024$) at baseline and follow-up. One trial investigated the relationship between changes in cognition and changes in cerebral amyloid or intra-abdominal fat after exercise training, and neither of these adaptations was related to changes in cognition.

Conclusions - The limited data available suggest that exercise may contribute to improvements in
cognitive function in T2DM or IR or IGT, but the results of these trials to date are heterogeneous, and most cognitive outcomes showed no significant benefit after exposure to exercise/physical activity. With only one trial meeting review criteria, there is insufficient evidence to document any potential mechanisms of exercise-related cognitive benefits such as changes in cerebral amyloid or intra-abdominal fat. Large-scale, high quality randomised controlled trials are required to determine if exercise improves cognition in this high risk cohort, and investigate putative mechanistic links between cognition, body composition, metabolism, and inflammation. Key words: Exercise, T2DM or IR or IGT, Cognitive Outcomes
3.2 INTRODUCTION

Diabetes mellitus (DM) is projected to affect 435 million adults by 2030,\(^1\) and as the prevalence rises with age from 12\% in people aged 65 to 70 to 15\% in people over age 80, older adults will continue to be disproportionately affected.\(^2\) T2DM, accounting for 85\% to 90\% of patients with DM, is a progressive decline in insulin sensitivity with insulin deficiency that results in sustained hyperglycaemia.\(^3\) DM is the leading cause of cardiovascular disease, kidney disease, vision loss, and neuropathy.\(^4\) Patients with T2DM have been found to present cognitive deficits, associated with reduced performance on multiple domains of cognitive function.\(^5\)–\(^8\) Higher levels of HbA1c have been negatively associated with cognitive performance on a number of tests in elderly and middle aged individuals.\(^5, 9\) Additionally, in elderly patients with T2DM, cognitive deficits in working memory and attention have been observed in the hyperglycaemic state during a glucose clamp.\(^10\)

Diet and exercise represent the initial treatment approaches in clinical practice to slow progression of metabolic disturbance associated with prediabetes and to assist with pharmacological treatment in established T2DM. Increased physical activity has clear beneficial physiological effects for older adults with T2DM or glucose intolerance or insulin resistance,\(^11, 12\) and more recently has been shown to benefit cognition as well.\(^13\)–\(^15\) Epidemiological evidence consistently links physical exercise with better cognitive performance,\(^13\) lower risks for dementia, and reduced pathological changes in the central nervous system (CNS).\(^14\)–\(^16\) Experimental studies have also reported benefits of aerobic and resistance training on cognitive function in older adults.\(^17, 18\) Furthermore, regular physical exercise has also potent therapeutic effects on glucose regulation and cardiovascular health, both of which when compromised may threaten cognitive integrity.\(^18\)–\(^20\)
Positive effects of aerobic exercise on cognition have been well documented in animal models and in aging clinical populations. There is evidence from cross-sectional and prospective brain imaging studies to suggest that aerobic exercise may reduce brain atrophy in older adults, changes that are most striking for brain regions that support executive control processes and memory.

Although it has been shown that exercise can enhance cognitive function, most studies have been in healthy elderly, and thus the applicability of these findings to older adults at high risk for cognitive decline are less well defined. Indeed, there are recent reviews of the cognitive benefits of physical activity, but there is no systematic review of the effects of exercise on cognitive function in people with T2DM or impaired glucose tolerance or insulin resistance to our knowledge. Given the increased risk for dementia posed by T2DM, it is important to define the utility of exercise or physical activity for this outcome in this cohort specifically.

Therefore, our objective was to systematically review the literature to identify the relative efficacy of various modes of structured exercise or habitual physical activity level in individuals of any age with T2DM or IR or IGT on any measure of cognition, including attention, visuo-spatial performance, memory, information processing speed, executive control processes, or global cognitive function. Our secondary aim was to identify the potential mechanisms underlying any cognitive benefits by examining relationships between changes in metabolism, body composition, markers of cerebral pathology including amyloid deposition, and cognitive changes after exposure to chronic exercise or physical activity in this cohort.
3. 3 METHODS

3.3.1 LITERATURE SEARCH

A systematic review of published literature investigating the effects of chronic exercise or physical activity exposure on cognition (including attention, visuo-spatial performance, memory, information processing speed, executive function, or global cognitive function) in individuals with T2DM, IR or IGT was conducted. An electronic database search was performed from 1966 to Dec 2013 using computerised databases including Medline (1966-2013), EMBASE (1966-2013), SportDiscus (1967-2013), CINAHL (1982-2013), PsycINFO (1966-2013), and Cochrane Controlled Trials Registry (3rd Quarter 2013) with the last search being conducted on 21 Dec 2013. The searches for the following categories were conducted using text words pertaining to cognition, exercise and diabetes. A combination of text-based terms in all fields was used to find records.

- Intervention: exercise, or training, or physical activity, or aerobic, or physical capacity, or aerobic capacity, or physical performance, or physical endurance, or motor activity, or resistance, or weight lifting, or strength, or power training, or strength training, or weight-training, or resistance-training, or resistance exercise

and

- Populations: individuals with diabetes, or insulin resistance, or hyperglycaemia, or impaired glucose tolerance.

and

- Outcome: cognition, or cognitive or mental or mental process, or memory, or brain, or neuropsychological, or neurological.

Finally, reference lists in all eligible papers and review articles identified from database searches were hand-searched for any additional papers missed by database searches for potential inclusion.
Non-English literature and unpublished theses were not included in the literature search.

3.3.2 Inclusion and Exclusion Criteria

Studies, regardless of design, were included if they met the following criteria:

1) The study design was a randomised controlled trial (RCT), non-randomised controlled trial (NRCT), or observational study.

2) Full-length article published in a peer-reviewed English language journal.

3) All studies in human subjects of any age and of either sex diagnosed with T2D or IR or IGT with a valid measure of insulin resistance or glucose homeostasis, including fasting glucose or insulin, glycosylated haemoglobin (HbA1c), Homeostatic model of assessment (HOMA-IR or HOMA2-IR), glucose clamp, intravenous glucose tolerance test, oral glucose tolerance test variables or meal tolerance test.

4) The intervention or exposure was any form of exercise training (defined as planned, structured, and repetitive physical activity which has as a final or intermediate objective, the improvement or maintenance of physical fitness) or reported participation in various levels of physical activity. If the study was an experimental trial, the exercise intervention did not need to be fully supervised but must have been prescribed, and quantifiable including self-administered questionnaires or activity monitors. If the study was observational, then it had to report level of physical activity of the cohort. Physical activity is defined as any bodily movements produced by skeletal muscles that result in energy expenditure. \(^{27}\)

5) The design of the study must have been such that the independent effects of exercise or physical activity could be analysed. In the case of multiple interventions (e.g., diet + exercise), one group must have been treated with diet/other intervention, another with
diet/other intervention + exercise, and both must have included individuals with T2DM, IGT or IR.

6) Any validated neuropsychological test of cognition reported at baseline and follow-up after exposure to exercise or physical activity for a minimum of 12 weeks.

7) Papers must have directly analysed the effects of changes in insulin resistance or other metabolic on the changes in cognitive function outcomes. Analyses included insulin resistance or other metabolic or other body composition as a independent variables using simply or in multiple regression models, unless the independent effects of changes in skeletal muscle could be determined from the statistical models presented.

8) Control group: For experimental studies, any kind of control group was eligible, including no contact, no treatment, waiting list, attention control, SHAM exercise, or alternative active treatment. For observational studies, cohorts had to be stratified by level of physical activity, with the least active stratum considered the control/low exposure group.

9) Control groups may have included participants who were healthy, or who had T2DM, IR, or IGT.

Trials were excluded for the following reasons:

1) Only animals were investigated.

2) Individuals without T2DM, IR, or IGT were enrolled.

3) The study reported only the effect of acute exposure to exercise or physical activity, acute exposure to exercise or physical activity is defined as less strenuous exercises for a shorter amount of time. For instance it could be half an hour on the cross trainer or a few minutes skipping (it may include studies of one bout, 2 bouts, 2 weeks, 4 weeks).

4) No validated test of cognitive function was reported as an outcome.
5) They were non-English language articles or unpublished papers; or the articles were reviews or abstracts.

### 3.3.3 SELECTION OF STUDIES AND DATA EXTRACTION

One author (RRZ) conducted the search and extracted all data. After eliminating duplicates, all papers identified by the search strategy were screened by the author, first by title and then by abstract. Two authors (RRZ and MF) determined final eligibility by reading the full text of potentially relevant studies. Trials were split into four groups:

1) Randomised controlled trials (RCTs),

2) Non-randomised controlled trials (NRCTs),

3) Cross-sectional studies, and

4) Prospective cohort studies.

Experimental studies were considered to employ control groups if one group was assigned an exercise intervention, and the other group was assigned to either non-exercise control, SHAM exercise control or an alternate form of exercise intervention. Quality assessment of all eligible papers was undertaken separately by these two authors, using an adapted Physiotherapy Evidence Database (PEDro), with the addition of one quality assessment item deemed pertinent to this review, namely ‘full supervision of exercise program’, which formed criterion point 12. Points were only awarded if the criterion was clearly satisfied. Any disputes were resolved by consensus, or by a third author (AOS) when necessary. Data were extracted regarding methodology of the study, cohort characteristics, exercise intervention or physical activity exposure, cognitive outcomes, and any relationships between changes in cognition and metabolism or other cohort characteristics. Data in this review are reported as mean ± SD. Data that were
reported as mean ± SEM were converted to mean ± SD. Authors were contacted for missing data whenever possible.

### 3.3.4 Data Analysis

A quantitative meta-analysis across studies was not carried out due to the heterogeneity of exercise interventions, outcomes assessed and measurement tools used. In experimental studies, between-group ESs (adjusted via Hedges’ bias-correction for small sample sizes) and 95% confidence intervals (CIs) were calculated for each outcome measure where applicable using formula 1:

\[
\text{between-group ES} = \frac{\text{change in treatment} - \text{change in control}}{\text{pooled baseline standard deviation (SD)}}.
\]

Formula 2: intra-group ES = \((\text{post-score} - \text{pre-score})/\text{baseline SD}\).²⁹

Final sample sizes excluding dropouts were used to calculate ESs, unless there had been imputation of missing data from dropouts. ES were interpreted according to the method of Cohen as: ‘trivial’ \((\leq 0.20)\), ‘small’ \((\geq 0.20 \text{ to } < 0.50)\), ‘moderate’ \((\geq 0.50 \text{ to } < 0.80)\) and ‘large’ \((\geq 0.80)\).³⁰ Significant level was set at \(p < 0.05\) unless otherwise indicated.

### 3.4 Results

#### 3.4.1 Studies Retrieved

Figure 3.1 displays the detailed results of the search process at each step. The search strategy identified 5759 studies while hand searching identified a further two studies. After the removal of duplicates, 3866 studies remained. Literature titles and abstracts were examined, and studies not meeting the eligibility criteria were excluded. The whole text of 47 studies was examined, and
five trials, reported in six citations (all aerobic exercise),\textsuperscript{31-35} were found to meet the criteria for review. This included two RCTs\textsuperscript{31, 34} one NRCT\textsuperscript{35} one prospective cohort study\textsuperscript{33} and two cross-sectional studies.\textsuperscript{32, 33}

\textbf{3.4.2 \textit{Study Quality Assessment}}

An evaluation of the study quality checklist items based on a modified PEDro is summarised in Table 3.1. Overall, the quality of the two RCTs\textsuperscript{31, 34} included in this review was moderate-high, receiving scores of 7 and 9 out of 12. The blinding of assessors and participants were common deficiencies,\textsuperscript{31, 34} exercise interventions were fully supervised in two\textsuperscript{31, 34} of the three trials, but one trial removed supervised training after 6 months and continued with a home-based program.\textsuperscript{31} Key outcomes were obtained in greater than 85\% of participants enrolled in each trial. The non-randomised controlled trial,\textsuperscript{35} prospective,\textsuperscript{33} and cross-sectional\textsuperscript{32, 33} and studies were of a low standard on the PEDro scale,\textsuperscript{32, 33, 35} with an average study quality was 5/12, (range 4 to 6).

\textbf{3.4.3 \textit{Study Design/Cohort Characteristics}}

A summary of study design and cohorts characteristics for each trial is shown in Table 3.2.1-3.2.4.

\textbf{3.4.4 \textit{Demographics}}

A total of 72 participants were enrolled across 5 studies, ranging from 16 to 1769 participants. Pooled sample size amongst RCTs was 58 (n= 28 and 30),\textsuperscript{31, 34} while 1711 participants were enrolled in non-randomised controlled trial,\textsuperscript{35} and prospective\textsuperscript{33} and cross-sectional studies.\textsuperscript{32, 33} The average age of cohorts across all trials was 65.9 years, with age ranging from 58.5 to 74 years.
Sex breakdown was provided in 4/5 study cohorts. Overall, one study included women only,\textsuperscript{33} while another one did not report sex.\textsuperscript{31} The remaining 3 studies\textsuperscript{32, 34, 35} were comprised of mixed cohorts. Body Mass Index (BMI) was reported in all but one cross-sectional study.\textsuperscript{32} Participants were overweight or obese with BMI $\geq 25$ kg/m$^2$,\textsuperscript{31, 33, 34} except for the NRCT where BMI was 22.9±2.5 kg/m$^2$.\textsuperscript{35}

\textbf{3.4.5 Diagnostic Criteria for T2DM and IGT}

Only 1 out of 5 studies (6 citations) reported diagnostic criteria for T2DM, as either fasting glucose $\geq 126$ mg/dL, or insulin resistant 100 to 125 mg/dL, or diagnosed diabetes.\textsuperscript{32} Among the remaining 4 studies, one study recruited participants registered as prediabetes, a fasting plasma glucose level <7.8 mmol/L and a plasma glucose level $\geq 7.8$ and <11.1 mmol/L two hours after carbohydrate loading.\textsuperscript{31} One study reported subjects meeting glucose tolerance criteria for prediabetes (140 mg/dL $\geq$ 2-h glucose < 200 mg/dL) or newly diagnosed (at the time of study screening) T2DM (2-h glucose $\geq 200$ mg/dL).\textsuperscript{34} Participants were diagnosed as diabetes using euglycemic clamp in one study,\textsuperscript{35} while one study reported revised criteria of the American Diabetes Association with T2DM medical records.\textsuperscript{33}

\textbf{3.4.6 Medications and Disease Burden}

In general, medication usage and disease burden reporting were sub-optimal or important elements missing in most studies. Two out of five studies\textsuperscript{32, 33} reported the participants’ diabetic medications,\textsuperscript{31-35} however these studies did not report if there were any changes in medications during the trial. Among these studies, one trial included some participants with insulin treatment.\textsuperscript{33} Participants in the 5 studies reported in 6 citations were only treated with oral agents.\textsuperscript{33}
or didn’t take diabetic medications.\textsuperscript{31, 32, 34, 35} One study explicitly excluded participants on oral hypoglycaemia therapy.\textsuperscript{34} Duration of diabetes was reported in one study and ranged from 1 to 15 years.\textsuperscript{33}

Only 2 studies published in 6 citations\textsuperscript{33, 34} reported medications other than diabetic medications, and only 1 study reported chronic diseases other than T2DM which included hypertension, cardiovascular disease, or exercise limitations.\textsuperscript{33} One cross-sectional study reported habitual physical activity level as “sedentary”, although precise definitions were not given.\textsuperscript{32} One study reported the treatment of anti-hypertensive\textsuperscript{34} and anti-depression medications.\textsuperscript{33}

\subsection*{3.4.7 Neuropsychological Assessment}

There was considerable heterogeneity in the cognitive outcome assessment tools employed across these studies, as shown in Table 3.3.1-3.34 making it difficult to directly compare outcomes between them. For example, global cognitive function was measured with the Telephone Interview for Cognitive Status forms of the Mini-Mental State Examination (TICS-MMS) in one trial published in two citations.\textsuperscript{33} Another study used both the MMS and the Saint Louis University Mental Status exam (SLUMS), defining cut-off points for MMS scores (>24) and SLUMS (>20 final as normal cognitive function). These definitions categorised participants as cognitively normal with the exception of 5 participants (6.8\%) in the cross-sectional study who were considered to have mild to moderate cognitive impairment.\textsuperscript{32} Participant score on the MMS who was 23 or lower were excluded.\textsuperscript{35} In addition, one trial used Story Recall and Attention Visual Retention, as well as Trail Making Test (TMT) and Stroop Interference Tests to assess the memory and attention;\textsuperscript{31} Another trial utilised Story Recall, Learning List, TMT, Task Switching, Stroop
Color-Word Interference, Verbal Fluency, and Self-Ordered Pointing measures to assess memory and executive function. Finally, one trial measured Word List, a subtest of the Alzheimer’s disease Assessment Scale (ADAS), Digit Symbol Test, a subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), Digit Symbol Test, a subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R), and TMT to evaluate the memory, complex psychomotor skills, and attention.

A total of 28 different cognitive outcome measures were administered (average 5/study, range: 2-7). Data from non-significant findings were not always provided. General cognitive function was measured using MMS, SLUMS, TICS-MMS, or overall global score. The majority of trials administered standardized neuropsychological tests with attention/executive function the most frequently measured domain, followed by memory and information processing.

3.4.8 Measures of Glucose Homeostasis and Insulin Resistance

A summary of the results can be found in Table 3.4 to 3.5. One trial utilised fasting glucose 126 mg/dL. The hyperinsulinaemic euglycaemic clamp (the gold standard measurement for insulin resistance) was only used in two trials, while only one trial used an oral glucose tolerance test to assess glucose tolerance and insulin sensitivity. One trial (2 citations) failed to report any measurement of insulin or glucose metabolism.

3.4.9 Measures of Body Composition

A summary of the results can be found in Table 3.6. Body composition was reported in all but
one cross-sectional study. One trial used computed tomography to measure intra-abdominal fat. Two studies reported measures to calculate % fat using computed tomography. The remaining one study (two citations) reported that 36% of participants were overweight or obese, with body mass index (BMI) mean of \( >30 \text{ kg/m}^2 \).

3.4.10 MEASURES OF EXERCISE CAPACITY

A summary of the results can be found in Table 3.7. Exercise capacity and changes in response to exercise/physical activity exposure were not reported in the majority of studies. Only 2 trials included measures of cardiorespiratory fitness, as measured by treadmill measures of \( \text{V}_\text{o}_2 \text{ peak} \). One trial measured the \( \text{V}_\text{o}_2 \text{peak} \) (L/min), while the remaining one trial did report the detailed measurement of \( \text{V}_\text{o}_2 \text{peak} \) (ml/kg/minute). No studies reported other non-aerobic domains of exercise capacity such as muscle strength, muscle power, six minute walk distance, gait speed, chair stand, or balance.

3.4.11 MEASURES OF \( \text{A}\beta_42 \) METABOLISM

A summary of the results can be found in Table 3.8. Only 1 trial included measures of \( \text{A}\beta_42 \), which were aging- and AD related biomarkers.

3.4.12 INTERVENTION CHARACTERISTICS

Table 3.2 provide an overview of the exercise training interventions among the experimental trials. For the cross sectional and prospective studies, physical activity exposure was also assessed by self-report questionnaires, including observational studies.
**Modality:**

Among the two RCTs, one trial investigated the effects of a combination of aerobic exercise and dietary restriction compared to a diet restriction plus stretching control group, and another prescribed aerobic exercise compared to a stretching control group. The single NRCT compared the effects of horseback riding therapeutic equipment (JOBA) aerobic training compared to a maintaining usual level of activity (walking) control group. This horseback riding therapeutic equipment (JOBA Matsushita Electric Works, Ltd., Japan), was developed as an attempt to imitate the passive movement of bending down and straighten up during a horse riding. The characteristic of the JOBA equipment is that it produces a simple movement which is enough to experience the feeling of a real horse riding and it also effectively provides place for muscular relaxation. Therefore, it is considered as a way to maintain muscular power and strength. In addition, this equipment causes an elevation of heart rate (55–69% of maximal heart rate), and is thus proposed to be able to improve aerobic fitness. However, no reports of improved aerobic capacity, muscle function or balance after JOBA interventions have been published to our knowledge. The single prospective cohort study compared the effects of highest habitual physical activity level to lowest physical activity level, while the cross-sectional study, derived from the same cohort, examined the difference between the highest and the lowest physical activity groups. Finally, another cross-sectional compared the cognitive function of regular exercise in a healthy group to exercise in a group with T2DM.

**Intensity:**

There was one trial of low intensity aerobic training, and two trials of moderate or high intensity aerobic training. One RCT study used diet control plus aerobic exercise and a non-exercise
diet restrict control group over 52 weeks. Aerobic exercise in Watson et al (2006) set the exercise intensity at 50% to 70% HRR over 12 week training intervention.\textsuperscript{31} One study prescribed high intensity aerobic exercise, consisting of 45-60 minutes of multiple modalities of aerobic training (stationary bicycle, elliptical trainer, or treadmill walking) with a gradual increase in exercise intensity during the first 6 weeks, which progressed to 60 minutes at 70-85% heart rate reserve during 11-26 weeks.\textsuperscript{34} One NRCT employed either jogging or walking on a treadmill with low intensity at 50% of maximum heart rate (heart rate max), which progressed to 70% of maximum heart rate reserve (HRR) over 12 weeks, and would be considered low intensity.\textsuperscript{35} Only Devore et al (2009) used one modality of exercise (metabolic equivalent),\textsuperscript{33} while the study of Colberg et al (2008) used multiple modalities of aerobic training (e.g. usual exertion, usual walking pace, stairs climbed, and city blocks walked).\textsuperscript{32}

\textit{Volume and Frequency:}

In the aerobic training or combined aerobic training with diet control studies, the volume varied from 45 to 60 minutes per session of continuous exercise,\textsuperscript{31,34,35} mean 50±9 minutes. Frequency ranged from 3 to 4 days per week.\textsuperscript{31,34,35} One self-report study was 180±18 minutes of moderate aerobic exercise 3 times a week.\textsuperscript{32} One did not report the volume and frequency.\textsuperscript{33}

\textit{Duration:}

Trial duration ranged from 12 to 52 weeks in the experimental studies,\textsuperscript{31,34,35} Supervision was removed during the maintenance phase in one study and participants were advised to continue exercise at home for the final 6 months.\textsuperscript{31} Two studies were between 12 to 26 weeks.\textsuperscript{34,35} Two cross-sectional studies reported a minimum duration of 1 years.\textsuperscript{32,33} In longitudinal studies, for
classification of physical exercisers, duration were defined as 4.2 years using questionnaire.\textsuperscript{33}

3.4.13 Control Conditions

Control conditions were highly variable and included diet,\textsuperscript{31} or stretching or balance,\textsuperscript{34} or usual activities.\textsuperscript{35} Three trials had active or SHAM control conditions including diet controls and low intensity aerobic exercise,\textsuperscript{31} stretching and balance,\textsuperscript{34} or normal walking.\textsuperscript{35} Two of the experimental trials reported supervision during the control condition.\textsuperscript{31, 34} The one prospective and two cross-sectional and studies described the control condition as a low level of habitual aerobic exercise/physical activity which was compared to the higher activity level condition, all unsupervised.\textsuperscript{32, 33}

3.4.14 Follow-up for Outcome Assessment

Results are reported in Table 3.2 All details and documents related to recruitment and screening are presented in the Appendix. Measurements were taken at baseline, midpoint, and post-training in two studies\textsuperscript{31, 34} and pre-post only in the 12-week JOBA study.\textsuperscript{35} However, the midpoint measure in the 26-week treadmill than others was not report.\textsuperscript{34} Only one longitudinal study had follow-up after exercise intervention at 4.2 years.\textsuperscript{33}

3.4.15 Adverse Events

Not reporting adverse events is considered a quality deficiency in terms of consort reporting requirements.
3.4.16 OUTCOMES MEASURES

A complete summary of outcomes, ESs (95%, CIS) is found in tables in Tables 3.3-3.9.

3.4.17 EFFECT OF EXERCISE INTERVENTIONS ON COGNITIVE FUNCTION

A summary of the results can be found in Table 3.3. Compared to a control group, aerobic was shown to improve executive function, while no effect was seen on memory in one RCT. Increases in delayed memory score was seen following aerobic training combined with diet control compared to a diet control group, while no beneficial improvement was found in executive function compared to diet control. Aerobic exercise was not found to have an effect on cognitive domain in one NRCT. Compared to the low activity level group, higher physical activity level had significantly better global cognitive function in two cross-sectional studies. However, no effects were reported for memory and global cognitive function in one longitudinal studies.

Effect sizes were calculated for all cognitive outcome measures, as detailed below. Twenty-six weeks of high intensity supervised treadmill walking has a small but positive significant effect on tests of cognitive flexibility (TMTB ES: 0.36; p=0.04), response inhibition (SCWI ES: 0.38; p=0.04), and Task Switching (ES: 0.39; p=0.03), but not Verbal Fluency (ES: 0.25; p=0.11) nor Self-Ordered Pointing Test (ES: 0.29; p=0.10) in older adults with impaired glucose tolerance. Similarly, there were no significant effects on verbal memory (ES=0.11).

The combined aerobic exercise and American Heart Association Step 2 Eucaloric Diet (AHAS2ED) resulted in large significant effects on one of two memory tests (Story Recall ES:
1.35; 95% CI: 0.48, 2.22), while no significant results were found for attention/executive function on the Trail Making Test and Stroop Interface Test.\textsuperscript{31} By contrast, no significant effects were revealed for memory (Word List Memory Immediate and Word List Memory Delayed), information processing speed (Wechsler Adult Intelligence Scale - Digit Symbol and Trail Making Test A), attention/executive function (Stroop Color-Word Test and Trail Making Test B), and global cognitive function in a trial of low intensity supervised JOBA exercise for 12 weeks.\textsuperscript{35}

In summary, four of the five studies (6 citations) reported significant benefits for at least one outcome; no significant effects were found in the two trials.\textsuperscript{33, 35} However, exercise was reported to result in improved delayed memory,\textsuperscript{31} executive function,\textsuperscript{34} and global cognition.\textsuperscript{32, 33} Overall, only 22% of outcomes were significant across all trials.\textsuperscript{31-35}

3.4.18 Effect of Physical Activity Exposure/Exercise Interventions on Insulin Sensitivity

Results are summarised in Table 3.4. Among the experimental trials, one RCT compared a combined moderate intensity aerobic exercise and dietary restriction (American Heart Association step 2 eucaloric diet) to dietary restriction (American Heart Association step 1 eucaloric diet) and stretching, with aerobic exercise/diet found to have a greater effect on insulin sensitivity (ES: -3.28; 95% CI: -4.41, -2.14; p=0.02) than diet and stretching, determined by 2-hour-OGTT glucose levels and 2-hour-OGTT insulin levels.\textsuperscript{31} High intensity aerobic training alone tended to improve glucose disposal rate (ES: 0.47; 95% CI: -0.33, 1.28; p=0.05),\textsuperscript{34} but not for fasting plasma insulin in aerobic group. There was no significant difference in metabolic clearance rate (ES: 0.97; 95 CI: -0.07, 2.02; p=0.24) or glucose infusion rate (ES: 0.66; 95 CI: -0.36, 1.67; p=0.99) between low intensity JOBA aerobic exercise compared to normal physical activity groups.\textsuperscript{35} Limited
data were available from the observational studies. In one cross-sectional study,\textsuperscript{32} higher physical activity levels (high daily stairs, flights and walking pace) were inversely related to insulin resistance ($r=-0.27$, $p<0.01$). Similarly, high weekday vigorous and weekend vigorous improved fasting insulin. However, the observational cohort study did not report any insulin metabolic data from either cross-sectional\textsuperscript{33} or prospective analyses.\textsuperscript{33}

### 3.4.19 Effect of Physical Activity Exposure/Exercise Interventions on Glucose Homeostasis

Results are reported in Table 3.5. None of the experimental studies reported a significant improvement in glucose homeostasis after any exercise intervention. A combined aerobic exercise and dietary intervention was not reported to be beneficial compared to diet and stretching group in one study.\textsuperscript{31} Comparing aerobic exercise to a stretch or balance as control group, aerobic exercise did not improve fasting plasma glucose (ES: -0.31; 95% CI: -1.10, 0.49; $p=0.44$) in one trial.\textsuperscript{34} There was also no difference in HbA1c (ES: -0.19; 95 CI: -1.18, 0.80; $p=0.72$) or fasting blood glucose (ES:-0.17; 95 CI: -1.15, 0.82; $p=0.21$) between low intensity JOBA aerobic exercise compared to usual physical activity groups.\textsuperscript{35} However, high levels of Daily stairs, flights in one cross-sectional study had a low glucose level as measured by HbA1c%.\textsuperscript{32} Moreover, fasting glucose was reversely related to weekend sitting, hours ($r=0.27$, $p<0.01$), weekday sitting, hours ($r=0.19$, $p=0.03$), and weekday light, hours ($r=0.17$, $p=0.04$).\textsuperscript{32} The other observational studies did not include data on glucose homeostasis.\textsuperscript{33}

### 3.4.20 Effect of Exercise Interventions on Body Composition

A summary of the results can be found in Table 3.6. In the experimental trials, aerobic training
alone was not found to decrease percent body fat in either of two trials compared to control groups. The combination of aerobic training and diet did not report a significant effect on BMI compared to diet control (p=0.16). Moreover, there was no difference between JOBA aerobic exercise compared to normal physical activity on BMI and percent body fat. In addition, high physical activity in cross-sectional and prospective studies was not reported to have any significant effect on body mass index compared to low physical activity. Effect sizes were trivial and non-significant for body mass index and percent body fat. The remaining one study reported a moderate ES for percent body fat, although non-significant. Together, these results suggest aerobic exercise had no significant beneficial effect on BMI and percent body fat.

### 3.4.21 Effect of Exercise Interventions on Peak Oxygen Uptake

A summary of the results can be seen in Table 3.7. A trend for an increase in relative peak oxygen uptake was observed in a combined aerobic training and diet program compared to a diet/stretching control group. Compared to non-exercise control group, aerobic exercise was shown to improve absolute peak oxygen uptake in one trial, with a small ES calculated (ES: 0.41; 95% CI; -0.39, 1.21; p=0.03).

### 3.4.22 Effect of Exercise Interventions on Ab42 Metabolism

A summary of the results can be found in Table 3.8. In a RCT, aerobic exercise tended to decrease plasma levels of Aβ42 compared to a non-exercise control group (ES: -0.62; 95% CI; -1.43, 0.19; p=0.07).
3.4.23 RELATIONSHIP BETWEEN CHANGES IN MEASURES OF COGNITIVE FUNCTION AND INSULIN RESISTANCE

A summary of the results can be found in Table 3.9. Significant relationships between changes in cognition and changes in insulin resistance were seen in all 3 out of 5 studies, and were only present amongst the RCT’s, the NRCT, and cross-section study, but not for prospective study. Specifically, increases in delayed memory were inversely related to changes in 2 hour OGTT insulin levels ($r=-0.52; p<0.05$) in the aerobic exercise plus diet group only, while no relationship was seen in the diet and stretching control group. Changes in delayed memory were correlated with improvements in glucose infusion rates ($r=0.64; p=0.024$) during a euglycaemic clamp, with a trend for metabolic clearance rate ($r=0.575; p=0.051$) in those who performed JOBA exercise, as well as in the usual physical activity control group. Changes in global cognitive function in participants performing aerobic training were inversely related to HOMA-IR ($r=-0.19; p=0.02$) and insulin level ($r=-0.13; p=0.03$). In the Thus, there is some evidence to suggest that improvements in insulin sensitivity are potentially contributory to cognitive adaptations or at least modified proportionally by exercise.

3.4.24 RELATIONSHIP BETWEEN CHANGES IN MEASURES OF COGNITIVE FUNCTION AND GLUCOSE HOMEOSTASIS

A summary of the results can be found in Table 3.10. A significant inverse association with changes in word recall and changes in HbA1c ($r=-0.627; p=0.029$) reported in one trial compared to stretch or balance. Higher fasting blood glucose was directly related to worse executive function ($r=0.611; p=0.035$) in this same trial. However, no such relationships between cognition and glucose changes were reported in those who performed aerobic training or aerobic
training plus diet control only, or in the control groups of these two trials.\textsuperscript{31,34} Thus, there is little support for improvements in glucose homeostasis as a mechanism for cognitive benefits of exercise in this cohort.

3.4.25 \textit{Relationship between Changes in Measures of Cognitive Function and Body Composition}

A summary of the results can be found in Table 3.11. Change in intra-abdominal fat was inversely correlated with changes in delayed memory within control participants who received diet and stretching, while no significant relationship was observed in those who received aerobic training and dietary intervention.\textsuperscript{31} No significant relationship was reported between changes in percent body fat and changes in cognition.\textsuperscript{34,35} in the 2 trials examining this. Thus, there is no evidence support for changes in body fat contributing to cognitive benefits of exercise. In addition, no relationships between cognition and VO2peak and biomarker were reported in two trials (Table 3.12 to 3.13).\textsuperscript{31,34}

3.5 \textbf{DISCUSSION}

The purpose of this review was to evaluate published research investigating the effects of exercise on cognitive outcomes in individuals with T2DM or IGT or IR. This was done to increase our understanding of the potential role that exercise may play in cognitive capacity in this specific cohort, given their increased risk of cognitive decline. This systematic review identified 2 RCTs, one NRCT, two cross-sectional and one prospective cohort studies of exercise or physical activity exposure in individuals with T2DM or IGT or IR. The quality of this literature was only moderate, and the majority of trials had samples too small for sufficient power to detect small effects. Only
one trial\textsuperscript{34} fulfilled most of the recommended PEDro criteria for trial internal validity. The lack of blinding of assessors, participants, and trainers in all trials reviewed is a serious limitation of this literature. The vast majority of cognitive outcomes (78\%) were non-significant, thus providing no strong or consistent evidence that aerobic exercise or lifestyle intervention or higher levels of habitual physical activity improve cognition or are associated with less risk of decline in individuals with T2DM or IGT or IR.

3.5.1 \textbf{Effect of Aerobic intervention on Cognitive Function}

The major finding of this review is that in three out of the five studies identified, physical exercise or lifestyle intervention was associated with beneficial effects on 14\% of memory, 33\% of executive function, and 11\% of general cognition tests in individuals with T2DM or IR or IGT. Prior studies in non-diabetes cohorts have mainly focused on aerobic exercise and linked it to improved executive function.\textsuperscript{22} In one study, moderate intensity aerobic exercise plus diet significantly improved delayed memory, even no significant change in tasks of executive function including selective and divided attention, cognitive flexibility, and working memory in older adults with glucose intolerance.\textsuperscript{31} Moderate to high intensity aerobic exercise were related to improve executive function and information processing speed, but not for verbal memory.\textsuperscript{34} Notably, participants were performed high physical activity were related to better global cognitive function, with data from both groups pooled for analysis.\textsuperscript{32} Similarly, results from Devore et al (2009),\textsuperscript{33} showed that high physical activity had better cognitive function within the highest physical activity group, and this relationship remained a significant after adjusting for age, education, and disability indicators. The lack of relationship reported within the one prospective study may be due to the chronic conditions such as brain pathology.\textsuperscript{33} The intervention delivered
during this particular trial was JOBA exercise,\textsuperscript{35} and it was concluded that the intervention was not of a sufficient intensity (55-69\% maximal heart rate or 40–59\% of VO\textsubscript{2}max) to induce significant improves in cognition. In summary, this small body literature about the efficacy of aerobic exercise for cognition in older adults with T2DM or IR or IGT is mixed and inconclusive. Much more information is needed about other modalities of exercise, as well as confirmation of any clinically relevant and sustained benefits of aerobic exercise.

The potential role of progressive resistance training (PRT) and cognitive function is of interest for a variety of reasons. First, reduction in adiposity and increase in muscle mass, which is targeted by PRT, has been specifically associated with improved insulin sensitivity, glucose control, and inflammation, \textsuperscript{37-40} which are in turn associated with a decreased risk of cognitive decline. Secondly, PRT may improve hypertension, dyslipidemia, and insulin and glucose regulation, which are important comorbidities of T2DM associated with cognitive impairment.\textsuperscript{20, 41} Third, PRT results in a range of positive benefits for neurobiological outcomes in animal and human studies, such as increased insulin-like growth factor-1 (IGF-1),\textsuperscript{42} increased brain derived neurotrophic factor (BDNF),\textsuperscript{43-45} neurogenesis,\textsuperscript{45} functional plasticity,\textsuperscript{46} decreased inflammatory cytokines,\textsuperscript{47, 48} decreased cortisol response to stressors, and improved cognitive function.\textsuperscript{45, 49} Specifically, PRT can increase IGF-1 levels, which may lead to improved neurogenesis and vessel remodeling in the brain.\textsuperscript{42} Currently, the inconsistent efficacy of aerobic training for cognitive outcomes in this review suggests that this modality may not be optimal or sufficient for targeting cognitive impairment in this cohort. Resistance training is theoretically uniquely grounded as an alternative exercise modality which may improve brain health and cognitive function by increasing growth factors and reducing the systemic risk factors.
3.5.2 Relationship between Changes in Cognition and Changes in Insulin Resistance

The small amount of evidence available suggests that better memory is partially explained by reductions in insulin resistance. Specifically, the results show that increases in insulin sensitivity (2-hour OGTT insulin levels) (Table 3.9) were related to a significant improvement in delayed memory. Furthermore, the improvements of memory were explained by increases metabolic clear rate and glucose infusion rate indicating improved peripheral insulin resistance (via hyperinsulinaemic-euglycaemic clamp). One study has shown the concomitant improvements in cognition and insulin resistance with individuals with T2DM or impaired glucose tolerance after aerobic exercise, again suggesting this as a potential mechanism of the cognitive benefit. In one case, improvements in IR during a hyperinsulinaemic-euglycaemic clamp were related to better memory, although no significant change in either measure was observed post-intervention. Low insulin resistance had better global cognitive function. The intervention delivered during this particular trial was JOBA exercise, and it was concluded that the intervention was not of a sufficient intensity to induce significant improvements in delayed memory, information processing speed, executive function, and global cognitive function, nor provide robust metabolic benefit. However, what the results do suggest is that improvements in insulin resistance were explained a portion of the cognitive changes. By contrast, this review did not provide support for reductions in hyperglycaemia as a mechanism of cognitive benefit in this cohort. However, it is acknowledge that this literature is small, and only of modest quality, and many other putative factors which could contribute to cognitive adaptation such as reductions in systemic inflammation or changes in growth factors were not measured in these trials. Thus, future robustly-designed studies should incorporate such mechanistic measures to substantively advance knowledge in this field.
3.5.3 **Relationship between Changes in Cognition and Changes in Glucose Homeostasis**

Much like insulin resistance, decreases in glucose homeostasis explained a significant portion of the variance in cognitive function. Specifically, they explained the reductions in HbA1c within 2 trials\(^{31,32}\) and the reduction in FBG\(^{35}\) (Table 3.10). With the limited data available, it is difficult to conclusively determine the specific role of changes in glucose homeostasis on cognition. However, the few relationships observed do suggest that increases in glucose homeostasis are independently related to improvements in memory, executive function, and global cognitive function.

3.5.4 **Implications for Exercise Interventions and Future Research**

Previous reviews have suggested that aerobic exercise and resistance training should form part of any lifestyle intervention aimed at improving the cognitive function and metabolic profile in healthy adults,\(^{16,50}\) However, much of the focus has been on cellular and molecular adaptations in the brain.\(^{21,51}\) This is the first review to focus on neurocognitive adaptations in response to exercise in older adults with T2DM, and attempt to identify any mechanic links between changes in cognition and changes in metabolism, body composition, neurtophic factor, and inflammation. The data from these trials presented in this review indicate that improvements in cognitive health not as consistently seen as in healthy elders, and those that do occur are partly explained by improvements in insulin sensitivity, with less evidence for links with glucose homeostasis or body composition changes or neutrophic factor or inflammation.

The findings from this systematic review support the view that one of the goals of exercise interventions for metabolic disease should be maximisation of cognitive benefits, but the exact
prescription to achieve this aim consistently remains elusive. Theoretically, optimal nutrition plus exercise may best influence insulin signaling, neurogenesis, neurotrophic factors, and plasticity in brain regions directly relevant to memory, and there is a need for more studies comparing isolated and combined lifestyle interventions to identify the most beneficial strategy.

With only six studies meeting the criteria for this review to date, further research is required in order to adequately address the relationship between the improvements in metabolic health and improvements in cognition in individuals with T2DM. In particular, the data analyses presented in these trials were performed as secondary analyses, and as such, there was not much discussion or exploration of the mechanistic link between the exercise and cognitive change. For example, although results of our review suggest that aerobic exercise decreased circulating levels of Aβ42 and increased VO2peak for subjects with better cognitive function in the aerobic exercise group relative to controls, this finding requires replication and extension, and its clinical relevances needs to be determined. Many other putative mechanistic factors remain to be studied in this regard as well. Additionally, little is known regarding the persistence of putative therapeutic effects on cognition following the termination of exercise. The training regimes were relatively short and some lacked sufficient intensity to optimise neurophysiological or neuropsychological change. Dose-response relationships between exercise dose (both volume and intensity) and cognitive outcomes in this cohort are completely lacking, and should also be a focus of additional investigation. Given that many risk factors such as insulin resistance, hyperglycemia, inflammation, obesity, and dyslipidemia exist in this cohort, it is possible that improvement in these risk factors is implicated in delayed cognitive decline after exercise exposure. Future studies should focus on controlled trials of aerobic exercise that include metabolism, body
composition, growth factors, and inflammation, and a broad range of cognitive domains, to address the gaps we have identified.

Importantly, all of the literature we have reviewed to date is focused on aerobic exercise and cognition in adults with metabolic disease. Notably, resistance training may directly target insulin sensitivity, glucose homeostasis, inflammation and catabolism, muscle mass and reduced adiposity, thus having many potential links to cognition as well. Additionally, it must be considered that other factors involved in the cognitive process response to PRT may play an independent role. However, rigorous clinical trials investigating the central and peripheral synergistic benefits of resistance training for improved cognitive function are lacking. Thus, PRT should be directly compared to aerobic training benefits for cognition in future trials in this cohort. Additionally, by identifying those who are likely to be unresponsive to an aerobic intervention, PRT interventions may be prescribed that are more likely to bring about improvements in cognitive health. Future investigations should therefore be specifically designed for the investigation of the isolated benefits of resistance training, and to provide novel, comprehensive data on possible proposed links between cognitive improvement, metabolism, inflammation, and whole-body-adaptation to resistance training in older individuals with T2DM.

Furthermore, future studies will also need to use cognitive measures which are comprehensive and more sensitive to longitudinal change, and provide long-term follow up to assess sustainability of any gains achieved during clinical trials. Arguably the most salient issue for the field is the expansion of outcomes to assess transfer of cognitive gains to activities of daily living, quality of life, and psychological well-being.
In conclusion, the limited data available suggest that exercise or lifestyle intervention improved some aspects of cognition in adults with T2DM, including executive function and delayed memory. Exercise-induced improvements in insulin sensitivity in particular were associated with the observed cognitive benefits, while there is insufficient evidence exploring any relationship with other physiological adaptations at this time. Future research in this field should include robust measures of body composition, metabolic profile, growth factors, and explore the genetic, inflammatory markers, clinical and physiological factors that potentially mediate the cognitive process. Such investigations will lead to a better understanding of the mechanisms underlying the direct relationship between cognition, body composition, and metabolic health, and ultimately to the design of interventions specifically targeting the need of specific individuals and cohorts, contribute to their physical, cognitive and psychological health, and ultimately improve quality of life.
3.6 REFERENCES


39. Mavros Y, Kay S, Simpson KA, et al. Reductions in C-reactive protein in older adults with type 2 diabetes are related to improvements in body composition following a randomized


<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Watson, 200631</td>
<td>RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
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<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>7</td>
</tr>
<tr>
<td>Colberg, 200832</td>
<td>CS</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
<td>N/A</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>4</td>
</tr>
<tr>
<td>Devore, 200933</td>
<td>CS</td>
<td>Yes</td>
<td>N/A</td>
<td>N/A</td>
<td>No</td>
<td>N/A</td>
<td>N/A</td>
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<td>Yes</td>
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<td>Devore, 200933</td>
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<td>No</td>
<td>N/A</td>
<td>N/A</td>
<td>Yes</td>
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<td>Yes</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Baker, 201034</td>
<td>RCT</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Yanagawa, 201135</td>
<td>NRCT</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>6</td>
</tr>
</tbody>
</table>
Points are only awarded when a criterion is clearly satisfied within a modified PEDro Scale

PEDro Scale: Physiotherapy Evidence Database Scale

CSS: Cross-sectional study

LS: Longitudinal study

N/A: Not applicable

Yes = 1

No or N/A = 0
Table 3.2.1 Study Design and Subject Characteristics (Randomised Controlled Trials)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study subjects</th>
<th>Metabolic Condition (Medication)</th>
<th>Total n</th>
<th>Control condition</th>
<th>Training modality</th>
<th>Active Treatment</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Year Reference</td>
<td>% male</td>
<td>Age (y)</td>
<td></td>
<td></td>
<td></td>
<td>Intensity</td>
<td>Volume (min)</td>
</tr>
<tr>
<td>Watson, 2006&lt;sup&gt;31&lt;/sup&gt;</td>
<td>NR</td>
<td>AT: 58.0± 9.7</td>
<td>CO: 60.6 ± 9.0</td>
<td>IGT (NR)</td>
<td>n=28 AT=15 CO=13</td>
<td>Stretching plus AHAS1ED</td>
<td>Aerobic exercise (treadmill plus AHAS2ED supervised)</td>
</tr>
<tr>
<td>Baker, 2010&lt;sup&gt;34&lt;/sup&gt;</td>
<td>35.7%</td>
<td>AT: 71.0±7.5</td>
<td>CO: 66.0±6.0</td>
<td>IGT/T2DM (Oral HG)</td>
<td>n=28 AT=19 CO=9</td>
<td>Stretching or balance</td>
<td>Aerobic exercise (Treadmill, stationary bicycle, or elliptical trainer.) supervised</td>
</tr>
</tbody>
</table>
Data is presented as Mean ± SD or Median (interquartile or range) or (±SD).

AHAS1ED: American Heart Association Step 1 Eucaloric Diet (total calories 30% fat, 50% carbohydrate, and 20% protein)

AHAS2ED: American Heart Association Step 2 Eucaloric Diet (total calories 30% fat, 7% saturated fat, 55% carbohydrate, and 15% protein)

HRR: heart rate reserve ((0.5 × [maximal heart rate - resting heart rate] + resting heart rate))

y: year

min: minute

wk: week

NR: Not reported

IGT: Impaired glucose tolerance

T2DM: Type 2 diabetes mellitus

HG: Hypoglycaemia

AT: Aerobic training

CO: Control
### Table 3.2.2 Study Design and Subject Characteristics ((Non-randomised Controlled Trials))

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study subjects</th>
<th>Metabolic Condition (Medication)</th>
<th>Total</th>
<th>Control condition</th>
<th>Training modality</th>
<th>Active Treatment</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Year Reference</td>
<td>% male</td>
<td>Age (y)</td>
<td>n</td>
<td></td>
<td></td>
<td>Intensity</td>
<td>Volume (min)</td>
</tr>
<tr>
<td>Yanagawa 2011&lt;sup&gt;35&lt;/sup&gt;</td>
<td>68.9%</td>
<td>68.9±3.8</td>
<td>n=16</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>AT: 71.6±3.8</td>
<td>AT=9</td>
<td></td>
<td></td>
<td>55-69% of maximal heart rate, 40–59% of VO&lt;sub&gt;2&lt;/sub&gt;max</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>CO: 70.1±3.7</td>
<td>CO=7</td>
<td></td>
<td></td>
<td>45</td>
<td>4</td>
</tr>
</tbody>
</table>
Data is presented as Mean ± SD or Median (interquartile or range) or (±SD)

y: year

min: minute

wk: week

NR: Not reported

T2DM: Type 2 diabetes mellitus

AT: Aerobic training

CO: Control

JOBA: Joba horseback riding simulation equipment

VO₂: oxygen consumption
### Table 3.2.3 Study Design and Subject Characteristics (Cross-sectional Studies)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study subjects</th>
<th>Metabolic Condition (medication)</th>
<th>Total n</th>
<th>Physical activity assessment method</th>
<th>Physical activity category</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Colberg, 2008&lt;sup&gt;32&lt;/sup&gt;</td>
<td>%male &lt;br&gt;33.8%&lt;br&gt;H: 55.5±1.0&lt;br&gt;LA: 57.5±1.3</td>
<td>T2DM (NR)</td>
<td>145&lt;br&gt;HA=74&lt;br&gt;LA=71</td>
<td>Modified (diabetes) version of the HAPAQ&lt;sup&gt;52&lt;/sup&gt; (One year recall)</td>
<td>Low Active (T2DM) High Active (Control)</td>
<td>American diabetes association criteria for diagnosis of T2DM, fasting glucose ≥126 mg/dL; insulin resistant between 100 to 125 mg/dL or diagnosed diabetes The cut-off points for MMS scores (&gt;24) and SLUMS (&gt;20 for high school educated, &lt;15 for less education) were used as the diagnosis of normal cognitive function in Community samples</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(%) Regular exercise, %</td>
<td>55.4&lt;br&gt;0.2±0.3</td>
</tr>
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</table>
Physical activity category classified according to the HAPAQ where possible (regular exercise is defined as subjects involving in at least 30 minutes of moderate aerobic exercise 3 times a week for a minimum of 1 year, while sedentary subjects engaged in 2 or fewer days of activity or activities of daily living (ADL) alone).

Data is presented as Mean ± SD or Median (IQR or range) or (±SD)

Gender is presented as %

Mean ± SD or Median (IQR or range)

Y: Year

NR: Not reported

T2DM: Type 2 diabetes mellitus

HA: Highest active

LA: Lowest physical active level

HAPAQ: Harvard Alumni Physical Activity Questionnaire

MMS: Mini-mental State Examination
SLUMS: Saint Louis University Mental Status Exam
### Table 3.2.4 Studies Design and Subject Characteristics (Cross-Sectional and Prospective Studies)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Study subjects</th>
<th>Metabolic Condition (medication)</th>
<th>Total n</th>
<th>Physical activity assessment method</th>
<th>Physical activity category a</th>
<th>Inclusion Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Devore, 2009&lt;sup&gt;33&lt;/sup&gt;</td>
<td>0%</td>
<td>T2DM (insulin treatment and oral hypoglycaemia)</td>
<td>n=1550</td>
<td>SAPAQ&lt;sup&gt;c&lt;/sup&gt; (cross-sectional)</td>
<td>3.38 (0.13-6.76)</td>
<td>Low active: 10.70 (6.77-15.50) Moderate active: 24.39 (15.54-112.23) High active: T2DM was diagnosed by a physician according to American diabetes association. Normal cognitive status was measured by neuropsychological assessment</td>
</tr>
<tr>
<td></td>
<td>% male</td>
<td></td>
<td>LA=512</td>
<td></td>
<td>10.70 (6.77-15.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age (y)</td>
<td></td>
<td>MA=520</td>
<td></td>
<td>24.39 (15.54-112.23)</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>HA=518</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Devore, 2009&lt;sup&gt;33&lt;/sup&gt;</td>
<td>0%</td>
<td>T2DM (insulin treatment and oral hypoglycaemia)</td>
<td>n=1352</td>
<td>SAPAQ&lt;sup&gt;c&lt;/sup&gt; (prospective)</td>
<td>3.38 (0.13-6.76)</td>
<td>Low active: 10.70 (6.77-15.50) Moderate active: 24.39 (15.54-112.23) High active: T2DM was diagnosed by a physician according to American diabetes association. Normal cognitive status was measured by neuropsychological assessment</td>
</tr>
<tr>
<td></td>
<td>% male</td>
<td></td>
<td>LA=NR</td>
<td></td>
<td>10.70 (6.77-15.50)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Age (y)</td>
<td></td>
<td>MA=NR</td>
<td></td>
<td>24.39 (15.54-112.23)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HA=NR</td>
<td></td>
<td></td>
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</tbody>
</table>
Physical activity category\textsuperscript{a} was classified according to the SAPAQ where (the average amount of time per week spent in the following activities during the past year: running (< 10 minutes/mile); jogging (>10 minutes/mile); walking or hiking outdoors; racquet sports; lap swimming; bicycling; aerobic dancing or use of exercise machines; other vigorous activities; and low-intensity exercise (e.g., yoga, stretching, toning)).

1 MET-hour\textsuperscript{b} is the amount of energy expended by sitting quietly for 1 hour. (MET values assigned were: 12 for running; 8 for stair-climbing; 7 for jogging, racquet sports, lap swimming, and bicycling; 6 for aerobic dancing, use of exercise machines, and other vigorous activities; and 4 for yoga, tretching, or toning.

An average of 5 reports\textsuperscript{c} was used to calculate the primary exposure over a median time period of 13.3 years (interquartile range, 12.3–13.8) between the first activity assessment and the initial cognitive interview.

Data is presented as Mean ± SD or Median (IQR or range) or (±SD)

Gender is presented as %

Y: Year

SD: Standard deviation

MD: Mean difference
NR: Not reported
T2DM: Type 2 diabetes mellitus
MET: Metabolic equivalent
HA: Highest active
MA: Moderate active
LA: Lowest physical active
SAPAQ: Self-administered physical activity questionnaire
### TABLE 3.3 COGNITIVE OUTCOMES

#### TABLE 3.3.1 COGNITIVE OUTCOMES (RANDOMIZED CONTROLLED TRIALS)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Domain</th>
<th>Method</th>
<th>Group</th>
<th>Pre-exercise (Mean ± SD)</th>
<th>Post-exercise (Mean ± SD)</th>
<th>Between group MD (95%,CI)</th>
<th>Between group ES (95%,CI)</th>
<th>Between group p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson, 2006$^{31}$</td>
<td>26</td>
<td>Memory (delayed)</td>
<td>SR$^b$</td>
<td>Exercise Control</td>
<td>6.30 ± 1.15*</td>
<td>3.65 ± 1.15*</td>
<td>-1.45 (-2.35,-0.55)</td>
<td>1.35 (0.48, 2.22)</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td></td>
<td>52</td>
<td></td>
<td>BVR$^b$</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>UTBC</td>
<td>UTBC</td>
<td>NS$^a$</td>
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<tr>
<td></td>
<td>26-52</td>
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<td>BVR$^b$</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>UTBC</td>
<td>UTBC</td>
<td>NS</td>
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<tr>
<td></td>
<td>26-52</td>
<td>Attention/ Executive function</td>
<td>TMT$^b$</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>UTBC</td>
<td>UTBC</td>
<td>NS</td>
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<td></td>
<td>26-52</td>
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<td>SIT$^b$</td>
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<td>UTBC</td>
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<tr>
<td>Citation</td>
<td>Time point (wk)</td>
<td>Outcomes</td>
<td>Method</td>
<td>Group</td>
<td>Pre-exercise (Mean ± SD)</td>
<td>Post-exercise (Mean ± SD)</td>
<td>Between group MD (95%, CI)</td>
<td>Between group Effect size (95%, CI)</td>
<td>Between group p value</td>
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<td></td>
</tr>
<tr>
<td>Baker, 2010&lt;sup&gt;34&lt;/sup&gt;</td>
<td>12-26</td>
<td>Attention/Executive function</td>
<td>VF&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>0.25</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TMTB&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>-0.21 (-0.28,-0.14)</td>
<td>0.36</td>
<td>=0.04</td>
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<td></td>
<td></td>
<td></td>
<td>TS&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>-54.49 (-68.25,-40.73)</td>
<td>0.39</td>
<td>=0.03</td>
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<td></td>
<td></td>
<td>SCWI&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>-121.88 (-155.66,-88.10)</td>
<td>0.38</td>
<td>=0.04</td>
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<td>Memory</td>
<td>SOPT&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>1.3 (-0.28,2.88)</td>
<td>0.29</td>
<td>=0.10</td>
</tr>
<tr>
<td></td>
<td>Short memory</td>
<td></td>
<td>SR&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>UTBC</td>
<td>UTBC</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Memory recall</td>
<td></td>
<td>LL&lt;sup&gt;e&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>UTBC</td>
<td>UTBC</td>
<td>NS</td>
</tr>
</tbody>
</table>
aNS was determined from p-value provided or confidence interval

bHigher scores indicate poorer function

cHigher scores indicate better function

Data with asterisk were estimated from graphs

Data is presented as Mean ± SD or Median (IQR or range) or (±SD)

wk: Week

SD: Standard deviation

MD: Mean difference

ES: Effect size

CI: Confidence interval

NR: Not reported

NS: Not significant

UTBC: Unable to be calculated
Between group effect size = (Change in Treatment – Change in Control) / Pooled baseline SD, where D indicates change.

Intra-group effect size = (post-exercise - pre-exercise) / pooled baseline SD

SR: Story Recall (immediate recall (maximal score=12) and Delayed Recall (maximal score=12))

BVR: Benton Visual Retention

TMT: Trail Making Test

SIT: Stroop Interface Test

VF: Verbal Fluency

DST: Digit Symbol Test (score=0-93), a subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R)

TMTB: Trail Making Test B

TS: Task Switching

SCWI: Stroop Color-Word Interference

SOPT: Self-Ordered Pointing Test

SR: Story Recall
LL: Learning Recall
### Table 3.3.2 Cognitive Outcomes (Non-Randomized Controlled Trials)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Domain</th>
<th>Method</th>
<th>Group</th>
<th>Pre-exercise (Mean ± SD)</th>
<th>Post-exercise (Mean ± SD)</th>
<th>Between group MD (95%,CI)</th>
<th>Between group Effect size (95%,CI)</th>
<th>Between group p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yanagawa, 2011&lt;sup&gt;35&lt;/sup&gt;</td>
<td>12</td>
<td>Verbal memory</td>
<td>Information processing speed</td>
<td>WLIM&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>21.67 ± 1.80</td>
<td>22.29 ± 1.38</td>
<td>1.27 (-0.92,3.46)</td>
<td>0.59 (-0.42, 0.60)</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WLDM&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>8.22 ± 1.86</td>
<td>7.57 ± 1.90</td>
<td>0.13 (-1.45,1.71)</td>
<td>0.08 (-0.90, 1.07)</td>
<td>1.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>WAISR-DST&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>42.44 ± 9.15</td>
<td>46.43 ± 15.30</td>
<td>4.40 (-39,14.19)</td>
<td>0.38 (-0.62, 1.38)</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Attention/Executive function</td>
<td>TMTA&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>53.44 ± 48.24</td>
<td>39.76 ± 12.57</td>
<td>12.86 (-27.55, 53.27)</td>
<td>0.46 (-0.54, 1.46)</td>
<td>0.53</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>SCWT&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>20.54 ± 11.22</td>
<td>22.57 ± 9.26</td>
<td>0.71 (-4.32,5.74)</td>
<td>0.14 (-0.84, 1.13)</td>
<td>0.79</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>TMTB&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>112.56 ± 37.08</td>
<td>134.06 ± 0.19</td>
<td>17.90 (-12.55, 48.35)</td>
<td>0.60 (-0.41, 0.41)</td>
<td>0.27</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Global cognitive function</td>
<td>MMS&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>26.33 ± 2.24</td>
<td>26.56 ± 1.99</td>
<td>0.04 (-34,1.24)</td>
<td>0.02 (-0.97, 1.00)</td>
<td>0.96</td>
<td></td>
</tr>
</tbody>
</table>
Higher scores indicate better function

Higher scores indicate poorer function

Data is presented as Mean ± SD or Median (interquartile or range) or (±SD)

wk: Week

NR: Not reported

SD: Standard deviation

MD: mean difference

ES: Effect size

CI: Confidence interval

WLIM: Word List (immediate memory), a subtest of the Alzheimer’s disease Assessment Scale

WLDM: Word List (delayed memory), a subtest of the Alzheimer’s disease Assessment Scale

DST: Digit Symbol Test (score=0-93), a subtest of the Wechsler Adult Intelligence Scale-Revised (WAIS-R)

TMTA: Trail Making Test A

TMTB: Trail Making Test B

SCWT: Stroop Color-Word Test
MMS: Mini-mental State Examination (maximal score=0-30)
<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Results</th>
<th>Calculation</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Year Reference</td>
<td>Domain</td>
<td>Method</td>
<td>Group</td>
<td>Physical activity levels</td>
<td>Between group MD (95%, CI)</td>
</tr>
<tr>
<td>Colberg, 2008</td>
<td>Cross-sectional</td>
<td>Global cognitive function</td>
<td>MMS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>HA (control)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>SLUMS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>LA (diabetes)</td>
<td>NR</td>
</tr>
<tr>
<td>Devore, 2009</td>
<td>Cross-sectional</td>
<td>Global cognitive function&lt;sup&gt;g&lt;/sup&gt;</td>
<td>TICS&lt;sup&gt;d&lt;/sup&gt;</td>
<td>HA (control)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Global cognitive function&lt;sup&gt;f,g&lt;/sup&gt;</td>
<td>Global (TICS&lt;sup&gt;d&lt;/sup&gt;, EBMT-IR&lt;sup&gt;d&lt;/sup&gt;, EBMT-DR&lt;sup&gt;d&lt;/sup&gt;, CF&lt;sub&gt;d&lt;/sub&gt;, TICS-WLDR&lt;sup&gt;d&lt;/sup&gt;, DSB&lt;sup&gt;d&lt;/sup&gt;)</td>
<td>HA (control)</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>EBMT-IR&lt;sup&gt;d&lt;/sup&gt;, EBMT-DR&lt;sup&gt;d&lt;/sup&gt;, TICS-IR, and TICS-DR&lt;sup&gt;d&lt;/sup&gt;</td>
<td>HA (control)</td>
<td>NR</td>
</tr>
</tbody>
</table>
**Table 3.3.4 Cognitive Outcomes (Prospective Study)**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Results</th>
<th>Calculation</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Year</td>
<td></td>
<td>Domain</td>
<td>Physical activity levels</td>
<td>Between group MD (95%, CI)</td>
<td>Between group ES (95%, CI)</td>
</tr>
<tr>
<td>Year Reference</td>
<td></td>
<td>Method</td>
<td>Group</td>
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<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>aDevore, 2009³³</td>
<td>Prospective</td>
<td>Global cognitive function&lt;sup&gt;g&lt;/sup&gt;</td>
<td>TICS&lt;sup&gt;g&lt;/sup&gt;</td>
<td>HA</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Global cognitive function&lt;sup&gt;e, g&lt;/sup&gt;</td>
<td>Global score (TICS&lt;sup&gt;e&lt;/sup&gt;, EBMT-IM&lt;sup&gt;e&lt;/sup&gt;, EBMT-DR&lt;sup&gt;e&lt;/sup&gt;, CF&lt;sup&gt;e&lt;/sup&gt;, TICS-WLDR&lt;sup&gt;e&lt;/sup&gt;, DSB&lt;sup&gt;e&lt;/sup&gt;)</td>
<td>HA</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>TICS-IR&lt;sup&gt;e&lt;/sup&gt;, EBMT-DR&lt;sup&gt;e&lt;/sup&gt;, TICS-IR&lt;sup&gt;e&lt;/sup&gt;, and TICS-DR&lt;sup&gt;e&lt;/sup&gt;</td>
<td>HA</td>
<td>NR</td>
</tr>
</tbody>
</table>
aSignificant difference in baseline measures was noted in paper and in our quality assessment of this trial.

bSignificance was determined from p-value provided or confidence interval.

cHigher scores indicate poorer function.

dHigher scores indicate better function.

eAnalyses of cognitive decline over 2 interviews included 1,352 women who additionally participated in the second cognitive assessment (follow-up exceeded 90% in the second and third cognitive interviews as well (mean time span over 3 interviews = 4 years)

fAn overall global score averaged together scores from all 6 of our cognitive tests (TICS<sup>d</sup>, EBMT<sup>d</sup>, CF<sup>d</sup>, TICS-WLDR<sup>d</sup>, DSB<sup>d</sup>).

gA verbal memory score averaged together scores from all 4 of our cognitive tests (EBMT<sup>d</sup> and TICS-WLDR<sup>d</sup>).

hAdjusted for age, education, initial cognitive score, time between cognitive interviews, disability indicators, use of antidepressant medication (yes/no), alcohol intake (none, 1–14 g/day, or 15 g/day), smoking (never, past, current), duration of diabetes (<5, 5–9, 10–14, or 15 years prior to initial cognitive interview), use of diabetes medication (none, oral medication only, insulin), body mass index (weight (kg)/height (m)<sup>2</sup>; <25, 25–29, or 30), and vascular factors (high blood pressure, high cholesterol, myocardial infarction, coronary artery bypass graft, transient ischemic attack, carotid surgery, and congestive heart failure—yes/no)

Data is presented as Mean ± SD or Median (IQR or range) or (±SD)

Wk: Weeks
NR: Not reported
HA: Highest active
LA: Lowest active
CI: Confidence interval
NR: Not reported
NS: Not significant
ES: Effect size
EBMT: East Boston Memory Test
EBMT: East Boston Memory Test of the Immediate Recalls and the Delayed Recalls
CF: Category Fluency
TICS: Telephone Interview for Cognitive Status + Immediate Recall
RR: Relayed Recall
DSB: Digital-Spam Backwards
TICS: Telephone Interview for Cognitive Status (maximal score=41)
MMS: Mini-mental State Examination (maximal score=30)
SLUMS: Saint Louis University Mental Status Exam
### Table 3.4.1 Insulin Resistance Outcomes (Randomise Controlled Trials)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Results</th>
<th>Calculation</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson, 2006</td>
<td>31</td>
<td>Insulin sensitivity</td>
<td>2-hour OGTT insulin levels (pmol/l)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>NR</td>
</tr>
<tr>
<td>Baker, 2010</td>
<td>26</td>
<td>Insulin sensitivity</td>
<td>2-hour OGTT insulin levels (pmol/l)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Exercise Control</td>
<td>5.90 ± 3.30 7.60 ± 2.50</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fasting plasma insulin (mU/mL)</td>
<td>Exercise Control</td>
<td>11.1±9.0 9.8±3.9</td>
<td>9.0±4.4 8.4±5.0</td>
</tr>
</tbody>
</table>
aValue in 6 month adjusted for baseline

bGDR= mean 30-minute glucose disposal rate 120 minute into the hyperinsulinemic-euglycemic clamp (HEC), adjusted for fat free mass in mg/kgFFM/min). Negative values represent high insulin sensitivity and glycemia control

Data is presented as Mean ± SD or Median (IQR or range) or (±SD)

Wk: Weeks

NR: Not reported

SD: Standard deviation

MD: Mean difference

ES: Effect size

CI: Confidence interval

OGTT: Oral glucose tolerance test

GDR: Glucose disposal rate
### Table 3.4.2 Insulin Resistance Outcomes (Non-Randomise Controlled Trials)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Results</th>
<th>Calculation</th>
<th>Statistics</th>
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</thead>
<tbody>
<tr>
<td>Author Year Reference</td>
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<td>Domain</td>
<td>Method</td>
<td>Group</td>
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</tr>
<tr>
<td>Yanagawa, 2011&lt;sup&gt;35&lt;/sup&gt;</td>
<td>12</td>
<td>Insulin sensitivity</td>
<td>GIR (mg/kg/min)</td>
<td>Exercise Control</td>
<td>Pre-exercise</td>
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<td></td>
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<td></td>
<td></td>
<td>(Mean ± SD)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>MCR (mL/kg/min)</td>
<td>Exercise Control</td>
<td>Post-exercise</td>
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<tr>
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<td></td>
<td></td>
<td>(Mean ± SD)</td>
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<td></td>
<td>Between group MD (95%, CI)</td>
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<td>Between group ES (95%, CI)</td>
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<td>Between group p value</td>
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<td></td>
<td></td>
<td>1.18 (-0.06, 2.42)</td>
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<td></td>
<td>0.59 (-0.33, 1.51)</td>
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<td>0.24</td>
</tr>
</tbody>
</table>

Data is presented as Mean ± SD or Median (IQR or range) or (±SD).

Wk: Weeks

SD: Standard deviation

MD: Mean difference

ES: Effect size

CI: Confidence interval

NR: Not reported


### TABLE 3.5 GLUCOSE HOMEOSTASIS OUTCOMES

*Table 3.5.1 Glucose Homeostasis Outcomes (Randomised Controlled Trials)*

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Results</th>
<th>Calculation</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author Year</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Watson, 2006³¹</td>
<td>26</td>
<td>Glucose tolerance</td>
<td>2-hour OGTT glucose levels (mmol/l)</td>
<td>Exercise Control</td>
<td>Between group MD (95%, CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.40 ± 1.10</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>9.40 ± 0.90</td>
<td>NR</td>
</tr>
<tr>
<td>Baker, 2010³⁴</td>
<td>26</td>
<td>Glucose homeostasis</td>
<td>FBG (mg/dL)</td>
<td>Exercise Control</td>
<td>105.0±30.0</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td>91.0±8.2</td>
<td>94.0±11.4</td>
</tr>
</tbody>
</table>

Data is presented as Mean ± SD or Median (IQR or range) or (± SD).

wk: Weeks

NR: Not reported

SD: Standard deviation

MD: Mean difference

ES: Effect size

CI: Confidence interval

OGTT: Oral glucose tolerance test
FBG: Fasting blood sugar
### Table 3.5.2 Glucose Homeostasis Outcomes (Non-Randomised Controlled Trials)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Results</th>
<th>Calculation</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author</td>
<td></td>
<td>Domain</td>
<td>Method</td>
<td>Group</td>
<td>Pre-exercise (Mean ± SD)</td>
</tr>
<tr>
<td>Year</td>
<td>Reference</td>
<td></td>
<td></td>
<td>Group</td>
<td></td>
</tr>
<tr>
<td>Yanagawa</td>
<td>2011</td>
<td>Glucose</td>
<td>HbA1c</td>
<td>Exercise</td>
<td>7.29 ± 0.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>homeostasis</td>
<td>(%)</td>
<td>Control</td>
<td>7.14 ± 0.61</td>
</tr>
<tr>
<td></td>
<td></td>
<td>FBS (mg/dl)</td>
<td></td>
<td>Exercise</td>
<td>128.44 ± 22.57</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>129.86 ± 24.72</td>
</tr>
</tbody>
</table>

Data is presented as Mean ± SD or Median (IQR or range) or (±SD).

wk: Weeks

NR: Not reported

SD: Standard deviation

MD: Mean difference

ES: Effect size

CI: Confidence interval

HbA1c: Glycosylated haemoglobin
FBS: Fasting blood sugar
### TABLE 3.6 BODY COMPOSITION

**Table 3.6.1 Body Composition (Randomised Controlled Trials)**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Domain</th>
<th>Method</th>
<th>Group</th>
<th>Pre-exercise (Mean ± SD)</th>
<th>Post-exercise (Mean ± SD)</th>
<th>Calculation</th>
<th>Statistics</th>
<th>Calculation</th>
<th>Statistics</th>
<th>Calculation</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson, 2006</td>
<td>26</td>
<td>IAFA (cm²)</td>
<td>Computer Tomography</td>
<td>Exercise Control</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>UTBC</td>
<td>NR</td>
<td>NR</td>
<td>UTBC</td>
<td>NR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>NR</td>
<td>24.7 ± 3.2</td>
<td>26.7 ± 4.3</td>
<td>-0.50 (-2.93, 1.93)</td>
<td>-0.13 (-0.75, 0.49)</td>
<td>0.16</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baker, 2010</td>
<td>26</td>
<td>Fat (%)</td>
<td>Dual energy X-ray absorptiometry</td>
<td>Exercise Control</td>
<td>NR</td>
<td>37.7 ± 6.6</td>
<td>42.6 ± 7.1</td>
<td>-0.00 (-5.62, 5.62)</td>
<td>0.00 (-0.79, 0.79)</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Control</td>
<td>NR</td>
<td>36.1 ± 6.0</td>
<td>41.0 ± 7.6</td>
<td>-0.00 (-5.62, 5.62)</td>
<td>0.00 (-0.79, 0.79)</td>
<td>1.00</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Data is presented as Mean ± SD or Median (IQR or range) or (±SD).

Fat% presented as percent fat distributed across the body.

IAFA: Intra-abdominal fat area

BMI: Body mass index

wk: weeks
SD: standard deviation
MD: mean difference
NR: not reported
ES: Effect size
CI: confidence interval
UBC: Unable to be calculated
### Table 3.6.2 Body Composition (Non-Randomised Controlled Trails)

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Domain</th>
<th>Method</th>
<th>Group</th>
<th>Pre-exercise (Mean ± SD)</th>
<th>Post-exercise (Mean ± SD)</th>
<th>Calculation</th>
<th>Statistics</th>
<th>Calculation</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yanagawa, 2011\textsuperscript{55}</td>
<td>12</td>
<td>Fat (%)</td>
<td>NR</td>
<td>NR</td>
<td>Exercise</td>
<td>16.24 ± 1.404</td>
<td>21.47 ± 1.648</td>
<td>NR</td>
<td>NR</td>
<td>0.67 (-0.34, 1.69)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Data is presented as Mean ± SD or Median (IQR or range) or (± SD).

Fat% presented as percent fat distributed across the body.

IAFA: Intra-abdominal fat area

wk: weeks

SD: standard deviation

MD: mean difference

NR: not reported

ES: Effect size

CI: confidence interval


<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Results</th>
<th>Calculation</th>
<th>Statistics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Year Reference</td>
<td></td>
<td>Domain</td>
<td>Method</td>
<td>Group</td>
<td>Pre-exercise (Mean ± SD)</td>
</tr>
<tr>
<td>Watson, 2006</td>
<td>26, 52</td>
<td>Peak oxygen uptake (ml/kg/min)</td>
<td>Submaximal aerobic exercise (treadmill test)</td>
<td>Exercise Control, Exercise Control</td>
<td>29.50 ± 7.10, 27.40 ± 5.60</td>
</tr>
<tr>
<td>Baker, 2010</td>
<td>26</td>
<td>Peak oxygen uptake (L/min)</td>
<td>Maximal aerobic exercise (treadmill test, stationary bicycle, or elliptical trainer)</td>
<td>Exercise Control</td>
<td>1.79 ± 0.60, 1.69 ± 0.30</td>
</tr>
</tbody>
</table>
Effect size model was adjusted for β-blocker use.

Data is presented as Mean ± SD or Median (IQR or range) or (±SD)

wk: weeks

MD: Mean difference

SD: Standard deviation

ES: Effect size

CI: Confidence interval

NR: Not reported
TABLE 3.8 PLASMA Aβ₄₂ METABOLIC OUTCOMES

<table>
<thead>
<tr>
<th>Citation</th>
<th>Time point (wk)</th>
<th>Outcomes</th>
<th>Results Pre-exercise (Mean ± SD)</th>
<th>Results Post-exercise (Mean ± SD)</th>
<th>Calculation Between group MD (95%, CI)</th>
<th>Calculation Between group ES (95%, CI)</th>
<th>Statistics Between group p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author, Year Reference</td>
<td>26</td>
<td>Aβ₄₂ᵃ</td>
<td>87.1 ± 64.9</td>
<td>66.0 ± 42.7</td>
<td>66.0 ± 42.7</td>
<td>79.9 ± 43.8</td>
<td>-42.10 (-96.52, 12.32)</td>
</tr>
<tr>
<td>BAKER (2010)</td>
<td></td>
<td>ELISA</td>
<td>Exercise Control</td>
<td>Control</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ᵃHigher Aβ₄₂ represents the worse function.
ᵇNegative effect size favor high active group in all cases, as expected lower Aβ₄₂.

Data is presented as Mean ± SD or Median (IQR or range) or (±SD)

wk: Weeks  Plasma levels of Aβ₄₂

SD: Standard deviation

MD: Mean difference

ES: Effect size

CI: Confidence interval

ELISA: Enzyme-linked immunosorbent assay

Aβ₄₂: Amyloid β₄₂
<table>
<thead>
<tr>
<th>Citation</th>
<th>Cognitive measurement</th>
<th>IR measurement</th>
<th>Time since last exercise bout</th>
<th>Relationship</th>
<th>r</th>
<th>p</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson, 2006&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Delayed memory</td>
<td>2-h oral glucose tolerance test insulin level (pmol/L)</td>
<td>NR</td>
<td>Change in delayed memory and change 2-hour oral glucose tolerance test insulin level</td>
<td>r= -0.52</td>
<td>p= 0.047</td>
<td>AT plus AHAS2ED group only</td>
</tr>
<tr>
<td>Colberg, 2008&lt;sup&gt;32&lt;/sup&gt;</td>
<td>General cognitive function</td>
<td>HOMA-IR Insulin (IU/mL)</td>
<td>NR</td>
<td></td>
<td>r= -0.19</td>
<td>p= 0.02</td>
<td>Control group (AHAS1ED)</td>
</tr>
<tr>
<td>Yanagawa, 2011&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Delayed memory</td>
<td>Euglycaemic Clamp (glucose infusion rate (mg/kg/min) and metabolic clearance rate (mL/kg/min))</td>
<td></td>
<td>Change in word recall (immediate) and change in glucose infusion rate Change in word recall (immediate) and change in metabolic clearance rate</td>
<td>r= 0.64</td>
<td>p= 0.024</td>
<td>Pooled sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>r= 0.575</td>
<td>p= 0.051</td>
<td></td>
</tr>
</tbody>
</table>

AHAS1ED: American Heart Association Step 1 Eucaloric Diet
AHAS2ED: American Heart Association Step 2 Eucaloric Diet
HOMA: Homeostatic Model Assessment

IR: Insulin resistance

NR: not report
TABLE 3.10 RELATIONSHIP BETWEEN CHANGES IN COGNITION AND CHANGES IN GLUCOSE HOMEOSTASIS

<table>
<thead>
<tr>
<th>Citation</th>
<th>Cognitive measurement</th>
<th>Glucose Homeostasis</th>
<th>Time since last exercise bout</th>
<th>Relationship</th>
<th>r</th>
<th>p</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson, 2006&lt;sup&gt;31&lt;/sup&gt;</td>
<td>NR</td>
<td>Fasting Glucose (mmol/l)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yanagawa, 2011&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Delayed memory</td>
<td>HbA1c (%)</td>
<td>NR</td>
<td>Change in word recall and change in HbA1c</td>
<td>r=-0.627</td>
<td>p=0.029</td>
<td>Pooled sample</td>
</tr>
<tr>
<td></td>
<td>Executive function</td>
<td>Fasting blood sugar (mg/dL)</td>
<td>NR</td>
<td>Change in Trail Making Test B and change in fasting blood sugar</td>
<td>r=0.611</td>
<td>p=0.035</td>
<td></td>
</tr>
</tbody>
</table>

HbA1c: glycosylated hemoglobin

NR: not reported
TABLE 3.11 RELATIONSHIP BETWEEN CHANGES IN COGNITION AND CHANGES IN BODY COMPOSITION

<table>
<thead>
<tr>
<th>Citation</th>
<th>Cognitive measurement</th>
<th>Body composition</th>
<th>Time since last exercise bout</th>
<th>Relationship</th>
<th>r</th>
<th>p</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Watson, 2006&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Delayed memory</td>
<td>Intra-abdominal fat (cm²)</td>
<td>NR</td>
<td>NR</td>
<td>r=0.62,</td>
<td>P=0.024</td>
<td>Control group (AHAS1ED)</td>
</tr>
<tr>
<td>Baker, 2010&lt;sup&gt;34&lt;/sup&gt;</td>
<td>NR</td>
<td>Fat%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Yanagawa, 2011&lt;sup&gt;35&lt;/sup&gt;</td>
<td>NR</td>
<td>Fat%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

AHAS1ED: American Heart Association Step 1 Eucaloric Diet

NR: Not reported
FIGURE 3.1 FLOW CHART OF PAPERS IDENTIFIED FROM SEARCH STRATEGY

- **Intervention**: n=1,269,586
- **Condition**: n=682,149
- **Outcome**: n=2,132,265

Combined Search: n=5754

- Excluded on basis of title or abstract: n=5722

Potentially Eligible Papers: n=32

- Papers excluded: n=27
  - Reasons:
    - No cognitive outcomes: n=9
    - Animal trials: n=18

Included Papers: n=5

- Randomised Controlled Trials: n=3
- Nonrandomised Controlled Trials: n=1
- Observational Studies: n=2
CHAPTER 4

RATIONALE AND METHODOLOGY OF THE GREAT2DO TRIAL: A RANDOMISED DOUBLE-BLIND, SHAM-EXERCISE CONTROLLED TRIAL OF POWER TRAINING IN OLDER INDIVIDUALS WITH TYPE 2 DIABETES MELLITUS
4.1 ABSTRACT

OBJECTIVES - The objective of the study was to assess the efficacy of power training as a therapeutic intervention in older adults with type 2 diabetes mellitus (T2DM), as well as its effects on comorbidities and physical function. This chapter provides the detailed rationale and methodology of a randomised double-blind, SHAM-exercise controlled trial of the Graded Resistance Exercise and T2DM in Older adults (GREAT2DO) Study. The cognitive function outcomes, which are the primary focus of this thesis, were secondary outcomes of the overall trial.

METHODS - Community dwelling men and women were recruited into a randomised controlled trial (RCT). Primary inclusionary criteria were sedentary, stable disease, and aged 60 years or older, with previously diagnosed T2DM. Exclusionary criteria included uncontrolled or fasting glucose consistently > 11.1mmol/L, significant cognitive impairment, non-ambulatory status or lower extremity amputation other than toes, current alcohol or substance abuse, contraindications to performance of resistance training or rapidly progressive or terminal illness. The study enrolled 103 subjects from July 2006 to December 2009, concluding the 12-month RCT phase in January 2011. Participants were randomly allocated using a 1:1 ratio via computer-generated blocks of 4, stratified by sex and use or non-use of insulin to either a supervised experimental group or SHAM-exercise control group (3 days/week × 12 moths). The experimental POWER training group performed high intensity high velocity power training (at 80% of maximal strength) of 8 major muscle groups, 3 days per week for 12 months. The SHAM-exercise group performed 3 sets of 8 repetitions on the same machines, but with no loading beyond the bar of the machine and the loads were non-progressive. Primary outcomes measured at baseline and 12 months were insulin resistance and glucose homeostasis. Secondary outcomes were neuropsychological test scores, psychological well-being, quality of life, cardiovascular and musculoskeletal function,
body composition, adipokines, and systemic and cytokine inflammation.

CONCLUSIONS - This study included all design and reporting requirements for RCTs, adhering precisely to Consolidated Standards of Reporting Trials (CONSORT) guidelines. The specific aim of this sub-study of the GREAT2DO trial was to determine whether the P training intervention in diabetes, a major risk factor for Alzheimer’s disease and vascular dementia, can reduce early decline in cognitive function and also identify the potential underlying mechanisms of adaptation in older adults at risk of further cognitive decline.
4.2 INTRODUCTION

The prevalence of T2DM increases with age\(^1,2\). This disease and associated comorbidities and complications such as cardiovascular disease, nephropathy, retinopathy, neuropathy, peripheral vascular disease and depression have a substantial negative impact on cerebral structure and function, quality of life, and higher mortality rates. Organ damage is a serious consequence of inflammation, abnormal glucose and lipid metabolism, and cardiovascular disease is the leading cause of morbidity and mortality in T2DM. Similarly, cognitive impairment can advance to dementia, a major challenge to sufferers, their caregivers, and the health care system.\(^3\) Clearly there is a continuing and urgent need to reduce this burden and define the best strategies to achieve this.

Recent studies suggest that T2DM is a risk factor for cognitive deficits in older adults.\(^4,5\) The underlying mechanisms are multifactorial. In older individuals with T2DM, the presence of much comorbidity likely contributes to this increased risk of cognitive impairment. Previous studies have reported that transient ischemic attacks (TIAs), stroke, or atherosclerosis are strong predictors of cognitive decline.\(^6\) Associations between high glycosylated haemoglobin (HbA1c) and cognitive decline have been demonstrated in older and middle aged individuals.\(^7\) Also, in older patients with T2DM, acute deficits in working memory and attention have been observed in the hyperglycaemic state during a glucose clamp.\(^8,9\) are some of the central abnormalities linking T2DM and dementia, and loss of muscle mass has been recently potentially implicated as well.\(^10\) A sedentary lifestyle is associated with increased risk of dementia, and it has been observed that regular moderate exercise during midlife is related to higher cognitive performance in later life.\(^11\) Physical inactivity also results in a chronic elevation of inflammatory biomarkers,\(^12\) which are also
observed in patients with dementia and T2DM. Furthermore, inflammatory mediators such as tumour necrosis factor alpha (TNF-α) are secreted from abdominal adipose tissue and previous findings have shown that abdominal obesity (more than whole body obesity) is associated with risk of cognitive decline in late life. In addition, higher muscle mass is associated with a 43% decreased risk of Alzheimer disease. Each of these diabetes-related comorbidities is potentially modifiable, and therefore an appropriate target for interventions.

The management of T2DM often includes a combination of dietary modifications, medications and the prescription of exercise. Specifically, the benefits of exercise include improved glycaemic control, increased insulin sensitivity, decreased adiposity, decreased inflammation, decreased blood pressure and decreased blood lipids, as well as treatment for many of the common comorbidities of T2DM, including obesity, cardiovascular disease, osteoarthritis, peripheral vascular disease, and depression, among others. Notably, these risk factors have been shown to improve cognitive function in other cohorts, although data on the effects of modifying them in T2DM specifically in relation to cognitive risk are lacking.

Current exercise guidelines for the management of T2DM encourage the use of aerobic or endurance training, as well as progressive resistance training (PRT) or weight lifting. PRT holds a unique advantage over endurance training in its ability to simultaneously decrease adiposity and increase skeletal muscle mass and associated metabolic and functional changes. PRT can address all components of the progression of type 2 diabetes. It has positive effects on performance tasks including muscle strength, 6-minute walk distance, aerobic capacity, balance, gait speed, chair stand, stair-climbing speed and power, and physical function.
Improvements in body composition following PRT are likely to contribute to the improvements in insulin sensitivity, glucose homeostasis, blood pressure, dyslipidaemia, physical performance, and markers of inflammation and catabolism, ultimately leading to improvements in cognitive function and quality of life in older adults with T2DM.\textsuperscript{12}

PRT has been shown to have positive effects on growth factors [e.g., brain-derived neural growth factor (BDNF) and insulin-like growth factor 1 (IGF-1)]\textsuperscript{27, 28} and the regulation of systemic inflammation,\textsuperscript{29, 30} so addressing multiple components related to brain function of older adults. Notably, PRT may sometimes be a more realistic exercise option in this cohort, as it is more feasible in elders with severe mobility impairment related to obesity, osteoarthritis, peripheral vascular disease, peripheral neuropathy or balance problems, accordingly having the potential for long-term adherence. In addition, PRT may be an appropriate and effective tool for the management of T2DM, and the beneficial whole body adaptation to PRT may lead to improvements in the cognitive health of individuals with T2DM.

A variant of PRT, power training (POWER), involves maximal velocity concentric (shortening) contractions and slow velocity eccentric (lengthening) contractions. The rationale for this type of training lies in the optimal recruitment of Type II muscle fibres induced by high velocity training,\textsuperscript{31, 32} and the knowledge that these are the specific fibres most atrophied with ageing and inactivity.\textsuperscript{33-36} In addition, losses of muscle power occur earlier and more precipitously than losses of muscle strength in older adults.\textsuperscript{37} Finally, muscle power has been more closely linked to functional disability and fall risk than muscle strength, thus building a rationale for POWER training in older adults as the specific modality of resistance training to employ.
As reviewed in Chapter 3, there have been two randomised controlled trials (RCTs), one non-randomised controlled trial, and two observational studies investigating physical activity or aerobic exercise in adults with T2DM or impaired glucose tolerance examining cognitive outcomes. However, no published rigorous clinical trials have investigated the central and peripheral benefits of power training for improved cognitive function in this cohort.

At the time of initiation of this trial the effects of resistance training in older adults with T2DM were just beginning to emerge. These studies were comprised of cohorts of participants, and only lasted for 3 and 4 months respectively. More recent studies also reported PRT has demonstrated benefits including improved fasting plasma glucose, HbA1C, insulin sensitivity as well as decreased abdominal adiposity and increased lean tissue in older adults with T2DM. These studies had some design flaws, including small sample sizes limiting conclusions. The aim of the overall GREAT2DO study was to rigourously investigate the effects of a 12-month power training program in older adults with T2DM. The hypothesised adaptations (see Figure 1) included changes in fitness, body composition, glucose homeostasis, insulin resistance, inflammation, body composition, physical performance, exercise capacity, and neuropsychological function. The GREAT2DO trial provided a unique opportunity, in the context of an RCT, to further address the relationship between cognitive function and T2DM, associated risk factors, and the ability to alter the trajectory of cognitive decline in this high risk cohort.

The remainder of this chapter will outline the methodology of the components of the GREAT2DO study specific to this thesis. A detailed description of this methodology can be found in the
Appendix A, Appendix B, and Appendix C.

4.3 METHODS

4.3.1 Study Design

The GREAT2DO trial is a longitudinal double-blind randomised, SHAM-exercise controlled clinical trial. Participants (n=103) were randomised to the experimental (high intensity, high velocity power training (POWER), or control condition (SHAM low intensity, non-progressive resistance training), for 12 months, in addition to usual medical care, with participants blinded to investigators’ hypotheses as to which was the experimental group. Blinded outcome assessments were conducted at 0, 6 and 12 months in all participants regardless of adherence level. Only baseline and 12-month outcomes were analysed for this thesis. Follow-up was continued for a total of 6 years, which is on-going, and is outside of the scope of this thesis.

The trial was registered with the Australian Clinical Trials Registry (ACTR) (ACTR No: ACTRN12606000436572). Ethical approval was obtained from Ethics Review Committee (Royal Prince Alfred Hospital (RPAH) Zone), Sydney South West Area Health Service (Ethics Committee Protocol No: X04-0096) and written informed consent was obtained from all participants. The assessments were conducted at Cumberland Campus of University of Sydney in Lidcombe New South Wales (NSW) Australia. Computerised Tomography (CT) Scans were performed at the Radiology Department of RPAH in Camperdown NSW Australia. The exercise training was conducted at either the Harbord Diggers Memorial Club (Freshwater Rehabilitation) in Manly NSW Australia or the Centre for STRONG Medicine, Balmain Hospital in Balmain NSW Australia.
Objectives and hypothesis

The primary objective of the GREAT2DO trial was to determine the efficacy of high intensity, high velocity progressive resistance training (POWER) on insulin resistance and glucose homeostasis in older adults with T2DM and metabolic syndrome, as measured by Homeostatic Model of Assessment of Insulin Resistance (HOMA2-IR) and HbA1c, as well as its effects on many secondary outcomes, including the focus of this thesis, cognitive function. Our secondary aim was to identify potential mechanisms of benefit for hypothesised cognitive function improvements, in particular modulation of cardiovascular risk profile, systemic inflammatory cytokines, growth factors, fitness levels and physical performance, and body composition.

Primary hypotheses of the GREAT2DO Study

Twelve months of supervised power training will significantly improve glucose homeostasis and insulin sensitivity relative to a SHAM exercise control condition (low intensity, slow velocity, non-progressive training).

Secondary hypotheses of the GREAT2DO

1. Power training will improve cognitive outcomes in the POWER training group in the domains of memory, information processing speed, attention, and executive function, relative to the SHAM control condition.

2. Power training will improve body composition, ambulatory blood pressure, cardiovascular risk profile including systemic and adipose tissue inflammation, resting metabolic rate, skeletal muscle morphology and metabolism, aerobic and musculoskeletal exercise capacity, habitual activity levels, sleep quality, psychosocial function, quality of life, gait and balance and physical function compared to the SHAM exercise control group.
3. Improvements in insulin sensitivity and glucose homeostasis, body composition, systemic inflammation and adipokines will be related to cognitive improvements at 12 months.

4.3.2 Sample Size Estimates

Sample size estimates were driven by hypothesised differences between participants randomised to receive POWER, compared to those randomised to receive SHAM exercise for the primary outcomes of the GREAT2DO trial: insulin sensitivity and HbA1c. Effect sizes (ESs) were calculated based on an average of published studies of PRT in diabetes/obesity\textsuperscript{22, 38, 49} (Table 4.1), and the largest available standard deviations used for conservative estimates of ES, as no previous studies of power training in this cohort exist. For these calculations, $\beta$ was set at 90\%, and $\alpha$ at 0.05, and a 10\% loss to follow-up was assumed. Effect sizes were calculated using G*Power 3.1.2 (Kiel, Germany).\textsuperscript{50} Sample size estimates for this cognitive sub study of GREAT2DO ($\alpha$ 0.05, $\beta$ 0.20) were based on planned comparisons for the main effects of POWER compared to SHAM exercise on our primary cognitive outcome: global cognitive function. Meta-analyses\textsuperscript{51} and review of published RCTs\textsuperscript{52} in older adults report ESs for a range of cognitive outcomes of approximately 0.59 for PRT, compared to 0.15 for control groups. Thus, we had sufficient power based on our primary outcome calculations to show an ES of 0.59 for the main effects of POWER vs. SHAM exercise ($n$ 47/group $\times$ 2 = 94) for this secondary cognitive outcome as well. According to our estimates, and assuming a dropout 10\% over one year, we inflated sample size needs for approximately 10\% drop out rate to account for anticipated attrition ($n$ =103).

4.3.3 Study Population

Between July 2006 and November 2009, 103 participants were recruited and randomised to receive
either 12 months of high intensity, high velocity power training (POWER) or SHAM exercise (low intensity, slow velocity, non-progressive exercise; SHAM). Participants were given no dietary or pharmacological treatment or counselling, but continued to be under their usual medical care and nutritional advice from their usual health care providers for the duration of the study.

4.3.4 Inclusion and Exclusion Criteria

Inclusionary criteria

Inclusionary criteria were based on diagnosed T2DM, age, and physical activity level. Participants were community-dwelling persons aged 60 or above and insufficiently active (no PRT; structured exercise \(\leq 1/\text{week} \); less than 150 min / week low or moderate-intensity walking or other aerobic exercise). Participants could be treated with diet alone, oral medications or insulin or combination at the time of enrolment.

Exclusionary criteria

Exclusionary criteria included significant cognitive impairment (dementia diagnosed or inability to understand informed consent), non-ambulatory status or lower extremity amputation other than toes, current alcohol or substance abuse, inability to comply with study requirements over the course of one year due to travel plans or other commitments, and specific contraindications to resistance training exercise, such as unstable cardiovascular disease, unrepairs aortic aneurysm, symptomatic hernias, proliferative diabetic retinopathy, or rapidly progressive or terminal illness. Temporary exclusions (any change in dosage or type of diabetic medications within the past 3 months, retinal laser surgery within 6 weeks, uncontrolled hypertension) were resolved prior to study enrolment and screening procedures. All inclusionary and exclusionary criteria were
determined by telephone screening questionnaire, review of medical records, and in-person history, physical exam, and maximal exercise tolerance testing by the study physician prior to enrolment.

4.3.5 Recruitment and Screening

Participants were recruited from newspaper advertisements, Diabetes Australia newsletter pamphlets, and direct communication to general practitioners and University of Sydney databases of volunteers. Subjects were screened for eligibility via initial telephone questionnaire, and the study enrolled 103 participants from July 2006 to December 2009, completing in January 2011. After confirming interest with eligible participants, an introductory letter was sent with information for assessment dates. A request for permission to access medical records was included and a medical release letter was sent to the general practitioner (GP) requesting patient assessment information. If there were no reasons for exclusion reported from the GP, a patient assessment information pack was given to each participant including all the details and dates of assessments. Confirmation letters were also sent at 6- and 12-months for follow-up assessments. All details and documents related to recruitment and screening are presented in the Appendix A.

4.3.6 Randomisation, Allocation and Concealment

Randomisation was at the level of the individual patient, stratified by sex and use or non-use of insulin, in blocks of 4 via a computer-generated randomisation scheme. The sequential treatment assignments were based on a computer-generated randomisation scheme (http://www.randomization.com, created by Dr Gerard E. Dallal, Tufts University). Randomization occurs at the completion of the entire baseline assessment. Where randomization occurs in person, assignments would be placed in sealed opaque envelopes and delivered to
subjects by an independent researcher with subjects designated to 12 month of an experimental POWER group (blue group) or SHAM exercise group (green group).

An investigator not involved in the study performed randomisation. Randomisation was concealed by emailing the randomisation assignment to the blinded study assessor at the conclusion of all baseline testing, who disclosed this information to the participant via telephone call. Two groups had an equal volume and frequency of contact with trainers in the 12 months of the study. All primary and secondary outcomes were obtained and analyzed by blinded assessors on different days to the training programs.

4.3.7 Intervention

Experiment intervention protocol: power training (POWER)

Experimental participants received high intensity power training of 8 major muscle groups 3 days per week under full supervision of research staff, using pneumatic resistance equipment (Keiser Sports Health Equipment, Ltd. Fresno, CA, USA). All trainers were Exercise and Sport Science Australia approved exercise physiologists, other allied health professionals with expertise in exercise and chronic disease treatment, or postgraduate students in exercise physiology at the University of Sydney. All exercise was supervised in the clinic/gym and overseen by onsite and offsite physicians via weekly case conferences. The exercises targeted large symmetrical muscle groups of the arms, legs, and trunk: seated row, chest press, leg press, knee extension, hip flexion, hip extension and hip abduction. A version of PRT known as power training was employed, in which the concentric contraction (lifting) was done as quickly as possible, while the eccentric contraction (lowering) was done over 4 seconds. The choice of power training as opposed to
traditional slow velocity PRT was based on a number of important factors:

1. Power training has never been investigated in older adults with T2DM.

2. Loss of muscle power is more precipitous than loss of muscle strength in older adults\textsuperscript{37}

3. Low muscle power is more closely related to functional impairment than low muscle strength in older adults\textsuperscript{53}

4. High intensity power training improves muscle strength, power and endurance and improves power more than slow velocity progressive resistance training.\textsuperscript{54}

5. The recruitment of atrophied Type II fibres (which are most closely related to losses of power and muscle mass in sarcopenia)\textsuperscript{55} is optimised by the requirement for both high velocity and high force contractions which define power training.\textsuperscript{54}

6. The cognitive requirements of generating maximal velocity with each contraction in power training may theoretically engage central nervous system (CNS) mechanisms that would stimulate neural and well as muscular adaptations better than slow velocity PRT.

For each exercise, participants performed 3 sets of 8 repetitions (2 sets of 8 on each leg for hip flexion, hip extension and hip abduction). The intensity was set at 80\% of the most recently determined peak strength (one repetition maximum, 1RM), re-assessed every 4 weeks. Where 1RM testing was not feasible, resistances were increased by targeting a Borg scale \textsuperscript{56} rating of perceived exertion between 15 and 18, which approximates 80\% of the 1RM.

As we age, muscle power fades even more swiftly than strength does. Using heavy loads during explosive resistance training (known power training) has been shown to be a safe and effective method for improving neuromuscular power and other physical performance outcomes in older adults compared to low velocity strength training alone.\textsuperscript{125} Although there are non-cognitive
reasons to study this form of training in older adults with diabetes, high speed power training had a positive effects on metabolic health in this cohort.

Power training was based on the fact that the attempt to contract at high velocity force contractions specifically is known\textsuperscript{126} to target a greater recruitment of type 2 fibers and increase neural stimulation than slow velocity contractions. Moreover, training novices to contract rapidly against a heavy load includes a cognitive component to the training session as the participant thinks about and plans for each maximal velocity contraction, which is more focused, difficult, and engaging than slow velocity training.

Control group intervention: SHAM

The SHAM exercise group trained on the same equipment, 3 times a week, under full supervision from the same trainers at different times of the day so as to remain blinded to the investigators’ hypotheses, with both interventions offered as potentially beneficial. These participants performed 3 sets of 8 repetitions on the same machines, but with no loading beyond the bar of the machine, using 1-2 second concentric and eccentric contraction speed. No interim 1RM testing and no progression took place. This regimen has been shown to produce minimal change in muscle function or mass, functional status, mobility, depression, aerobic capacity, or other clinical outcomes.\textsuperscript{54}

4.3.8 Adverse Events

A weekly questionnaire administered by a trainer, in person or by phone was used to monitor adverse events. Furthermore, any changes in health status, medication, or health care utilisation
and the reasons for any missed sessions were determined in all participants. Any musculoskeletal or cardiovascular event attributable to testing or training was defined *a priori* as an adverse event.\(^{57}\)

### 4.3.9 Outcome Measures

The primary outcomes of this study were HOMA2-IR, measured 96 hours after the last exercise bout in each participant, and HbA1c. The time interval of 96 hours was chosen to minimize any potential residual effects of the last bout of resistance training on insulin sensitivity,\(^{58-60}\) as we were primarily interested in long-term training adaptations. The secondary outcome that was the focus of this thesis was cognitive function, including domains of memory, information processing speed, attention/executive function, and global cognitive function. Other secondary outcomes included all of the components of metabolic syndrome, body composition, cardiovascular profile, exercise capacity, functional performance, health status, measures of energy expenditure, physical activity and quality of life. It was hypothesised that improvements in cognitive function would be related to the chronic changes in insulin sensitivity and glucose homeostasis, as well as changes in adiposity, skeletal muscle mass, exercise capacity, and inflammatory profile of participants.

All measurements were completed at baseline, 6 and 12 months in the POWER and SHAM participants by blinded assessors at a laboratory facility separate from the training site, to prevent un-blinding of assessors. A 24-hour food recall was performed on the day of the baseline assessment, and participants were asked to follow the same diet prior to subsequent assessments at 12 months. The domains of assessment of the GREAT2DO trial at each time-point were the following:

**Insulin Resistance and Glucose Homeostasis:**
HOMA2 computer model for insulin resistance (HOMA2-IR), insulin sensitivity (HOMA2-%S) and beta cell function (HOMA2-%B), fasting glucose, HbA1c, insulin and c-peptide levels, diabetic medication inventory and dosages.

**Cardiovascular Disease Profile:**
Heart rate variability, pulse wave velocity, pulse wave analysis, ankle-brachial index (ABI), blood pressure (24-hr ambulatory, brachial, central, and postural).

**Lipid Metabolism:**
Intramuscular lipid content estimated from CT scan attenuation of thigh muscle, total, low density, high density cholesterol, triglycerides.

**Muscle Metabolism:**
Heat Shock Protein 72 (HSP72), phospho-Jun N-terminal Kinase (pJNK), Tumour Necrosis Factor-α (TNF-α), Insulin-like Growth Factor-1 (IGF-1), Interleukin-6 (IL-6) in vastus lateralis muscle biopsies.

**Adipokines, Inflammatory Markers:**
High Molecular Weight (HMW) Adiponectin, total Adiponectin, Adiponectin ratio, TNF-α, and IL-6 in adipose tissue biopsies. C-reactive protein (CRP), HMW Adiponectin, total Adiponectin, and Adiponectin ratio in serum.

**Exercise Capacity and Functional Status:**
Muscle strength, power, and endurance, habitual and maximal gait speed, static and dynamic balance, six-minute walk distance (6WMD), chair stand time, and stair climb power.

**Body Composition:**
Anthropometry, total fat mass and skeletal muscle mass via bioelectrical impedance, waist circumference, neck circumference, BMI, sagittal diameter, abdominal visceral and subcutaneous adipose tissue area, thigh muscle area, mid-thigh muscle subcutaneous adipose tissue area, mid-thigh muscle intermuscular adipose tissue area, and mid-thigh muscle attenuation by CT scan.

**Resting Metabolic Rate:**
Assessed over a 30-min steady-state period via indirect calorimetry.  

**Energy Balance:**
Habitual physical activity, sleep, and sedentary behavior via the Physical Activity Scale for the Elderly (PASE) and accelerometry (Actigraph; ActiGraph LLC, Pensacola, FL, USA) and dietary intake (Food Frequency Questionnaire of Bloch).

**Psychosocial Function and Quality of Life:**
Geriatric depression scale, Ewart's Self-efficacy Scale, Pittsburg Sleep Quality Index, and Medical Outcomes Survey Short Form-36 (SF-36) version two questionnaires.

**Cognitive Function:**
Word List subtests of the Consortium to Establish a Registry for Alzheimer’s disease (CERAD),
The following methodology relates to the domains of assessment specific to this thesis. A more detailed methodology for these outcomes can be found in Appendix B.

**Anthropometry**

Morning fasting stretch stature (wall-mounted Holtain stadiometer, Holtain Limited, Crymych Pembs., UK) was measured in triplicate to the nearest 0.1cm. The participant was barefoot with the feet together and heels, buttocks, and shoulder blades against the wall, or as close to this position as possible (if the vertical position of the body was distorted due to skeletal pathology it may have been just the buttocks against the wall mount). The head of the participant was positioned in the Frankfort plane. The participant was asked to take a deep breath, and the investigator applied upward pressure using a pistol grip to achieve maximal elongation of the spinal column. The headboard was then lowered onto the participant’s head to attain the height measurement. The average of the three values was used.

Naked weight [weight in gown (kg) – weight of gown (kg)] was measured in the morning, with the patient fasting, in triplicate to the nearest 0.01kg. The average of the three values was used. The gown was weighed prior to being worn by the participant. Participants were instructed to change into the gown, removing all clothing (except underwear), jewellery and accessories where possible.

Waist circumference (WC) was obtained with Lufkin (W606PM) flexible steel tape measure by a
number of methods for data collection and the ISAK protocol was used for this analysis. Measures were recorded by an experienced anthropometrist with technical measurement errors <1%.

Demographics, Health status, Medications and Treatment Plan

Participants were asked routine questions to obtain demographic information, as well as their current health status relating to the presence of other chronic diseases. Participants also provided a list of all their current medication and dosages. Medical records were also hand-searched to extract any information not provided by the participant. Each participant’s treatment plan in individual with diabetes was then determined and scored as either diet only, oral hypoglycaemic only, insulin only or oral hypoglycaemic and insulin.

Whole Body Measures of Body Composition

Total fat mass and skeletal muscle mass were determined using bioelectrical impedance analysis (BIA; RJL Systems, Inc., Clinton, MI, USA). All participants were fasting and BIA was performed at a similar time of day for all participants, after a minimum 12-hour fast. BIA was performed on the right side for all participants, with the participant supine, wearing only the gown (as described for naked weight). The signal electrode of the right hand was placed on the proximal interphalangeal joint of the middle finger, while the detecting electrode was placed on the dorsal aspect of the wrist along an imaginary line bisecting the styloid process of the ulna. The signal electrode of the right foot was placed over the base of the proximal phalange of the second toe. The detecting electrode was placed on the edge on the anterior aspect of the ankle along an imaginary line bisecting the medial malleolus. Participants were instructed to have their
arms by their side and their legs apart so their thighs were not touching if possible. The presence of a pacemaker is a contraindication for the use of BIA, and thus, participants with pacemakers were excluded from this measurement. Percent body fat and fat-free mass were estimated using bioelectrical impedance (BIA-101: RJL Systems, Detroit, MI, USA). The average of 3 measurements taken early in the morning after a 12-hour fast, was used to calculate fat mass and fat-free mass using the formula developed by Lukaski and colleagues for older adults. Skeletal Muscle Mass was calculated from the following formula:

\[
\text{Skeletal Muscle Mass} = 0.401 \left( \frac{\text{Height}^2}{\text{Resistance}} \right) + 3.825 \times \text{(sex)} + \text{age} \times (-0.071) + 5.102
\]

Height is in cm; Resistance is in Ohms; Sex: men = 1 and Women = 0; Age is in years

Total fat mass was determined by using BIA, by subtracting lean body mass from naked weight to determine total fat mass. Lean body mass was determined using the following equation:

\[
\text{Lean Body Mass} = -4.03 + 0.734(\text{Ht2/BIA}) + 0.116(\text{BW}) + 0.096(\text{Xc}) + 0.984(\text{sex}) \times \text{height (Ht) in cm, BIA resistance in ohms (average of 3 measures), naked body weight (BW) in kg, Xc reactance in ohms and sex coded 1 for men and 0 for women.}
\]

Regional Measures of Body Composition

Computed tomography (CT) (GE High Speed CTI Scanner, MIL, USA at the Royal Prince Alfred Hospital, Sydney) was used to quantify visceral adipose tissue (cm2) (VAT), mid-thigh muscle cross sectional area (cm2) (CSA) and mid-thigh muscle attenuation (an index of intramyocellular lipid content). For CT scans of the abdomen, a 1-mm slice was performed at the mid-point of the iliac crest and lowest rib. This was located by palpation with the patient supine and arms rose above the head. A marker placed at the site was visible on the scout image to set up scanning.
coordinates. A line was drawn from the femoral notch to the marker and the linear distance was recorded. This was designed to enable replication of follow-up scans. Settings were kV: 100 and mA: 170 (depending on participant’s abdominal mass) with displayed field of view (DFOV) 45-48 (depending on participant size). For CT scans of the mid-thigh, a 1-mm slice was performed at the mid-point of the inguinal crease to the proximal pole of the patella measured with the participant supine and knee flexed. A marker placed at the site was visible on the scout image and a linear distance from the femoral notch to this marker was recorded to replicate follow-up scans. Settings were kV: 100 and mA: 170 with displayed field of view (DFOV) 25 (depending on participant size).

Scan Images
Scan images were analysed according to optical density by a blinded investigator using NIH Image software (Version 1.63, National Institutes of Health) programmed with specific macros to quantify cross-sectional adipose tissue. To determine VAT, macros were programmed to select the outer perimeter extending from the paraspinal muscles to the anterior abdominal muscles. The program calculated this measure by summing the area within the selected perimeter occupied by pixels with optical density in the range of 140 to 240. Mid-thigh muscle density (unitless measure) was calculated according to a specific optical density range (10-113) chosen to best discriminate muscle from fat and bone. Co-efficient of repeatability, determined using a Bland-Altman plot on a subset of 10 scans was found to be excellent at 0.49 for VAT and 0.44 for mid-thigh CSA. CT scan data were not available in one participant due to body mass exceeding the specifications of the scanner bed.
Exercise Capacity and Functional Status

Dynamic Muscle Strength

Lower extremity peak strength was assessed using digital K400 Keiser pneumatic resistance machines (Keiser Sports Health Equipment, Inc., Fresno, CA). One Repetition Maximum (1 RM) tests were performed according to de Vos and colleagues on chest press, seated row, bilateral knee extension, bilateral knee flexion, bilateral leg press. Strength tests were performed twice at baseline approximately 10 days part, and the higher of the 2 results was recorded as the 1RM.

Muscle Power

Muscle power was assessed approximately one hour after the second muscle strength test. Participants were instructed to push the load once as fast as possible at 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% and 100% of their baseline 1RM. The force, average velocity, work and average power during the concentric phase of each contraction were recorded. The highest average power produced using the loads tested was recorded as the peak power.

Six-minute Walk Distance

Walking endurance was assessed using the six-minute walk test, which is a proxy for overall cardiovascular endurance capacity (aerobic capacity) and in older adults it may be determined by muscle strength and endurance, balance, orthopaedic or neurologic abnormalities, and other problems. Participants were instructed that they were to “cover as much ground as possible in six minutes” by “walking as fast as they can the entire time”. They were encouraged and reminded of the task at least every 30 seconds during the test to minimise slowing down. The number of metres travelled at the end of 6 minutes was recorded to the nearest cm from the wheel.

Gait Speed
Gait speed was recorded as the normal walking speed of the participant in an open path of at least 10 metres using an ultrasonic transmitting device (Ultra-timer Glasgow, Scotland) attached to the participant with a belt. The average of the two trials was recorded and distance walked over two metres was converted to velocity (m/s). Maximal gait speed velocity was recorded as the maximal walking speed over 2 metres. The better of two trials was recorded.

**Balance**

Balance was assessed in progressively more challenging positions, gradually narrowing the base of support and then removing visual input. The conditions were: Wide Stance, Narrow Stance, Semi-tandem Stance, Tandem Stance, One-Leg, Eyes open, One-Leg and Eyes Closed. The success of each test was recorded over 15 seconds, recording the time of balance maintained, with higher scores indication better balance.

**Stair Climb**

Stair climb was used as an indicator of lower extremity power. Two trials were conducted on a 9-step stair climb with a one-minute rest between trials. The faster of two tests was recorded using vertical stair height and body mass to convert to Watts. Power was calculated from the formula: \( P (\text{watts}) = (M \times D) \times 9.8/t \) Where: \( M = \) Body mass (kg), \( D = \) Vertical distance (m), \( t = \) Time (s) and, \( D = \) vertical height of the staircase = height of 1 step in metres \( \times \) number of steps.

**Chair Stand**

Chair stand test is used as a proxy for lower extremity power, or the ability to generate high forces rapidly, primarily utilising the hip extensor and knee extensor muscle groups. Participants were
asked to attempt 5 complete sit-to-stand repetitions from seated to fully erect without the use of hands if possible. The time and the number completed were recorded, as well as any use of hands required.

Neuropsychological Assessments

All cognitive questionnaires were administrated privately by a blinded trained interviewer using visual prompts at baseline where necessary. Each test was chosen because of excellent psychometric properties to screen for cognitive impairment and minimal sensitivity to changes in cognitive function over time. Cognitive testing took place in a fed state (after breakfast), and before any physical testing on that day to standardise known effects of fasting and acute exercise on cognitive performance. The tests represent memory, processing speed, executive function, and global cognitive Function. Administration time was approximately 30 to 45 minutes to complete all tests described in more detail below.

**Word List Subset of CERAD**

Word List subset of Consortium to Establish a Registry for Alzheimer’s disease (CERAD) neuropsychological battery is composed of Word List memory, Word List Recall, and Word List Recognition. It would provide an easy-to-use, normative-based summary score of memory performance that could be used to identify level of cognitive impairment and aid in differentiating AD, mild cognitive impairment (MCI), and normal aging.

*Description*
The Word List Memory task was administrated privately by a trained interview to test the participant’s ability to remember newly learned information. The participant was asked to read 10 common nouns printed on separate cards in the CERAD flipbook. The 10 words were presented at a constant rate of one word every two seconds and then participants were asked to recall as many words as possible. Three trials were given with alternate order of words. Score was the total number correctly recalled words after all three trials. The score ranges from 0-30. Administration time was about 5 minutes.

The second memory test was Word List Recall. The Word List Recall determines how well participants remember the words from the original list after a distraction task (the medication review). Participants were asked to recall as many words as possible from the previously presented 10-word memory task. Administration time was about 5 minutes and the score range for each trial ranges from 0-10.

The Word List Recognition task tests the participant’s ability to remember words that were previously included in the word list and words that were not in the list. Participants were asked to identify the word they had seen before. The score consists of the number of correct “yes” responses and “no” responses. Administration time was approximately 5 minutes. Best control score (yes) is 10.

Word List Subset of CERAD: Psychometric Properties

Validity

An earlier study showed a correlation between CERAD Word List Memory with 60 seniors (14
with initial AD and 46 without AD) with the Screening Test for Alzheimer’s Disease with Proverbs (r=0.61; p=0.000). These data agree with those of Bertolucci et al, who found the Word List Memory tests to be sensitive and specific for the diagnosis of cognitive impairment. Moreover, Morris et al showed the CERAD Word List Memory (r=0.85), word recall (r=0.85), and word list recognition (r=0.74) were related to MMS in 350 patients with a diagnosis of AD and 275 control participants.

Reliability

For Word List Memory (subset of CERAD), a correlation between duplicate measurements was reported to range from 0.80 to 0.91 in 238 patients with mild or moderate AD. Reliability was determined in the same study. The correlation between test 1 and test 2 was lower for Word List Memory (r=0.68-0.83), Word List Recall (r=0.43-0.63), and for Word List Recognition (r=0.44-0.52) due to ceiling effects. On all measures, correlations were lower for control participants than for AD patients because of ceiling effects. Inter-rater reliability of Word List Recall was high, assessed by intraclass correlation coefficients (r=1.0). Similarly, a correlation between duplicate measurements was reported to range from 0.64 to 0.74 in 20 patients with mild or moderate AD. Finally, it discriminates between individuals with dementia or these without; its sensitivity ranged from 74.2 to 85.7 (85.7% for Word List Memory, 74.2% for Word List Word List Recall, and 87.1 for Word List Recognition) and its specificity ranged from 82.4 to 87.1 (87.1% for Word List Memory, 82.4% for Word List Word List Recall, and 87.1 for Word List Recognition). Bertolucci et al suggest that the cognitive tests (CERAD Word List Memory, Word List Word List Recall, and Word List Recognition) is as effective as the Mini-mental State Examination when used to screen for dementia. However, Clark reported that the influence of
age and educational levels on the word list subset of CERAD contributes to higher variability in memory and delayed recall in cognitive impairment and AD patients than in normal control groups, resulting in a weak correlation of 0.33 for test-retest reliability. Given the lack of any significant cognitive impairment at baseline in our participants, these tests were considered to have very acceptable validity and reliability.

Trail Making Test

The Trail Making Test is a neuropsychological test of visual attention and task switching. It consists of two parts (Trail Making Test Part A and Trail Making Test Part B) in which the subject is instructed to connect a set of 25 dots as fast as possible while still maintaining accuracy. It can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning. It is also sensitive to detecting several cognitive impairments such as Alzheimer's disease and dementia.

Description

The Trail Making Test (TMT) is one of the most widely used instruments in neuropsychological assessment as an indicator of speed of cognitive processing and executive functioning. The test consists of two parts (test A and B). The direct score of each part is represented by the time of completion of the tasks. In addition to direct scores, the B-A difference score have been used for clinical proposals as the purest indicators of certain cognitive operations or specific markers of brain damage. Both parts of the TMT consist of 25 circles distributed over a sheet of paper. In Trail Making Test Part A (TMTA), the circles are numbered 1 – 25, and the participants draw lines to connect the numbers in ascending order. In Trail Making Test Part B (TMTB), the circles
include both numbers (1 – 13) and letters (A – L); as in TMTA, and the participant draws lines to connect the circles in an ascending pattern, but with the added task of alternating between the numbers and letters (i.e., 1-A-2-B-3-C, etc.). The participant was instructed to connect the circles as quickly as possible, without lifting the pen or pencil from the paper while being timed. If the participant makes an error, it was pointed out immediately and the participant allowed to correct it. Errors affect the participant's score only in that the correction of errors is included in the completion time for the task. It is unnecessary to continue the test if the participant has not completed both parts after five minutes have elapsed. Administration of the each trial requires approximately 5 minutes. Higher score represents worse information processing speed and executive function. Apart from these two direct scores, Lezak\textsuperscript{90} has proposed additional indexes to better describe the cognitive skills required to complete the TMT. The difference score (B–A) is meant to remove the speed component from the test evaluation, representing pure executive function.\textsuperscript{90} Higher score represents worse information processing speed and executive function.

TMTA, TMTB, and Difference Score (Psychometric Properties)

\textit{Validity:}

Trial Making Tests A & B have been validated for assessment of healthy normal cognitive function, cognitive impairment and dementia, and appear to have high validity. Performance on the TMT has been shown to be significantly correlated with a variety of other tests that measure information processing speed in young and older healthy populations. For example, scores on the TMT-A significantly correlated with the GO/no GO Task ($r=-0.34$)\textsuperscript{91} and Adjusting-Paced Serial Addition Test ($r=0.33$)\textsuperscript{92} in young healthy people. Significant associations between TMT-A and Digit Symbol ($r=-0.29$), Controlled Word Association Test ($r=-0.26$), efficiency of alphabet ($r=0.44$),
and finger tapping (r=−0.45) have been demonstrated in older people. Moreover, correlations between TMT-A and Objects Finding Test have been reported in five groups of brain injury patients (r=−0.41, r=−0.93, r=−0.68, r=−0.60, r=−0.70, respectively) and with Hidden Patterns Test only in nonaphasic patients (r=−0.61, r=−0.58, r=−0.54). The TMT-A score has also been correlated with IQ (measured with WAIS-R; r values between r=−0.37 and r=−0.49) in traumatic brain injury and neuropsychiatric groups. The TMT-B score has been correlated with MMS (r=−.027), Controlled Word Association Test (COWAT; r=−0.31), Boston Naming Test (BNT; r =−0.23), and Animal Naming (r=−0.31) in healthy controls. Performance on TMT-B has also been shown to be strongly correlated with IQ measured with Wechsler Adult Intelligence Test-Revised (r=−0.37 to 0.49) in patients with brain injury. Furthermore, TMT-B has been correlated with MMS (r=−0.40), COWAT (r=−0.33), and Boston Naming Test (r=−0.41) in neurologically impaired patients.

Score on TMT-B-A correlated with Stroop Color-Word (r=0.55, r=0.49), Controlled Word Association Test (r=0.38, r=0.32) and Wisconsin Card Sorting Test Percent Error (r=0.34, r=0.32) in neurologically impaired patients.

Reliability

The inter-rater reliability of TMT scores has been examined in one report by having two pairs of examiners record the performance in 18 healthy participants. The inter-rater reliability for the TMT-A and B sum scores was very high at 0.94 and 0.90, respectively. One study has shown that the inter-rater reliability coefficients for the TMT-A five subsections ranged from 0.933 to 0.994 and the Part B five subsections ranged from 0.881 and 0.997, and the TMT-B five subsections ranged from 0.881 and 0.997, and the difference score between TMT-B and TMT-A ranged from 0.94 to 0.96 in healthy older adults. Neuropsychological battery assessed the twice
tests to a sample of 29 medical students and reported modest correlation coefficient values; 0.46 for TMT Part A and 0.44 for TMT Part B. Charter also administrated the TMT to healthy subjects on two occasions using a retest period, the overall stability scores using a coefficient of concordance was 0.95 for TMT Part A and 0.94 for TMT Part B in a sample of over 300 subjects that included 123 normal control subjects. In normal 487 participants, test-retest reliability and inter-rater reliability coefficients for time scores of Parts A and B were shown as 0.78, 0.99 and 0.73, 0.93, respectively. In a samples of 15 cerebral injury patients reliability values were 0.79 for TMT Part A and 0.85 for TMT Part B. Retest reliability of TMT A and B in recruited patients with depression was between 0.76 and 0.89 and between 0.86 and 0.94, respectively.

3MS

The Mini Mental State Examination (MMS) was designed to provide a brief, standardized assessment of cognitive status that would serve to differentiate between organic and functional disorders in older patients. The test has moderate to high levels of test-retest and interrater reliability in clinical and community populations and adequate to good sensitivity and specificity for detecting and tracking the progression of cognitive impairment associated with neurodegenerative disorders such as Alzheimer’s disease in patient samples. However, its validity is weaker in detecting mild dementia. The revised test, known as the 3MS, was significantly better than the MMS in identifying cognitive impairment and dementia among older persons in the population-based Canadian Study of Health and Aging.

Description

A summary form for the administration and scoring of the 3MS is presented in the Appendix C.
and can be reproduced on one side of a standard (8.5 in. x 11 in.) sheet of paper. 3MS is a revision of the MMS that includes four additional items (date and place of birth, word fluency, similarities, and delayed recall of words) to sample a wider range of cognitive abilities an expended range of scores from 0-30 to 30-100. On the back side of the same sheet, CLOSE YOUR EYES (all in capital letters, approximately 12 in. high) can be printed in the upper part, and two intersecting pentagons (each side 1 in, long) can be drawn in the lower part. Enough blank space is left to record the participant's drawing and writing.

Compared with the MMS, the 3MS has more standardized administration and more graded scoring; it also assesses a broader variety of cognitive domains and covers a wider range of difficulty levels. The 3MS can extract more information about the subject's cognitive status than the MMS; it is also more sensitive than the MMS in detecting within-individual changes over time.

3MS Score (Psychometric Properties)

Validity

Three studies that proposed higher 3MS cutoff scores of between 77 and 78 found sensitivity ranged from 69 to 88% specificity ranged from and 76 to 90 % for the detection of clinically diagnosed dementia or cognitive impairment individuals with dementia and 1092 participants without dementia.\textsuperscript{71, 107, 109, 110} Performance on the 3MS has been shown to be significantly correlated with a variety of other tests that measure global cognition including the Brief Interview of Mental Status (r=0.74-0.79),\textsuperscript{110} Cognitive Performance Scale (r=0.62-0.65),\textsuperscript{110} MMS (r=0.94),\textsuperscript{111} and other aspects of cognitive functioning\textsuperscript{107} in a wide variety of populations.

Reliability
The 3MS is a highly reliable measures of global cognitive function. Several studies examining the reliability of the 3MS suggest that it has adequate reliability, with internal consistency ranged from 0.72 to 0.91, and test-retest from 0.48 to 0.87, and interrater reliability ranged from 0.81 to 0.98. One study reported the internal consistency of the 3MS obtained Cronbach’s alphas of 0.82 and 0.88 in older patients with no mild cognitive impairment (n=406) and AD (n=119) stratified for two age groups (65-79 and 80-89) and two educational levels (0-8 and 9+ years), respectively. Two studies that examined the internal consistency of the 3MS obtained Cronbach’s alphas of 0.91 and 0.87 in older patients living in community (n=885) and older adults from community and institution residents (n=1166), respectively. Grace et al reported stability of the 3MS in a hospitalized stroke population and found that the 3MS was a significantly better predictor of functional independence than the MMS. In elderly individuals without dementia, the test-retest reliability of the 3MS was found to be 0.78 over a 3 year interval in patients with older adults (n=228) and 0.67–0.47 over a 5- to 10-year interval in patients in community-dwelling elderly people (n=3255). The interrater reliability for the 3MS was high in one study, and reported the overall pairwise intraclass correlation coefficient estimate was 0.98 (95% CI 0.97–0.99), and intraclass correlation coefficient estimates for individual rater pairs ranged from 0.95 to 0.99 in older people without cognitive impairment. Graham et al reported slightly high inter-rater reliability of the 3MS in in a sample of 2,914 elderly (age 65 years+) Canadians from the Canadian Study of Health and Aging for screening a community prevalence study of dementia and cognitive impairment (Inter-rater reliability was high: kappa = 0.81 for dementia/no dementia; kappa = 0.74 for normal/cognitive impairment, not dementia/dementia). Performance on the 3MS is significantly related to age and education for individuals with and without cognitive impairment or dementia. Individuals with 8 or fewer
years of formal education perform more poorly than those with more than 8 years of education. Some authors suggest that the 3MS should be adjusted so that a cutoff points of 77-78/100 or below is used for those with 8 years of education or less and a score of 80 or below for well-educated individuals. Finally, it discriminated between with dementia or cognitive impairment and those without; it had high sensitivity and specificity, suggesting that 3MS test is as effective as the MMS when used to screen for dementia or cognitive impairment.

Questionnaires
All questionnaires were interviewer-administered by a trained interviewer, in a private room using visual prompts. All questionnaires including habitual physical activity, psycho-social and quality of life were widely used, previously validated questionnaires in cohorts similar to this one.

Psychological Assessment
The Geriatric Depression Scale is used to assess an older person’s level of depression with simple yes/no response set, and the thirty item screening test has been reported to be satisfactory. Overall this self-report assessment depressive symptoms can be calculated by summing scores ranging from 0-30, with higher scores indicating higher distress. Administration time typically ranges from 5 to 10 min.

Quality of Life
The SF-36® Health Survey version 2 (SF-36v2) is a generic outcome measure designed to
examine a person’s perceived health status. The Physical & Mental Health Summary Scales include eight generic health concepts, selected from the Medical Outcomes Study (MOS), and MOS researchers selected and adapted questionnaire items and developed new measures for a 36-item Functioning and Well-Being Profile the source for SF-36® items. The SF-36v2 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. Higher scores represent better health status. Additionally, the scale scores can be aggregated into two distinct higher-order summary scores: a physical component summary (PCS) and a mental component summary (MCS). The component summary scores are standardized using normative data from the 1998 America general population with a mean score of 50 and a standard deviation of 10.

Physical Activity

Habitual physical activity levels were assessed using the Physical Activity Scale for the Elderly (PASE) questionnaire, where higher scores reflect increasing amounts of habitual structured and unstructured physical activity.

Systemic Inflammation

During blood sampling, extra blood was sampled and the serum stored for future analysis of high-sensitivity CRP. CRP was measured in duplicate by enzyme-linked immunosorbent assay (ELISA) (eBIOSCIENCE, Camarillo, CA), with the average value used in statistical analyses. The lowest detectable concentration was 0.01mg/L. Co-efficient of variation was required to be less than 20%, otherwise a third measurement was performed. The average intra-assay co-
efficient of variation was 6.4%.

Adiponectin

During blood sampling, extra blood was sampled and the serum stored for future analysis of serum adiponectin. Serum adiponectin was measured in duplicate by enzyme-linked immunosorbent assay (ELISA) (eBIOSCIENCE, Camarillo, CA), with the average value used in statistical analyses. The lowest detectable concentration was 0.01 mg/L. Co-efficient of variation was required to be less than 15%, otherwise a third measurement was performed. The average intra-assay co-efficient of variation was 7.2%.

4.3.10 Covariates

Covariates specified a priori for all cognitive test analyses were age, sex, and educational history. This was because extensive literature suggests that these factors may influence performance on some of these tests.⁸⁶, ¹¹², ¹²⁰

4.3.11 Statistical Analysis

The intention-to-treat (ITT) strategy was used as our primary analytic treatment of the data without imputation for missing time points. Normally distributed data were described as mean ± SD; non-normally distributed data as median (range) or frequencies. Non-normally distributed data were log-transformed for use with parametric statistics. Nonparametric tests were used if assumptions of normality were not met despite transformation. Comparisons of baseline characteristics between groups were made using Chi Square tests for categorical data and a one-way ANOVA for normally distributed continuous data. The Mann-Whitney U test was used for
non-normally distributed continuous data.

Mixed models of baseline and 12-month outcomes, adjusted for baseline values and *a priori* or potential confounders identified after inspection of baseline correlations were constructed to test our primary and secondary hypotheses. We included the main effects of TIME, GROUP, as well as for the interaction term (Group × Time) to identify isolated training arm significance. Baseline age, sex, years of education, and baseline cognitive scores were used as covariates in these mixed models.

Relationships of interest and predictors of changes in cognitive function and other secondary outcomes were analysed with simple and multivariate linear regression models as appropriate. Relative ESs were calculated for all outcomes. Calculations of ES were adjusted via Hedges’ bias-corrected ES for small sample sizes, and interpreted as ‘trivial’ (<0.20), ‘small’ (≥0.20 <0.50), ‘moderate’ (≥0.50 <0.80), or ‘large’ (≥0.80). Ninety-five percent CIs for the relative ES were calculated. The following formula was used: Mean differences and between-group and/or intra-group effect sizes (ESs) were calculated for both groups. For group 1, between-group ES adjusted via Hedges’ bias-corrected for small sample sizes and 95% confidence intervals (CIs) were calculated for each outcome measure where applicable using formula 1: between-group ES = (D treatment – D control)/pooled baseline standard deviation (SD), where D indicates change. For group 2, an intra-group ES was calculated for each treatment arm using formula 2: intra-group ES = (post-score - pre-score)/baseline SD. For group 2, a between-group ES was also calculated using formula 1 outlined above. Final sample sizes excluding dropouts were used to calculate ESs, unless there had been imputation of missing data from dropouts. Prior to
calculating ESs, data were manipulated if necessary to derive means and SDs as follows:

1. When sample size exceeded 25 and the mean was not reported, the median was substituted for the mean. In sample sizes <25, means were calculated using the following formula: \( x \approx (a + 2m + b)/4 \), where \( m = \) median, \( a = \) the smallest/minimum value, and \( b = \) the largest/maximum value.\(^{123}\)

2. If data were presented as mean and range or interquartile range then SDs were calculated using the following formulae: SD= one quarter of the range or SD= four fifths of the interquartile range

3. Values reported as standard error (SE) were converted to SD using the following formula: \( SD = SE/\sqrt{n} \), where \( n = \) number of subjects. SPSS (Version 20 for Windows, Cary NC: SAS Institute Inc) was used for all data analysis. All two-tailed p values less than 0.05 and/or ES 95% CIs exclusive of 0 were accepted as statistically significant.

### 4.4 CONCLUSIONS

The GREAT2DO trial conformed to all design and reporting requirements for randomised controlled trials recommended by the CONSORT group.\(^{124}\) This was the first RCT of power training as a potential non-pharmacological intervention that targets the pathophysiology of T2DM and multiple associated comorbidities in older adults. It was also the first study of anabolic exercise for cognitive improvement in older adults with T2DM. Through this investigation, we aimed to contribute to better treatment for physical and cognitive health, and ultimately improve quality of life for older adults with T2DM.
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Competing interests

The authors have no conflicts of interest.
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CHAPTER 5

THE GREAT2DO STUDY: BASELINE CHARACTERISTICS OF OLDER ADULTS WITH TYPE 2 DIABETES MELLITUS IN A RANDOMISED CONTROLLED TRIAL OF POWER TRAINING
5.1 ABSTRACT

Objectives – Diabetes is associated with cognitive impairment and dementia. However, mechanisms and mitigating factors require further study. We explored some potential factors related to baseline cognitive function of older adults with type 2 diabetes mellitus (T2DM) who were enrolled in the Graded Resistance Exercise and T2DM in Older adults (GREAT2DO) study, a randomised double-blind, SHAM-exercise controlled trial. The overall purpose of the study was to assess the efficacy of a one-year power training intervention compared to a SHAM-exercise control on metabolic profile, comorbidities, and health outcomes associated with T2DM. The specific focus of this chapter is to explore any relationships between baseline cognitive function and metabolic profile, inflammatory markers, body composition, physical performance and exercise capacity in the cognitive sub-study of the GREAT2DO study.

Methods – Cross-sectional data in 103 older adults over 60 years of age with T2DM participating in a clinical trial of exercise were analysed. Primary characteristics of interest were cognitive measures (memory, processing speed, executive function, and global cognitive score) and fasting glucose, glycosylated haemoglobin (HbA1c), fasting insulin, and insulin resistance and pancreatic beta cell function assessed by the Homeostasis Model Assessment 2 (HOMA 2) computer model. Secondary characteristics of interest were to investigate health status, including chronic diseases, body composition, pro-inflammatory factor C-reactive protein (CRP), adipokines, depressive symptoms, quality of life, and habitual physical activity level, and physical performance (chair stand, stair climb, gait velocity, balance, and 6-minute walk distance).

Results - The health status of our cohort was generally more impaired than reported averages for older adults with T2DM in Australia. Specifically, they had higher levels of abdominal obesity and BMI, prevalence of hypertension, higher triglycerides, and lower high-intensity lipoprotein
(HDL) cholesterol than reported for this cohort. Additionally, the use of insulin and oral diabetic medications were all higher compared to adults with T2DM in Australia. Notably, their physical performance was lower than healthy people of similar age. Multiple linear regression models adjusted for age, sex and years of education were constructed for all potential predictors of each cognitive test. In these analyses, higher 6-minute walk distance (β=0.22, p=0.04) and lower sagittal abdominal diameter (β=-0.21, p=0.03), and higher total adiponectin (r=0.25, p=0.04) were related to better memory (a higher score on Word List Recall.), as hypothesised. Lower 6-minute walk distance (β=-0.21, p=0.05), slower chair stand time (β=0.34, p=0.001), lower stair climb power (β=-0.29, p=0.02), and higher CRP (β=-0.30, p<0.001) were related to a worse information processing speed score (Trail Making Test A), again as hypothesised. Contrary to our hypotheses, however, overall muscle mass, thigh muscle area, thigh subcutaneous adipose tissue area, intramuscular adipose tissue area, thigh muscle lipid density, total abdominal adipose tissue area, visceral adipose tissue, abdominal subcutaneous adipose tissue area, HbA1C, fasting insulin, insulin resistance (IR), beta cell function, and depressive symptoms, quality of life, and habitual physical activity were not associated with any cognitive domains (memory, information processing speed, pure executive function, and global cognitive function) (p>0.05), and higher fasting glucose was paradoxically associated with better memory (Word List Recall; β=0.20, p=0.02).

**Conclusions** – Better physical performance, lower central adiposity, higher adiponectin levels and lower systemic inflammation were each related to better cognitive function in some domains in this cohort of older adults with T2DM, after adjustment for age, sex and education. Thus, exercise interventions targeting improvements in body composition and inflammatory profile in obese older adults with T2DM should be explicitly tested as a strategy to improve cognition and reduce dementia risk in this cohort and may result in better physical performance as well.
improvements may be independent of, or not dependent upon, changes in metabolic profile including glucose homeostasis and insulin resistance.
5.2 INTRODUCTION

The prevalence of diabetes is increasing, with estimates that it will affect 435 million adults by 2030, and it is a leading contributor to premature mortality and morbidity globally. The most common form, T2DM is characterised by insulin resistance and relative insulin deficiency that results in sustained hyperglycaemia. The aim of treatment is to maintain normal glucose levels in order to prevent comorbidities and complications. Comorbidities and complications of T2DM such as retinopathy, neuropathy, nephropathy, and cardiovascular disease, amputation, depression, low physical performance, increased adiposity and decreased muscle mass, and inflammation, lead to profound psychological consequences, reduced quality of life, and increased economic burden. In patients with T2DM, this treatment initially consists of dietary restrictions and exercise. Oral hypoglycemic medications or insulin injections are prescribed in later stages.

Diabetes is associated with cardiovascular comorbidity and mortality and is associated with a higher risk of cognitive dysfunction due to both vascular dementia and Alzheimer’s disease (AD). Individuals with diabetes are more likely to present with early cognitive impairment and frank dementia than individuals without diabetes. Precise mechanisms for this diabetes-related cognitive decline remain unclear; however, many studies have demonstrated that previous transient cerebral ischemia, stroke, myocardial infarction, or atherosclerosis are all strong predictors of cognitive dysfunction.

Increasing evidence has demonstrated that a link between some of the features of diabetes (e.g., fasting glucose, HbA1C, fasting insulin, insulin resistance and beta cell function) also exists. Some cross-sectional and longitudinal studies have found a negative association between HbA1c
and cognitive function,\textsuperscript{11-13} while others have found no association\textsuperscript{14, 15}. Acute hyperglycaemia has been shown to impair cognitive function,\textsuperscript{16, 17} Other studies have shown no effect of acute hyperglycemia on cognitive function.\textsuperscript{13, 18, 19} Paradoxically, associations between high HbA1c and better cognitive function have been demonstrated in elderly individuals with or without diabetes.\textsuperscript{20, 21} Thus, evidence about metabolic profile and risk of cognitive impairment are mixed and require further study.

Body composition has also been shown to predict cognition in some cohorts. Several cross-sectional studies showed that higher obesity up to a mean age of 72 years was negatively associated with cognition,\textsuperscript{22-25} whereas two studies (mean age > 73) reported a positive association between obesity and cognitive performance in older individuals without diabetes.\textsuperscript{22, 25, 26} Prospective studies show similar results to cross-sectional studies, findings being somewhat age dependent and contradictory. One study found that obesity was related to cognitive decline.\textsuperscript{27} The other two studies showed that higher obesity levels predicted better cognitive performance\textsuperscript{28} or less decline in cognitive function.\textsuperscript{26} There is also recent data demonstrating that weight loss is associated with poor cognitive performance in older adults,\textsuperscript{29-32} which reflects a large literature about the negative associations of unintended weight loss in old age, including excess morbidity, frailty, and mortality compared to those with stable or increasing weight. Overweight in middle age has been strongly linked to later-life cognitive decline,\textsuperscript{33, 34} although again data are not consistent. For example, data from the Framingham studies showed that higher BMI was an independent predictor of cognitive decline.\textsuperscript{23, 27, 35} By contrast, higher BMI in non-demented middle-aged adults was shown to be unrelated to cognitive function.\textsuperscript{36} Finally, a recent analysis of the Health, Aging and Body Composition (ABC) Study cohort investigating the effects of total fat and visceral adiposity
has shown that total fat and sagittal abdominal diameter had a significant and inverse relationship
with global cognitive function as measured by Modified Mini-mental State Examination (3MS).\textsuperscript{37}
Additionally, higher muscle mass has been associated with a decreased risk of Alzheimer’s disease
(AD).\textsuperscript{38} Several studies have shown a greater risk of cardiovascular disease and metabolic
disorders with overweight and obesity.\textsuperscript{8, 39, 40} Several cardiovascular risk factors and diseases are
linked to risk of dementia.\textsuperscript{8, 39, 41} Therefore, the relationships between body composition,
comorbidity, and cognition are complex and inconsistent across demographic cohorts, and there is
little information specifically in diabetes, where the cognitive risks are higher than average.

Another feature of T2DM which is relevant to cognitive risk is systemic inflammation. C-
reactive protein (CRP) is a marker of chronic inflammation that has been shown in epidemiological
studies to predict future cardiovascular disease and neurodegenerative diseases\textsuperscript{42, 43} and has been
associated with T2DM and metabolic syndrome components in a cohort of healthy women.\textsuperscript{44}
Inflammation may also be observed in older people with T2DM and dementia.\textsuperscript{45} Many previous
studies have shown the relationship between cardiovascular disease, metabolic syndrome, T2DM,
and cognitive dysfunction\textsuperscript{10, 46-48} Emerging evidence suggests that CRP may be a cognitive
decline and AD biomarker,\textsuperscript{39-52} although no association has been found in other studies.\textsuperscript{51, 53, 54}
Two longitudinal studies showed associations between increased levels of inflammatory
biomarkers and decreased cognitive ability in the cognitively healthy ageing population.\textsuperscript{50, 55}
Few studies have investigated the association between inflammation and cognition specifically in
patients with T2DM. However, a cross-sectional study published in 2010 found that raised
plasma levels of interleukin-6, tumor necrosis factor-alpha and CRP were associated with poorer
cognitive ability in people with T2DM.\textsuperscript{56} These associations persisted after adjustment for the
patients prior cognitive ability. However, evidence of causality remains speculative from such investigations.

Adiponectin modulates the sensitivity to insulin, glucose homeostasis and fatty acid catabolism, and has potent anti-inflammatory properties.\textsuperscript{57, 58} Reduction in circulating adiponectin levels has been implicated in the development of insulin resistance syndrome and visceral obesity. Reduced adiponectin levels have been related to many clinical and psychological disorders, such as obesity, diabetes and depression.\textsuperscript{59-61} The presence of insulin resistance, hyperglycemia, pro-inflammatory cytokines in the brain adjacent to amyloid plaques may contribute to the progression and acceleration of AD-related neurodegeneration.\textsuperscript{62, 63} Despite its theoretical relevance, few studies have evaluated the relationship between circulating levels of adiponectin and cognitive function. In small clinical sample of patients with AD, mild cognitive impairment (MCI) and controls, adiponectin levels were significantly decreased in individuals with MCI and AD as compared to elderly controls.\textsuperscript{64} Chan et al reported that high concentrations of adiponectin (10 μg/ml) were protective against amyloid beta induced neurotoxicity in Sw-APP transfected SH-SY5Y cells exposed to oxidative stress conditions, further supporting adiponectin might be protective against AD.\textsuperscript{65} However, other studies did not find significant differences in circulating adiponectin levels between AD and healthy elderly controls and also did not found an association between adiponectin levels and higher risk of cognitive decline and dementia in dementia-free older adults.\textsuperscript{67} Thus, evidence about adiponectin and risk of cognitive impairment are mixed and require further study.

Better physical function has also been related to cognition in cohorts not selected for T2DM. The
6-minute walk distance (6WMD) test, originally designed to be a proxy for cardiovascular endurance capacity (aerobic capacity), is associated with grey matter volume in the left middle temporal gyrus, middle occipital gyrus, and hippocampus in older adults with mild cognitive impairment, in addition to being related to muscle strength and endurance, balance, orthopedic or neurologic abnormalities, and other problems in older adults. In this study, a better 6MWD was also related to better memory. Recently, a positive association was observed between the 6WMD and MMS score in older outpatients with chronic heart failure. Similarly, a significant association between memory and 6WMD was seen in older individuals with multiple commorbidities. These findings from epidemiological studies are supported by randomised controlled trials (RCTs) that have shown that older adults (both healthy and with chronic conditions) who begin exercise programs may have significant improvement in both physical function and cognition. Such studies have reported associations between physical functional performance such as balance, gait speed, chair stand time, stair climber power, and cognitive function in older individuals, but not to date in older individuals with T2DM.

Thus, despite the above supportive evidence across varied cohorts, there are no published data to our knowledge that simultaneously examine glucose homeostasis and insulin resistance, regional fat and muscle distribution, inflammation, adiponectin, and physical function within a single cohort. Perhaps more importantly, these relationships have not been examined exclusively within a metabolically-compromised cohort, such as older individuals with T2DM, in whom a more complete understanding of these relationships might have significant therapeutic relevance. Therefore, the primary purpose of this sub-study cross-sectional analysis was to examine measures of glucose homeostasis (glycosylated haemoglobin, HbA1c) and insulin resistance (HOMA2-IR)
in relation to cognition at baseline in a cohort of older adults with T2DM enrolled in a randomised 
clinical trial of resistance training. Secondary analyses included the relationships between 
measures of visceral adipose tissue (VAT), total abdominal adipose tissue (TAAT), subcutaneous 
(abdominal) adipose tissue (SCAT), sagittal diameter (SAD), skeletal muscle mass, thigh muscle area, total fat mass, serum CRP, serum adiponectin, and 6MWD, balance, gait speed, chair stand, 
stair climb power, and cognition. Consistent with recently published data, our hypotheses were 
as follows:

1) Metabolic profile (fasting glucose, HbA1c, fasting insulin and IR) would be inversely related 
to cognitive function at baseline

2) Adiposity (TAAT, VAT, SCAT, SAD and total fat mass) would be inversely related to cognitive function at baseline

3) Muscle mass (mid-thigh CSA and whole body skeletal muscle mass) would be positively related to cognitive function at baseline

4) Low-grade systemic inflammation (CRP) would be inversely related to cognitive function at baseline

5) Serum adiponectin would be positively related to cognitive function at baseline

6) Physical performance (total balance time, 6MWD, gait speed, chair stand and stair climb performance, and muscle strength) would be related to better cognitive function

5.3 METHODS

5.3.1 STUDY DESIGN

Participants for this cross-sectional investigation consisted of 103 older adults with T2DM who 
were recruited for the on-going GREAT2DO study. The GREAT2DO study is a randomised,
double-blind, SHAM exercise controlled trial investigating the effects of one year of power training (high velocity, high intensity progressive resistance training) on a number of outcome measures. These included HOMA2-IR, HbA1c, body composition, lipid profile, systemic inflammation, neuropsychological status, exercise capacity, physical performance, health status, and quality of life. The data used for the purpose of this investigation were collected at baseline. The trial was registered with the Australian Clinical Trials Registry (ACTR) (ACTR No: ACTRN12606000436572). The study protocol was approved by Ethics Review Committee (Royal Prince Alfred Hospital (RPAH) Zone), Sydney South West Area Health Service (Ethics Committee Protocol No: X04-0096) and written informed consent was obtained from all participants. The assessments were conducted at Cumberland Campus of the University of Sydney in Lidcombe New South Wales (NSW) Australia. Computerised Tomography (CT) Scans were performed at the Radiology Department of RPAH in Camperdown NSW Australia. The exercise training was conducted at Freshwater Rehabilitation in Manly NSW Australia or the Centre for STRONG Medicine, Balmain Hospital in Balmain NSW Australia by research staff at each site. A description of the overall study design is provided in Chapter 4.

5.3.2 Eligibility and Exclusionary Criteria

Inclusionary criteria were: sedentary (no resistance training; structured exercise ≤ 1/week; less than 150min/week low or moderate-intensity walking or other aerobic exercise), aged 60 years or older, previously diagnosed T2DM and stable glucose control with no significant changes in medications for the previous 3 months. Exclusionary criteria included: significant cognitive impairment, non-ambulatory status or lower extremity amputation other than toes, current alcohol or substance abuse, inability to comply with study requirements over the course of one year due to
travel plans or other commitments, and specific contraindications to resistance training exercise, such as unstable cardiovascular disease, unrepaired aortic aneurysm, symptomatic hernias, proliferative diabetic retinopathy, or rapidly progressive or terminal illness. Temporary exclusions (any change in dosage or type of diabetic medications within the past 3 months, acute illnesses, retinal laser surgery within 2 weeks, uncontrolled hypertension or newly diagnosed coronary artery disease) were resolved prior to study enrolment and baseline assessments. Participants could be treated with diet alone, oral medications, insulin or a combination at the time of their enrolment.

5.3.3 Recruitment
Participants were recruited from July 2006 until December 2009 from publicity in media, advertisements in local newspapers, General Practitioner (GP) lists, Diabetes Australia newsletters and pamphlets, completing the 12-month RCT phase in 2011.

5.3.4 Sample Size
Sample size estimates were driven by hypothesised differences between the experimental and control participants in the primary outcomes of the trial: insulin sensitivity and HbA1c, based on an average of published studies of progressive resistance training in diabetes/obesity.\textsuperscript{80-83} This sample size was also sufficient for testing secondary hypotheses regarding all components of metabolic syndrome as well, with $> 90\%$ power, alpha of 0.05, assuming 10\% loss to follow-up (See Table 5.1). Largest available standard deviations (SDs) were used for conservative estimates of effect size (ES). In our experience in fully supervised training of older adults with frailty/chronic disease, dropout averages 10-15\% over 12 months. Therefore, we inflated sample
size needs for approximately 10% drop out rate to account for anticipated attrition (n = 103). In addition, sample size estimates (alpha 0.05, beta 0.20) were also calculated for the secondary planned comparisons for the main effects of power training on our cognitive outcome: global cognitive function as assessed by 3MS. The assumptions were as follows: our meta-analyses\textsuperscript{84} and review of published RCTs in older adults\textsuperscript{85} revealed ESs for a range of cognitive outcomes of approximately 0.59 for resistance training compared to 0.15 for control groups. Thus, we had approximately 60% power to show a relative ES of 0.44 for the main effect of power training vs. control on global cognition.

5.3.5 Screening Procedure

Potential participants underwent initial telephone interview and screening using questionnaire followed by a physician history and physical examination. If eligible after physician screening, the remainder of the baseline physical performance testing was completed, followed by baseline cognitive tests and CT scan. If following screening a participant was temporarily excluded for abnormal stress test or other acute illness, he or she may have entered the study following appropriate treatment and medical review.

5.3.6 Demographics, Health Status, Medications and Treatment Plan

Participants were asked routine questions to obtain demographic information, as well as their current health status relating to the presence of other chronic diseases. Participants also provided a list of all their current medication and dosages. Medical records were also hand searched to extract any information not provided by the participant. Each treatment plan in patients with diabetes was then determined and scored as either diet only, oral hypoglycemic only, insulin only
or oral hypoglycemic and insulin. Participants remained under the usual care of their physicians, and were asked not to alter their habitual dietary intake and report any changes in physical activity outside of that prescribed in study.

5.3.7 OUTCOMES

Primary Outcomes

Blood samples were taken at Cumberland of University of Sydney in Lidcombe, NSW Australia, and were sent to Douglass Hanley Moir, Sydney, Australia (www.dhm.com.au) for analysis. Fasting blood tests were analysed for HbA1c, glucose, insulin, C-peptide, inflammatory profile, and lipids. Homeostatic Model of Assessment of Insulin Resistance (HOMA2-IR) was calculated with glucose and c-peptide values using the validated calculator (accessed at http://www.dtu.ox.ac.uk). Sixteen participants with insulin treatment were deleted from HOMA calculations only, as recommended by Wallace et al (2004). HOMA2-IR was calculated using C-peptide and glucose because of the effects of long-acting insulin use and of fatty liver on insulin clearance in participants. HOMA2-IR has been shown in multiple studies to correlate with the hyperinsulinemic/euglycemic clamp, however, due to its feasibility; it is a far more clinically accessible index of IR. Complete details of methods are described in Chapter 4.

Secondary Outcomes

Cognitive Assessment

All measures were administered by blinded assessors at baseline at a laboratory facility separate from the training site, to prevent un-blinding of assessors. Each test was chosen because of excellent psychometric properties and minimal sensitivity to practice effects. Cognitive testing
took place in a fed state (after breakfast), and before any physical testing on that day to standardise known effects of fasting and acute exercise on cognitive performance. The tests represent memory, processing speed, executive function, and global cognitive function. All assessments were administered by the same exercise physiologist trained in administering the included tests.

The tests have been described in Chapter 4. In brief, the Word List is a subtest of the Consortium to Establish a Registry for Alzheimer’s disease, which assesses immediate and delayed memory. It has been used extensively to measure cognitive function in cognitively intact individuals, and its score is well correlated with measures of physical function and future cognitive decline.

**Word List subtest of the Consortium to Establish a Registry for Alzheimer’s disease**

To investigate verbal memory we used three different tests: Word List Memory, Word List Recall, and Word List Recognition, which were a subtest of the Consortium to Establish a Registry for Alzheimer’s disease (CERAD).\(^{89,90}\) It has been used extensively to measure cognitive function in cognitively intact individuals and in AD. The participant was required to read 10 words and then asked to repeat as many words as they could recall in any order (immediate memory). The range of scores is 0-30. After a distracting task, lasting at least 5 minutes, the participants were asked to recall the 10-word list again (delayed memory). The words were evaluated as either correct or incorrect by the tester. The word list recognition task tests the participant’s ability to remember words that were previously included in the word list and words that were not in the list. Participants were asked to identify the word they have seen before. Score consists of the number of correct “yes” responses and “no” responses. Administration time is approximately 5 minutes. Normal control score (yes) is 10. For all 3 tests, higher scores indicate better memory.
Trail Making Test Part A & B and difference score (Trail Making Test Part B minus Trail Making Test Part A)

Trail Making Test Part A\(^9\) was administered to test information processing speed. Trail Making Test Part A (TMTA) consists of 25 numbers, which must be connected in arithmetic order. This test presumably reflects speed of information and motor ability. Attention and Executive functions were assessed with Trail Making part B (TMTB),\(^9\) consisting of numbers and letters, which must be connected by alternating 1-A-2-B etc. TMTB minus TMTA is a more pure measure of executive function than TMT-B because it minimizes visuo-perceptual and working memory demand.\(^9\)

3MS

The 3MS is a screening tool to assess global cognitive function.\(^9\) It can also identify changes in cognitive function for elderly individuals without dementia and may identify individuals in the prodromal phase of dementia. Complete details of methods are described in Chapter 4.

Muscle Function and Physical Performance

Muscle Strength

Lower extremity peak strength was assessed in Newtons (N) or Newton-metres (M-m) using digital K400 Keiser pneumatic resistance machines (Keiser Sports Health Equipment, Ltd., Fresno, CA, USA). One Repetition Maximum (1 RM) tests were performed at baseline approximately 10 days apart, and the higher of the 2 results was recorded as the 1RM according to de Vos and colleagues.\(^9\) Muscle strength was tested bilaterally on chest press, seated row, knee extension, and knee flexion and unilaterally on hip abduction and hip extension. Previous randomised
controlled trials from our research lab have reported a coefficient of variation (CV) for these exercises as mean 13.1%, range 9.8% – 21.7%.95

**Muscle Power**

Muscle power was assessed approximately one hour after the second muscle strength test. Participants were instructed to push the load once as fast as possible at 20%, 30%, 40%, 50%, 60%, 70%, 80%, 90% and 100% of their baseline 1RM (the higher of the 2 days of strength testing). The force, average velocity, work and average power during the concentric phase of each contraction were recorded. The highest average power produced using the loads tested was recorded as the peak power.

**Walking Endurance**

The 6-minute walk test was chosen as a measure of walking endurance, as it has been shown to be strongly associated with physical activity levels and overall cardiovascular endurance capacity (aerobic capacity). In the older adult, it may be determined by muscle strength and endurance, balance, orthopedic or neurologic abnormalities, and other problems.68 Each participant was instructed to cover as much ground as possible within the 6 minutes and notified that they were allowed to sit down and rest if needed, however to start walking again as soon as possible. If participants needed to stop during the test for any reason and the total distance covered in 6 minutes was recorded to the nearest 0.1 metre. Each participant completed the 6-minute walk twice at the baseline assessment, with each test scheduled 10 days apart. The better of 2 trials was recorded at baseline to allow for learning effects. Previous RCTs from our research lab have reported at the coefficient of variation for this test as mean 3.0%, (range 0.0 % – 13.0%).95
**Static Balance**

Static balance test performed using Rossiter-Fornoff and colleagues\(^9^6\) was used to assess static balance. Standing static balance test was assessed for up to 15 second in six different positions without the use of an assistive device in the following order: (1) Wide stance (feet parallel and hip width apart), (2) Narrow stance (feet side by side and touching), (3) Semi-tandem stance (feet parallel and the toes of one foot at the level of the in-step and touching the other foot), (4) Tandems stance (toes of the foot touching the heel of the other foot), (5) Single leg stance eyes open, (6) Single leg stance eyes closed. Total static balance was calculated by summing the time recorded for each of the 6 stances.\(^9^6\)

**Gait Velocity**

Gait velocity was measured using an Ultra-timer (DCPB Electronics, Glasgow, Scotland, UK). Participants were asked to walk with any habitual assistive devices at their self-selected normal and maximal speed for 2-3 trials. Gait velocity was defined as the mean of the 2 closest trials for habitual speed, and the highest value for maximal speed.

**Stair Climb**

Maximal stair climb was used as a proxy for lower extremity power.\(^9^7\) Two trials were conducted of the 9-step stair climb with 60 seconds rest between each trial. The time taken for each test was recorded to the nearest 0.01 second and the best of the 2 test results was used to calculated stair power using following formula.\(^9^7,9^8\)

\[
\text{Power (Watts)} = \frac{\text{Body Weight (N)} \times \text{Height of Stairs (m)}}{\text{Ascent Time (s)}}
\]
Chair Stand

The five chair stand test, performed according to Guralnik and colleagues\textsuperscript{99} was used as an index for lower extremity power/balance. Participants were instructed to sit in a chair with arms folded at chest level and to complete 5 stands consecutively as quickly as possible. At the completion of each stand, legs were to be straight, and with each return to sitting, the back was to touch the back of the chair. The assessor used a handheld stopwatch and timing was commenced after the assessor said ‘go’ and was stopped the participant achieved a full erect standing position for the 5\textsuperscript{th} time. Time taken, as well as numbers of stands completed and whether arms were used were recorded.

Body Composition

Anthropometry

Morning fasting stretch stature (wall-mounted Holtain stadiometer, Holtain Limited, Crymych Pembs., UK) and naked weight [weight in gown (kg) – weight of gown (kg)] were measured in triplicate to the nearest 0.1cm and 0.01kg respectively. Body mass index (BMI) was calculated from fasting naked weight and stretched stature measurements.\textsuperscript{100}

Waist circumferences were measured with a Lufkin flexible steel tape by a number of methods for data collection and International Society for the Advancement of Kinanthropometry (ISAK) protocol\textsuperscript{100} was used for analysis. Measures were recorded by an experienced anthropometrist with technical measurement errors < 1%.

Bioelectrical Impedance Analysis
Total fat mass and skeletal muscle mass were determined using bioelectrical impedance analysis (BIA); RJL Systems, Inc., Clinton, MI, USA. All participants were fasting and BIA was performed in the morning, at a similar time of day for all participants.

Skeletal Muscle Mass (SMM) was calculated from the following formula.\(^{101}\)

\[
SMM = 0.401 \times (\text{Height}^2 / \text{Resistance}) + 3.825 \times \text{sex} + \text{age} \times (-0.071) + 5.102
\]

Height is in cm; Resistance is in Ohms; Sex: men = 1 and Women = 0; Age is in years.

Total fat mass was determined using BIA, by subtracting fat free mass from naked weight to determine total fat mass. Fat free mass was determined using the following equation.\(^{102}\)

\[
\text{Fat Free Mass} = -4.03 + 0.734(\text{Ht}/\text{BIA}) + 0.116(\text{BW}) + 0.096(\text{Xc}) + 0.984(\text{sex}) \text{ with height (Ht) in cm, BIA resistance in ohms (average of 3 measures), naked body weight (BW) in kg, Xc reactance in ohms and sex coded 1 for men and 0 for women.}
\]

**Computed Tomography**

Computed tomography (CT) (GE High Speed CTI Scanner, MIL, USA at the Royal Prince Alfred Hospital, Sydney) was used to quantify total abdominal adipose tissue (TAAT), abdominal subcutaneous adipose tissue (SCAT), visceral adipose tissue area (VAT), sagittal abdominal diameter, total thigh muscle, thigh subcutaneous adipose tissue area, mid-thigh muscle cross sectional area (CSA), intramuscular adipose tissue, and thigh muscle lipid density. *For CT scans of the abdomen*, a 1-mm slice was performed at the mid-point of the iliac crest and lowest rib. This was located by palpation with the participant supine and arms raised above the head. A marker placed at the site was visible on the scout image to set up scanning coordinates. A line was drawn from the femoral notch to the marker and the linear distance was recorded. This
was designed to enable replication of follow-up scans. Settings were kV: 100 and mA: 170 (depending on participant’s abdominal mass) with displayed field of view (DFOV) 45-48 (depending on participant size).

For CT scans of the mid-thigh, a 1-mm slice was performed at the mid-point of the inguinal crease to the proximal pole of the patella measured with the participant supine and knee flexed. A marker placed at the site was visible on the scout image and a linear distance from the femoral notch to this marker was recorded to replicate follow-up scans. Settings were kV: 100 and mA: 170 with displayed field of view (DFOV) 25 (depending on participant size).

Image Analysis

Scan images were analysed according to optical density on a Macintosh iBook G4 (Apple; Sunnyvale, CA, USA), by a trained investigator in a blinded manner. NIH Image software (Version 1.63, National Institutes of Health) was programmed via specific macros to quantify cross-sectional areas of muscle, bone and adipose tissue. To determine VAT, macros were programmed to select the outer perimeter extending from the paraspinal muscles to the anterior abdominal muscles. The program calculated this measure by summing the area within the selected perimeter occupied by pixels with optical density in the range of 140 to 240. Thigh muscle attenuation (an index of intramuscular lipid) was calculated using a template set up in Excel (Microsoft) based on the ‘average’ density for thigh pixels in a specific optical density range (10-113) chosen to best discriminate muscle from fat and bone. Higher numbers reflect more intramuscular lipid (less dense muscle). Co-efficient of repeatability, determined using a Bland-Altman plot on a subset of 10 scans was found to be excellent at 0.49 for VAT and 0.44 for mid-
thigh CSA.\textsuperscript{103} CT scan data were not available in 1 participant due to body mass exceeding the specifications of the scanner bed.

**Questionnaires**

All questionnaires were interviewer-administered by a trained interviewer, in a private room using visual prompts. Participants were asked routine questions to obtain demographic information, as well as their current health status relating to the presence of other chronic diseases. All questionnaires including habitual physical activity, psycho-social and quality of life were widely used, previously validated questionnaires in cohorts similar to this one.

**Physical Activity**

Habitual physical activity levels were assessed using the Physical Activity Scale for the Elderly (PASE) questionnaire,\textsuperscript{104} valid instruments for the assessment of physical activity in epidemiology studies of older people.\textsuperscript{104} Higher scores reflect increasing amounts of habitual structured and unstructured physical activity.

**Quality of Life**

Health-related quality of life was assessed using Version 2 of the Medical Outcomes Survey 36-item Short-Form (SF-36v2) questionnaire,\textsuperscript{105} which was constructed to stratify minimum psychometric standards necessary for group comparisons involving health concepts that are not specific to any age, disease, or treatment group.

**Depressive Symptoms**
Depressive symptoms were assessed using Geriatric Depression Scale (GDS). The GDS is a self-report mood symptom checklist with simple yes/no response set. The directionality of the answers scored for depression changes randomly and the questionnaire itself has been well validated in older adults. All participants were also asked to complete the Geriatric Depression Scale (GDS), which is a screening test for depression with scores ranging from 0 to 30.

Systemic Inflammation

High-sensitivity CRP was measured in duplicate by enzyme-linked immunosorbent assay (ELISA) (eBIOSCIENCE, Camarillo, CA), with the average value used in statistical analyses. The lowest detectable concentration was 0.01mg/L, and the intra-assay co-efficient of variation was 6.4%. CRP analysis was available in 89 participants.

Adiponectin

During blood sampling, extra blood was sampled and the serum stored for future analysis of serum adiponectin. Serum levels of adiponectin (eBioscience, San Diego, CA, USA) and human SAA (BioSource, Amarillo, CA, USA) were measured in duplicate with enzyme-linked immunosorbent assay kits according to instructions of the respective manufacturers, with the average value used in statistical analyses. The lowest detectable concentration was 0.01mg/L. Co-efficient of variation was required to be less than 15%, otherwise a third measurement was performed. The intra-assay coefficient of variations of the adiponectin were 10%.

5.3.8 Covariates

Covariates for cognitive outcome models specified a priori were age, sex, and educational history.
In addition, other factors considered for inclusion as confounders were occupational history, burden of chronic disease (medications and diagnoses), nutritional supplements, and habitual physical activity level.

5.3.9 *Statistical Analysis*

Outcomes were measured by blinded assessors and analysed using Statview (Version 5.0 for Windows, Cary NC: SAS Institute Inc). Data were inspected for normally visually and statistically. A sample was considered skewed if the standard error of the mean was $\leq -1$ or $\geq 1$. All distributed data are expressed as mean ± standard deviation or median and range or frequencies, as appropriate. Non-normally distributed data were log transformed if possible for use with parametric statistics. Any value of zero was treated as 0.0001 for the purpose of statistical analysis. Comparisons of variables between groups were performed using a one-way ANOVA. The Mann-Whitney U test was used for non-normally distributed continuous data. Multiple linear regressions were used to estimate the independent relationship between either each of the cognitive measures and other variables after controlling for age, sex, and education. These relationships were evaluated the other variables and cognitive domain separately by sex when adjusted age and years of education, as appropriate. All p values of less than 0.05 were considered statistically significant.

5.4 RESULTS

Details of recruitment are included in the study recruitment flow chart (Figure 5.1).
5.4.1 Demographics

The characteristics of the study participants are summarized in Table 5.1. The average age of the participants was 67.9±5.5 years (ranging from 60 to 83), and consisted of 52 men (50.5%) and 51 women (49.5%). Participants were predominantly Caucasian, married, and had completed high school or tertiary level education. Approximately 80% of participants reported alcohol consumption and nearly one-third on a daily basis. Nearly 62% of the cohort had a smoking history, but less than 5% were current smokers.

5.4.2 Health Status

This cohort of adults with T2DM was more obese than the general Australia population in similar age ranges, and they were characterised by a higher number of chronic diseases ranged from 2 to 11 with an average of 5.1±1.9. The medications used in our cohort (75% of the participants took oral diabetic medications, 16% were on insulin, and 11% used both) were similar to recent data from diabetes treatment in Australia where 17% of Australians with diabetes aged 55 or over were prescribed insulin, and 74% of them were prescribed oral diabetic medications, 15.5% were on insulin, and 5% used both.

5.4.3 Metabolic Measures

Glucose Level and HbA1c

Measures of glucose level in our group (7.3±2.4 mmol/L) were similar to two studies, or better than other previous studies. Glucose were generally well controlled by medications in this cohort. Glycaemic control, as indicated by %HbA1c (7.1 ±1.1), was similar to other studies, or better.
in all but one prior study of exercise and T2DM. Our findings may be viewed according to relatively well-controlled glycaemia in this cohort, which may have blinded potential relationships cognitive domains with improvements in glucose homeostasis after power training.

**Insulin Sensitivity**

The average insulin level for this cohort (9.4±4.9 mU/L) was higher than reported for some populations in resistance or aerobic exercise studies but similar to others. Compared to other studies of adults with T2DM, this cohort had lower insulin level than younger, but similar to another study in similar age normal groups. Beta cell function (%B: 110.8±4.5) was higher or lower than other reported measures for these studies with T2DM cohorts. Our group had a lower insulin resistance index (2.9±1.1) to younger, older and similar age groups, compared to other cognitive studies with T2DM. The mean HOMA insulin resistance for our cohort was lower than reported for older population without T2DM.

**5.4.4 Physical Performance**

**Muscle Strength and Power**

Total muscle strength of our cohort was 25198.6±836.1 N, which was 27% higher than the total strength reported in people in the same age group (over 60 years old, 1899±644 N). Total muscle power of our cohort was 1549.2±653.4W, similar to that reported in de Vos’ study (1708±643 W), whose participants were not specifically selected for diabetes, but enrolled in a power training study.

**Walking Endurance**
Average 6MWD for the cohort was 547.6±86.3 m, which was approximately 17% lower than the distance reported in healthy people in a similar age group (55-75 years old, 659±62 m),\textsuperscript{127} and 13% lower than another study which recruited healthy people in a similar age group (50-85 years old, 631±93 m).\textsuperscript{128} These findings are consistent with reported impairments in physical function in older adults with T2DM compared to age-matched peers.\textsuperscript{129, 130} The average 6MWD for men (569.3±92.6 m) and women (523.0±89.1 m) in our study was lower than that reported for men (647.9±201.8 m) and women (579.3±159.8 m) with healthy older adults.\textsuperscript{131}

**Gait Speed**

Seventy-six percent of our cohort was below the normal habitual gait velocity for healthy older adults in the same age group of 1.3 m/s\textsuperscript{33}.\textsuperscript{132} In addition, 18% of our cohort was below the 1.0 m/s threshold for elevated risk of health-related outcomes (persistent and severe lower extremity limitation, death, and hospitalisation within 1 year).\textsuperscript{133}

**Chair Stand**

Our cohort had worse chair stand time (12.1±2.7 sec) compared to older healthy populations\textsuperscript{134-137} but similar to other studies.\textsuperscript{138-140} Compared to other chair stand studies of adults with T2DM this, our cohort were similar in chair stand to some,\textsuperscript{141, 142} or lower than others.\textsuperscript{143-146}

**Stair Climb Power**

Compared to other stair physical performance studies of healthy adults, our cohort had similar stair climber power to older,\textsuperscript{147} or lightly lower than similar age group.\textsuperscript{148} Our sample for stair climb power (370.4±126.6 w) was lower than the values described in other cohort with diabetes (434±72
w) and diabetes neuropathology (407±88 w).149

5.4.5 Body Composition

The baseline descriptive statistics for body composition are presented in Table 5.1.

BMI

The average BMI for our cohort was similar to some studies81, 112, 150 or higher than others.151-153 Compare to other body composition studies of adults with T2DM, this cohort had similar BMI to younger,154-156 older157 and similar age group158 and for women also.159 BMI values for both men (30.3±4.4 kg/m$^2$) and women (32.9±6.0 kg/m$^2$) in our study was comparable to reported values for men and women with diabetes.160

Total Abdominal Adipose Tissue

The average total abdominal adipose tissue area for our cohorts (421.6±117.6 cm$^2$) was lower than other reports in the cohorts with T2DM.157 The mean values of total abdominal adipose tissue for both men (56.8±20.0 cm$^2$) and women (113.1±50.5 cm$^2$) in our study was comparable to reported values for men and women with older adults with T2DM and impaired glucose tolerance.157

Visceral Adipose Tissue

Compared to other resistance or combined exercise studies or body composition analysis of adults with T2DM, for our cohort in our study, the average visceral adipose tissue (215.0±89.2 cm$^2$) was similar to other reports at L4-L5112, 161 and L2-L3.155 The visceral adipose tissue of men in our study (258.7±83.4 cm$^2$) was higher than other groups of men with T2DM154, 157, 162 whereas the
women (169.6±70.9 cm²) in our study had similar visceral adipose tissues to these groups, or slightly lower than others. Two women in our study had very low visceral adipose tissue values of 33.86 cm² and 26.44 cm².

Abdominal Subcutaneous Adipose Tissue

The combined sex sample mean for abdominal subcutaneous adipose tissue area (206.7±90.4 cm²) was much less than the values described in other cohorts with diabetes. The mean of the combined sample of our cohort for thigh muscle area was much lower than slightly more obese adults with T2DM selected over wider age groups who were slightly older. The values reported for similarly aged women by Cuff and colleague were much higher than ours.

Thigh Muscle Area

The mean of the combined sample of our cohort for thigh muscle area was much lower than slightly more obese adults with T2DM selected over wider age groups who were slightly older. The values reported for similarly aged women by Cuff and colleague were much higher than ours.

5.4.6 QUALITY OF LIFE, PSYCHO-SOCIAL STATUS AND PHYSICAL ACTIVITY LEVEL

Total SF-36 MCS scores were slightly higher (48.8±10.8, 45.1±9.2), than those reported in healthy people in the same age group in Australia (45.86 ± 9.03, 44.57 ± 10.75, respectively). Physical Activity Scale for the Elderly (PASE) score of our cohort was 116±60, similar to that reported in Cinzia (111.91 ± 50.39), whose participants were selected for obesity. Average GDS for the cohort was normal at 6.9±5.3, which was approximately 4% lower (better) than reported in healthy people in a similar age group (71-75 years old, 7.2±5.6), and 13% higher than another study.
which recruited healthy people in a similar age group (50-85 years old, 5.75±4.34).128

5.4.7 Recruitment Results
A total of 427 people were assessed for eligibility, and 103 (24.1%) of those were eligible for randomisation, see Figure 5.1. Reasons for exclusion were not meeting study criteria (5.6%), medical reasons (2.1%), too young (1.2%), too physically active (16.4%), too far to travel (8.2%), inability to commit to the study protocol (33.3%), no longer interested in participating (3.5%), work commitments (2.6%) and other (3.0%). One hundred and three participants recruited provided data for these baseline analyses.

5.4.8 Inflammation and Adipokines
The average of our cohort for CRP (3.9±4.2) was similar to one,164 or much less than values than other reports in older adults with T2DM,165 but had higher CRP than younger without diabetes164 Measures of High Molecular Weight adiponectin were similar to166 or lower than one study with T2DM167 and total adiponectin were similar to one study,166 lower than measures values reported coronary heart disease in young group.168

5.4.9 Cognitive Function Tests
The average score in Word List Memory for our cohorts (21.3±3.9) was lower than other reported for intact cognitive older adults with combined exercise studies,169 but similar to others.90, 170 Word List Recall was similar to one,89 or lower170 than the reported measures for these exercise studies without T2DM cohorts. Our group was similar in Word List Recognition to some140 or
slightly lower than cohorts.\textsuperscript{90}

Our combined cohort had TMTA (40.6±12.6) higher than another\textsuperscript{170} but similar to that reported in a slightly more obese group with T2DM.\textsuperscript{111} The average TMTB in our study (95.2±42.5) was higher than one study\textsuperscript{170, 171} or slightly lower than that reported \textsuperscript{111} but similar values\textsuperscript{172} reported for aged people. Pure executive function in our cohorts was lower values reported\textsuperscript{111, 172} in older adults with T2DM but higher than one reported without diabetes and dementia.\textsuperscript{170} Measures of 3MS (94.1±4.8) was higher than other reported in same age group with diabetes,\textsuperscript{173} but similar to values in one study who were slightly older.\textsuperscript{37}

\textit{5.4.10 Relationship between Cognition and Age, Education, and Sex or Health Status or Compliance}

Results are presented in Table 5.2 and 5.3. We adjusted the analyses for several factors that may confound the association of the variable of interest and cognitive function, including age, sex and educational level, as detailed below.

The decline of cognitive domains most frequently seen with advancing age is a reduction of verbal memory, attention, and executive function. In our study, we found that older age was associated with more impaired cognitive function, including Word List Memory (r=-0.33; p<0.01), Word List Recall (r=-0.34; p<0.01), information processing speed (r=0.29; p<0.003), executive function (r=0.22; p=0.028), and global cognitive score (r=-0.24; p=0.02). Moreover, every one year increase in age was also associated with a 0.33-point lower Word List Memory score (p<0.01), a 0.34-point lower Word List Recall score (p<0.01), a 0.12-point lower Word List Recognition score,
a worse score (i.e., 0.29 seconds) on the Trail Making Test A (p<0.003), a worse score (0.22 seconds, p<0.05) on Trail Making Test B, and 0.24-point lower on 3MS. These findings are in general agreement with the findings reviewed by Singh-Manoux and Beeri.\textsuperscript{174, 175} Therefore, in order to assess the relationships among cognitive domains and metabolism, physical performance and body composition; age was added to these models to minimise confounding. Educational level is well known to be related to cognitive function.\textsuperscript{85, 176, 177} In our cohort, higher years of education was related to Word List Recall (r=0.22; p=0.03) and Word List Recognition (r=0.21; p=0.03), pure executive function (r=-0.25; p=0.01), with a trend for Word List Memory (r=0.18; p=0.08), information processing speed (r=-0.18; p=0.07), executive function (r=-0.18; p=0.08) and. Health status such as duration of diabetes was associated with pure executive function (Trail Making Test B minus Trail Making Test A) (r=0.20; p=0.04). Total no. of Medications was significantly associated with Word List Recall (r=-0.30; p<0.01) and Word List Recognition (r=-0.31; p<0.01)) No association between global cognition (3MS) and education was found in our cohort. There were also nosignificant relationships between total no of diseases and any cognitive domain tests. Subsequent regressions were adjusted for educational level based on these relationships therefore.

Sex differences related to cognitive function, body composition, and inflammatory markers\textsuperscript{178, 179} have been established. In our trial, there were significant sex differences between Word List Memory (p=0.001), Word List Recall (p=0.002). A trend for Word List Recognition (p=0.08) and 3MS (p=0.06) were present. Women have higher Word List Memory, Word List Recall, and global cognitive scores than men. For this reason, sex differences should be considered for a clear understanding of the mechanisms related to body composition and metabolic abnormalities.
of T2D associated with cognitive decline not confounded by sex differences in all these variables. Healthy status and compliance were not related to any domains of cognition (p=0.19-0.99).

All analytic models were thus adjusted for age, and years of education and sex, in view of pre-existing literature and our own data presented above. In addition, due to the major differences between men and women in many variables, we also performed regressions stratified by sex, and adjusted for age and education, in order to look at relationships within each sex separately.

5.4.11 RELATIONSHIPS BETWEEN MEASURES OF METABOLISM AND OF COGNITION

Fasting glucose
There was a significant unexpected positive relationship between higher fasting glucose and better delayed memory (r=0.26, p<0.01) (Table 5.3). The relationship between fasting glucose and Word List Recall remained after controlling for age, sex, and education in a multiple regression model (β=0.23, p=0.02) (Table 5.4 and Figure 5.2). When stratified by sex, however, no relationship was found between fasting glucose and any of the cognitive domains. No other cognitive tests were related to fasting glucose. Therefore, this may be a spurious finding.

HbA1c
Contrary to our expectations (Table 5.4), HbA1c was not related to Word List Memory (β=-0.02, p=0.82), Word List Recall (β=0.16, p=0.08), Word List Recognition (β=0.10, p=0.32), information processing speed (β=0.14, p=0.16), attention (β=0.13, p=0.20), executive function (β=0.08, p=0.41), or global cognitive function (β=0.04, p=0.71), adjusting for age, sex, and educational history. When stratified by sex, there were still no significant relationships found.
Fasting insulin

Unexpectedly (Table 5.4), fasting insulin was also not related to any of the cognitive tests (p>0.05). When stratified by sex, there was still no association between fasting insulin and any of the cognitive tests.

Beta cell function

There were no significant relationships between HOMA2-%Beta and memory, information processing speed, executive function, and global cognitive function, again contrary to our hypotheses. When stratified by sex, HOMA 2 % Beta remained unrelated to any of the cognitive domain tests (Table 5.4).

Insulin resistance

Contrary to our hypotheses (Table 5.4), HOMA2-IR was not related to Word List Memory (n=86, β=-0.02, p=0.80), Word List Recall (n=86, β=-0.07, p=0.51), information processing speed (n=86, β=-0.15, p=0.18), attention (n=86, β=-0.18, p=0.09), executive function (n=86, β=-0.12, p=0.26), or global cognitive function (n=86, β=0.13, p=0.25) adjusted for age, sex, and education. Stratification by sex did not alter these non-significant results.

5.4.12 Relationships between Physical Performance and Cognitive Function

Associations between measures of exercise capacity and cognition are presented in Table 5.5. As expected, for the whole cohort, longer 6 Minute Walking Distance (6MWD) was related to better Word List Recall (β=0.22, p=0.04; Figure 5.3), with a nearly significant trend for information processing speed (β=-0.21, p=0.05; Figure 5.5). The relationship between 6WMD and Word List
Recall persisted only in men (men; n=52, β=0.29, p<0.05, women; n=50, β=0.11, p=0.16) when stratified by sex. Consistent with expectations, information processing speed was significantly associated with stair climb power (β=0.34, p=0.001; Figure 5.6) and chair stand time (β=-0.29, p=0.02; Figure 5.7). However, when stratified by sex, the significant relationship between information processing speed and chair stand was only significant in women (women; n=50, β=0.51, p=0.000; men; n=52; β=0.26, p=0.13). No significant associations muscle strength, muscle power, balance, gait speed with any cognitive domains was found.

5.4.13 Relationships between Measures of Body Composition and Cognition

Associations between measures of body composition and cognition are presented in Table 5.6. As expected, sagittal abdominal diameter was inversely related to Word List Recall (β=-0.21 p=0.03; Table 5.11 and Figure 5.4). When stratified by sex, sagittal abdominal diameter remained significant for men (men; n=52, β=-0.35, p=0.009; women; n=49, β=-0.12, p=0.39), with no relationship seen in women. There was a trend towards an association between total abdominal adipose tissue (β=-0.17, p=0.06) and subcutaneous abdominal adipose tissue (β=-0.20, p=0.08) and Word List Recall. Contrary to our hypotheses, no significant relationships between visceral adipose tissue, thigh subcutaneous adipose tissue, intramuscular adipose tissue, mid-thigh cross-sectional area, thigh muscle lipid density, skeletal muscle mass, or fat mass and any of the cognitive tests was observed in the multiple regression analyses after adjusting for age, sex, and years of education, nor when stratified by sex.
5.4.14 Relationships between Psychosocial Status, Physical Activity and Cognitive Function

Results are presented in Table 5.7. Using multiple linear regression models, unexpectedly, higher physical activity level (PASE) was positively related to pure executive cognitive tests ($\beta=0.29$, $p=0.01$; Table 5.7 and Figure 11). However, the gender effects relationship between cognitive function and PASE remained a trend in men ($n=39$, $\beta=0.29$, $p=0.06$), with no relationship seen in women ($p=0.10$).

Depression and SF-36 MCS and PCS scores were not significantly related to any cognitive domains ($p=0.17-0.97$) in the overall cohort. However, when stratified by sex, there was a significant relationship between depression score and executive function in women (TMT-B; $n=48$, $\beta=0.30$, $p=0.04$, and TMT-B minus A; $n=48$, $\beta=0.32$, $p=0.03$), but not in men. As hypothesised, more depressive symptoms were associated with worse executive function on these tests of executive function in the women.

5.4.15 Relationship between Inflammation and Adipokines and Cognition

As expected, for the whole cohort (Table 5.8 and 5.15), higher serum CRP was related to slower information processing speed ($n=88$, $\beta=0.30$, $p<0.01$; Figure 5.8). However, when stratified by sex, the relationship between CRP and information processing speed was stronger in women ($n=42$, $\beta=0.35$, $p=0.05$), and attenuated and no longer significant in men ($n=46$, $\beta=0.27$, $p=0.06$). Contrary to our expectations, however, serum CRP was not related to Word List Memory ($n=88$, $\beta=-0.01$, $p=0.97$), Word List Recall ($n=88$, $\beta=-0.11$, $p=0.28$), Word List Recognition ($n=88$, $\beta=-0.13$, $p=0.44$), attention/executive function ($n=88$, $\beta=-0.02$, $p=0.87$), pure executive function ($n=88$,
β=-0.13, p=0.21), or global cognitive function (n=88, β=-0.04, p=0.87).

As hypothesised, serum total adiponectin was directly related to Word List Recall (n=39, β=0.25, p=0.04; Table 5.16; Figure 5.9), but not related to other tests of cognitive function (p=0.11-0.91). When stratified by sex, the relationship between high serum adiponectin and Word List Recall was stronger in women (n=19, β=0.59, p<0.01) but not present in men (n=20, β=0.12, p=0.53). Higher serum HMW adiponectin: adiponectin ratio was related to better pure executive function (n=39, β=-0.43, p=0.01; Table 5.17 and Figure 5.10), but no other cognitive tests (p=0.25-0.78). When stratified by sex, this remained significant for men (men; n=20, β=-0.49, p=0.02) and was slightly attenuated in women (n=19, β=-0.44, p=0.08).

5.5 DISCUSSION

To our knowledge, this is the first investigation examining the relationship of indices of insulin resistance and glucose homeostasis, physical performance, body composition, and systemic inflammation to a wide range of cognitive tests including immediate memory, delayed memory, information processing speed, attention/executive function, and global cognitive function specifically in a clinical cohort of older adults with T2DM. Furthermore, it is the first investigation to simultaneously examine glucose hemostasis, insulin resistance, physical performance, body composition, and systematic inflammation within the same cohort, and measure adipose tissue and muscle mass using two distinct body composition techniques (BIA and CT scan). Previous investigations have used only abdominal fat, or measures of muscle mass or 6MWD or muscle strength, or glucose control and insulin resistance, or CRP in healthy participants. Our comprehensive assessment of multiple physiological
characteristics represents a major advance over previously published investigations. We have demonstrated that 6MWD, stair climb power, sagittal abdominal diameter, systematic inflammation, adipokines (adiponectin) are related to specific cognitive domains in this cohort.

In general, our baseline cognitive test results suggest that a ceiling effect was present for some cognitive domains in our cohort, which might have obscured some relationships between insulin resistance, glucose homeostasis, physical performance, body composition, CRP, adiponectin, and cognitive capacity.

5.5.1 HEALTH STATUS

Our cohort was primarily overweight or obese, and this percentage (97%) was higher than a similar age group (approximately 71% in people aged 55 or over not selected for diabetes) reported by Australian Bureau of Statistics. The medications used in our cohort (67% of the participants took oral diabetic medications, 16% were on insulin, and 14% used both) were very similar to medications used by older adults with diabetes in Australia. For example, 18% of people with diabetes and aged 55 or over in Australia are prescribed insulin, and 72% of them take oral diabetic medications.

Generally speaking, the health status of our cohort (97% overweight or obese; 44% high total cholesterol; 79% raised triglycerides; 77% reduced HDL cholesterol; 74% hypertension, 3% stroke, 18% cardiovascular disease) was worse than the health status of people with diabetes in Australia (59.6% overweight or obese; 51.2% high total cholesterol; 20.5% raised triglycerides; 23.1% reduced HDL cholesterol; 28.8% hypertension). However, this comparative data is from AusDiab (The Australian Diabetes, Obesity and Lifestyle Study), which included a representative
sample of those aged 25 or over with diabetes. This broader age range likely explains the lower prevalence of comorbidity.

Our cohort is comparable to other resistance training or combined resistance and aerobic exercise studies that have analysed Caucasian populations. Other reports have included Latino,\textsuperscript{81} Asian Indian,\textsuperscript{151, 152} Japanese\textsuperscript{153} population with T2DM. Sample sizes of these intervention were typically small in two randomised controlled trial which included combined training and combined versus single mode trial in participants with T2DM.\textsuperscript{112, 150} Another non-randomised controlled trial which included aerobic training in 16 participants with T2DM reported age, education, cognitive function, and glucose control similar to our cohort.\textsuperscript{186} The age, BMI, and general health status of our cohort was similar to other studies of adults with T2DM participating in resistance training alone\textsuperscript{187} and similar to another Australian sample.\textsuperscript{115}

5.5.2 Measures of Metabolism and Cognitive Function

Glucose control and cognitive function

We hypothesised that metabolic disturbance would also be related to lower cognitive performance, but the associations we found for one test of memory were unexpectedly positive between higher fasting glucose level and better delayed memory, even after adjusting for age, sex, and educational level. Given that it was not present when stratified by sex, and no other cognitive tests were related to glucose, it may be a spurious finding.

We did not see any relationship of HbA1c and cognition, contrary to our hypotheses. Others have shown that glucose level was negatively related to cognitive decline.\textsuperscript{120} Another study
demonstrated that a cognitive benefit is achievable in reasonably well-controlled T2DM adults (mean age of 60 years; glycated hemoglobin levels less than 8.0%) with no evidence of dementia (using the MMS) or depression, who further improve their blood glucose control through use of diabetic medications (ie, insulin sensitizers).172, 188 For those subjects, treatment-induced reductions in fasting plasma glucose levels were accompanied by improvements in cognition (ie, working memory). The lack of relationship in our cohort is not fully understood at this time, but there are several possibilities. It is possible that the lack of association of cognitive function with HbA1c could be attributed to the tight level of glycaemic control (7.1±1.1%) with glucose-lowering drugs in the cohort, which was much lower than earlier diabetes exercise studies. Secondly, cognitive function was relatively intact in our subjects for many of the tests. Thus, the combination of relatively intact cognitive function and good metabolic control in this cohort may have obscured potential relationships between cognition and glucose homeostasis seen in some previous literature.

Insulin resistance and cognitive function

It was also hypothesised that higher beta cell function would be related to better cognitive performance, but no associations were found between HOMA2-%beta and any cognitive domains. The role of insulin and insulin resistance on cognition in patients with diabetes is obscure, especially in the elderly. Previous studies that investigated the relationship between insulin resistance and cognitive function suggested a number of possible biological mechanisms that could be involved, including accumulation of oxidative stress with advanced glycation end products120, 121 and also decreased cortical glucose utilisation, particularly in the hippocampus and entorhinal cortex. Insulin resistance may also cause Tau phosphorylation and neurofibrillary tangle
formation, and increased beta amyloid aggregation.\textsuperscript{122} Although it is difficult to address the role of these suggested mechanisms, the current literature suggests that insulin resistance and hyperinsulinemia are important for cognitive decline, especially in elderly women.\textsuperscript{189}

Our results were inconsistent with the current literature supporting the evidence for insulin resistance resulting in cognitive dysfunction.\textsuperscript{189} It is possible that our cohort had cognitive function which was too well preserved, precluding demonstration of such relationships. In addition, most previous studies established the mean values to assess insulin resistance in adults with T2DM ranging from 3.875 to 5.825 for the HOMA index.\textsuperscript{120,190} When compared with our data, these insulin resistance indices were much higher. Thus, in our study, the relationships between insulin and insulin resistance and cognition may have been obscured by intensive medication management, which may both control glycaemia and improve insulin sensitivity (metformin). Moreover, the effect of insulin resistance on cognition might be long-term, as others have reported the effects of higher insulin level on global cognition and verbal memory up to 10 years later.\textsuperscript{191} Additionally the HOMA2 calculation will estimate lower insulin resistance than the gold standard euglycaemic clamp. The HOMA2 model has been validated as a measure of fasting insulin resistance reflective of hepatic insulin sensitivity\textsuperscript{87, 88} However, one of the limitations of this methodology is that it does not directly reflect whole body or peripheral sensitivity in skeletal muscle.\textsuperscript{192} Thus, additional studies are needed to clarify the association between insulin resistance and cognition, using precise measures of whole body insulin resistance and a broader range of metabolic control and cognitive function, as well as via long term follow-up.
5.5.3 RELATIONSHIP BETWEEN PHYSICAL PERFORMANCE AND COGNITIVE FUNCTION

It has been reported that poorer physical fitness and low physical activity are related to cognitive decline in people at risk for diabetes. Our study showed that cognitive function (Word List Recall and Trail Making Test A) was negatively related to 6MWD, chair stand time, and stair climb power. To our knowledge, this is the first evidence to show that cognition in older people who have already developed T2DM is associated with poor physical function and low exercise capacity. The physical function and exercise capacity tasks which were related to worse cognitive decline are composite measures of mobility, lower extremity, strength and power, balance, aerobic capacity, underlining the clinically important impact of cognitive function on ability to function independently in this cohort.

T2DM and its common complication, central and peripheral neuropathy, may lead to sensory and motor deficits, which can result in mobility-related dysfunction, alterations in gait characteristics and balance impairments. Patients with peripheral neuropathy of diabetes have lower gait velocity, decreased cadence, shorter stride length, increased stance time and higher step to step variability compared to healthy controls. Moreover, these patients have less ankle moment and ankle power, as well as a different onset and cessation time of muscle activity. In addition, reductions in exercise capacity, sit to stand, and stair climb power in T2DM complications have been related to impaired physical function, neurologic abnormalities, impaired muscle mass, strength, aerobic capacity and balance. Gait speed or strength or muscle mass or aerobic capacity are the components of exercise capacity most strongly associated with cognitive function in the literature, while the executive function and attention domains of cognition are most consistently related to exercise capacity. Additionally, in our cohort, higher insulin resistance
was related to worse physical performance, including 6MWD, habitual gait speed, and chair stand power.

Mechanisms linking these factors to cognition may include changes in muscle metabolism. For example, contracting muscles secrete so-called myokines that mediate an anti-inflammatory effect,\textsuperscript{199, 200} and have been related to increased brain blood flow volume, increased insulin level in the brain, higher brain derived neurotrophic factor (BDNF), and improved neuroplasticity, as well as improved.\textsuperscript{200-206} This may be one explanation for the link between exercise capacity, physical function and cognition. The mechanisms of this association will need to be investigated by subsequent intervention trials.

5.5.4 \textbf{RELATIONSHIP BETWEEN MEASURES OF BODY COMPOSITION AND COGNITIVE TEST SCORES}

This analysis of 103 individuals with established T2DM demonstrated a clear inverse relationship between cognitive function and central obesity as measured by the SAD and other measures after adjusting for age, educational history, and sex. This is in agreement with Kanaya et al,\textsuperscript{37} who showed the same relationship amongst the health ABC cohort. Their investigation however involved a cohort that included older adults with and without diabetes (average 3MS score 90). Our study was the first to include exclusively older men and women, all with T2DM. Kanaya (2009) reported that this relationship was weakened when those with overt diabetes were included in the analyses,\textsuperscript{37} but our data by contrast show a strong inverse relationship between central obesity measure SAD and Word List Recall still exists within this particular cohort. In fact, our multiple regression models suggest that contribution of SAD to Word List Recall among this cohort is greater than that of other measures of central obesity, supporting the fact that SAD is closely
linked with the amount of metabolically unfavorable depots of abdominal fat and thus may become a good predictor of risk of cognitive decline.

Several studies have examined the effect of overweight on cognitive function. Some longitudinal studies have found that a higher BMI is associated with increased risk of developing dementia, while others have found no association. Fewer studies have evaluated the association between adiposity and cognitive function or decline in intact cognitive older adults with T2DM. We found 2 prospective studies that evaluated the effect of BMI on cognitive function. The first observed 1423 individuals in the Framingham Heart Study for 4 to 6 years and found that higher BMI was associated with worse cognitive function scores in men. The second study was performed in 5607 postmenopausal Danish women observed for 7 years; it examined baseline body weight, yearly change in weight, and central fat mass by whole-body dual x-ray absorptiometry. The authors found a protective association of body fat mass with cognitive impairment in the elderly women and showed that those who lost the most weight had the worst cognitive performance at follow-up. Neither of these studies had baseline measures of cognitive function or more precise measures of regional adiposity. Our findings that sagittal abdominal diameter as a mark of visceral adipose tissue have greater cognitive decline is consistent with the Framingham results, and our finding that men show an inverse associations with visceral adipose tissue, sagittal abdominal diameter, and subcutaneous abdominal adipose tissue and cognitive change is consistent with the Danish study. We have extended the literature by observing that total body fat and subcutaneous abdominal fat are the 2 adiposity measures that have the strongest effect on cognitive change in men.
Our study is the first to more closely examine regional adiposity measured computed tomography. Surprisingly, our direct measure of visceral fat, which has been most closely tied to poor metabolic outcomes, had only a borderline significant association with cognitive change. There were effects of VAT in men. This may be because only the men had high enough VAT to show relationships with cognition.

Our findings demonstrate that increasing levels of sagittal diameter abdominal diameter are strongly associated with worsening cognitive function in older persons with diabetes. Men show inverse associations between adiposity and cognitive change. Future studies should confirm these longitudinal associations with adiposity and cognitive change and investigate why adiposity has inverse associations in men but not in women.

5.5.5 Relationship between Psychosocial Status, Physical Activity, Quality of Life and Cognitive Function

Physical Activity

Previous studies have examined the effect of physical activity level on cognitive function. Some longitudinal studies have found that a higher physical activity is associated with better cognitive function,\textsuperscript{211, 212} while others have found no association.\textsuperscript{213} Fewer studies have evaluated the association between physical activity and cognitive function or decline in adults with T2DM. We found 2 experimental studies that evaluated the effect of physical activity on cognitive function.\textsuperscript{214} The first study for 26 week intervention and found that higher physical activity was associated with better cognitive function scores.\textsuperscript{214} The second study was performed higher physical exercise for 26 weeks; it examined the effects of exercise on cognition.\textsuperscript{215} Unexpectedly, there
was a significant positive association between Physical Activity Scale for the Elderly and executive domain of cognition in the multiple regression model. The relationship remained unexplained by other variables. Although literature was mixed with regard to the association physical activity levels with cognitive function, particularly in cross-sectional studies, the majority of physiological data would suggest that higher levels of physical activity was beneficial for cognitive function according to our original hypothesis. The results of the intervention in our trial would hopefully clarity the role of anabolic interventions such as power training on cognitive function in this cohort with T2DM.

Geriatric Depression Scale

T2DM has been linked to an increased risk of cognitive impairment and shown higher prevalence of depressive symptoms, and depressive symptoms might be related to cognitive impairment.\(^\text{216-222}\) Although it is known that depression, mild cognitive impairment (MCI), and dementia are highly prevalent chronic conditions associated with social support, biomedical factors, and economic burdens, since it has been reported that depressive symptoms are related to white matter and lacunae abnormalities\(^\text{223}\) and severity of diabetic complications.\(^\text{224}\) There is less literature that evaluates the effects of depression on cognitive function with T2DM. Recent studies in health maintenance organization populations examined whether depression was associated with an increase in the risk of all-cause dementia among patients with diabetes.\(^\text{221,222}\) One study, among nearly 4000 patients with T2DM, found a doubling of the risk of dementia diagnosis for patients with depression after 3 to 5 years of follow-up.\(^\text{221}\) The another one study of nearly 20 000 patients with T2DM also found a doubling of the risk of a dementia diagnosis for patients with depression after 3 to 5 years of follow-up.\(^\text{222}\) These studies were limited by their reliance on medical record
diagnoses of dementia, which lack sensitivity and are prone to ascertainment bias. Our study is the first to more closely examine depression measured GDS. Surprisingly, our direct measure of depression, which has been most closely tied to poor metabolic outcomes, had no significant association with cognitive change. It is possible that our sample size for depression is too small to identify the negative benefits.

Quality of Life

Cognitive dysfunction in older adults with T2DM is relatively well described. Cognitive impairment may subsequently contribute to reduced fulfilment in work life and social life as well as in a reduction in health-related quality of life (QoL). To our knowledge, there is less literature that evaluates the effects of quality of life identified only in the context of the mental and physical health limitations domain on change in cognitive function.

Prior studies examining the relationship between cognitive impairment and QoL have revealed inconsistent results. One study have examined the effect of quality of life on cognition, using either Mental or physical health composites of the MSQOL-54 were not predicted by cognitive functions in Benedict’s report. Cognitive status was not identified as a quality of life predictive factor by Amato et al. Similarly, results of other investigations indicated an absence of significant relations between cognitive measures (i.e., memory, executive function, and global cognitive function) and the PCS and MCS scales of the SF-36. In contrast, in Montel’s study, a negative impact of cognitive impairment was identified only in the context of the mental health limitations domain of the SEP-59 questionnaire. Other authors have reported a more obvious association between cognitive deficits and self-reported quality of life outcomes. Benito-Leon’s
study reported associations between lower cognitive scores (MMS) and lower quality of life levels. Therefore, the relationships between QoL and cognitive function are complex and contradictory. These relationships may be sensitive to the method used to measure and define relative deficiencies of quality of life, as well as the specific cognitive impairment.

T2DM are at greater risk for reduced functional abilities and poorer quality of life. Cognitive impairment may have a profound effect in the treatment management of T2DM in older patients (i.e., poorer adherence to medication; dietary and physical activity recommendations). Other work showed greater cognitive impairment among older adults with T2DM is related with poorer disease care management and adherence. Previous animal studies have shown physical activity to improve insulin resistance and attenuate neuroautonomic dysregulation and improve cognitive function among rats. Similarly, other studies have shown that lower scores on clinical neuropsychological tests of memory, executive function and global cognitive function have been associated with lower scores on measures of QoL among those with chronic disease. The lack of relationship in our cohort is not fully understood at this time, but there are several possibilities. Our cohort with diabetes are likely to have less advanced brain pathology and relatively intact cognitive function assessed by the stranded cognitive test battery we used, possibly due to their good glucose control. Another possibility for their preserved cognitive function could be the generally low levels of depression in the group with diabetes, possibly due to their high social support. Both social support positive affect could potentially blunt any potential negative effects of cognition on the emotional and physical domains of health-related QoL. However, we were unable to confirm the impact of social support because this data was not collected in our study.
5.5.6 Systematic Inflammation and Cognition

We have shown for the first time that CRP level and cognitive function in the older adults with T2DM were inversely related. In agreement with our data, Mariano et al concluded in an Edinburgh T2DM Study that elevated CRP levels were positively related to worse information processing speed. Others have shown CRP to be associated with cognitive decline in healthy individuals. Our findings also support previous studies that have demonstrated deleterious effects of inflammation on cognition. It is known that CRP is an independent risk factor for cardiovascular disease, and previous studies have also suggested a relationship with cognitive decline. These findings are not fully understood at this time, but a possible explanation as to why CRP seems to be particularly detrimental to information processing speed during diabetes may be linked to the damage to cerebral small vessels. Low grade systemic inflammation mediated by CRP may lead to increased blood–brain barrier permeability, impairment of endothelial function, toxic elevations of intracellular calcium, and local inflammation in the brain. Moreover, associations of the low-grade inflammatory CRP with frontal white matter changes were found by others. This may be why we found an association with poorer information processing speed in our study.

Cognitive dysfunction can have a significant impact on quality of life including disability, daily care, exercise capacity, and mortality and has been associated with metabolic syndrome and diabetes-comorbidities such as hypertension, hyperlipidemia, and even obesity, which lead to increase low-grade inflammatory levels that ultimately impaired in cognition. Thus, serum CRP is inflammatory biomarker for cognitive diseases that warrant validation in future intervention studies.
5.5.7 *Serum Adipokines and Cognition*

As hypothesised, higher circulating adiponectin levels and HMW adiponectin relative to total adiponectin ratio showed a significant correlation with scores on Word List Recall (delayed memory) difference score between Trail Making Test B minus Trail Making Test A (measure of pure executive function), after controlling for age, sex, and educational levels. Others have shown that plasma total adiponectin was positively related to cognitive function.²⁴⁹

Adiponectin is the most abundant anti-inflammatory adipokine. Several studies have reported that high levels of adiponectin are related to decreases in the expression of inflammatory cytokines, such as TNF-α and NF-kB activation.⁵⁸ Increased adiponectin levels also induce the production of other anti-inflammatory molecules like IL-10 and IL-1 receptor antagonist.²⁵⁰ The presence of pro-inflammatory cytokines in the brain tissue adjacent to amyloid plaques may contribute to the progression and acceleration of AD-related neurodegeneration.⁶³ Conversely, elevated levels of TNF-α and IL-6 are able to inhibit adiponectin transcription in the adipocyte.²⁵¹ Therefore, it is possible that lower adiponectin levels may have a dual effect on the physiopathology of cognitive impairment by stimulating pro-inflammatory cascades and inhibiting anti-inflammatory cascades, thus favoring the higher pro-inflammatory state observed in MCI and AD.²⁵² In addition, as adiponectin regulates brain metabolism and sensitivity to insulin,²⁵³ its reduction may contribute to the deregulated glucose metabolism and mitochondrial dysfunction observed in AD.²⁵⁴

In a previous prospective epidemiological study, increased adiponectin levels were associated with increased risk of dementia and AD in participants with no evidence of cognitive decline, particularly in women.⁶⁴ However, another population-based study did not find a significant
association between adiponectin levels and cognitive impairment in older individuals.\textsuperscript{66, 67} Differences in the sample size, characterisation of cognitive status of included participants, and presence of clinical comorbidities might explain discrepant results observed among current available studies. In addition, these distinct results observed for adiponectin levels may be, in part, due to the heterogeneous nature of the pathologic changes in the preclinical stages of dementia and AD.\textsuperscript{255} Therefore, additional studies, preferentially including participants across multiple cohorts, are needed to help to disambiguate the relationship between circulating adiponectin levels and the risk of cognitive function. Thus, the consistency and clinical relevance of adiponectin findings remains speculative and requires further study.

Implications and future direction

Notably, the main implication from the current investigation is that when considering the cognitive health of an individual, it is important to consider sex, age, exercise capacity, physical function, central adipose tissue, systemic inflammation, and anti-inflammation. While physical inactivity, central obesity, and inflammation are well-known contributors to cognitive decline, our multiple regression model suggests that exercise capacity, physical function, central adipose tissue, and systemic pro- and anti-inflammatory profile are related to cognitive function, independent of age, sex and years of education. Furthermore, lower exercise capacity was related to higher CRP, insulin resistance, and sagittal adipose diameter, as well as lower muscle mass in our cohort, suggesting these factors may confound or mediate associations with cognition observed in this and other studies. Similarly, inflammatory mediators such as CRP are related to adipose tissue as well as insulin resistance, and may be potentially mediators of the relationship to cognition.
Given the above findings, the use of resistance training, or other anabolic interventions which lead to improvements in exercise capacity, body composition, CRP, insulin resistance, and adiponectin would thus be theoretically beneficial for cognition. This unique form of exercise has the ability to reduce adipose tissue and systematic inflammation, and increase skeletal muscle mass while concomitantly increasing exercise capacity. Indeed, clinical trials utilizing PRT show this to be true. Furthermore, improvements in health outcomes following an exercise program can be seen in patients with T2DM due to improvements in body composition (decreased fat, increased skeletal muscle), insulin resistance, inflammation, and exercise capacity. Importantly, hypothesised pathways linking cognitive impairment to T2DM are multiple and complex, including insulin resistance in brain, decreased neuroplasticity and cerebral atherosclerosis, among others. Improvements in systemic inflammation, insulin resistance, exercise capacity, and body composition are possible with PRT, and could be ultimately beneficial to preservation of cognitive function in this cohort therefore.

The cross-sectional nature of this investigation doesn’t allow for the determination of causality. In theory, it is possible that low cognitive function causes lower physical activity and therefore leads to metabolic deteriorations, low-grade inflammation, and increased fat and reduced muscle mass. Anabolic interventions would still be indicated in this case, as they may serve to combat lower exercise capacity associated with insulin resistance, inflammation, and increased fat and reduced muscle mass. To verify our results, large-scale prospective and mechanistic studies are needed to examine this important issue of etiology vs. consequence of body composition and exercise capacity relationships to cognition. It is quite likely that bi-directional relationships exist between exercise capacity and cognition. Theoretically higher exercise capacity may be
involved in the pathogenesis of cognitive protection mediated by higher physical activity level, leading to reduced insulin resistance, inflammation, and reduced fat and increased muscle mass. If such causality is determined, development of optimal therapeutic strategies may minimise progression of cognitive decline associated with T2DM.

One major limitation of this study is the cross-sectional design; thus causal inferences about these relationships cannot be made. Secondly, due to participant burden constraints, our analyses were restricted to the use of the HOMA2-IR, an estimate of fasting hepatic insulin resistance. Whole body insulin sensitivity measures such as a the hyperinsulinaemic/euglycaemic clamp would have provided more specific data related to skeletal muscle and adipose tissue insulin sensitivity and glucose disposal. Thirdly, the total fat mass and skeletal muscle mass were measured using BIA. Finally, CRP has been shown to independently predict cognitive deficit within this cohort, and thus its relationship to body composition, insulin resistance and glucose homeostasis is of significant interest. However, it must be considered that other pro-inflammatory cytokines such as TNF-α and interleukins 1 and 6 (IL-1 and IL-6) are known to independently be associated with cognitive function. To verify our results, prospective analyses between cognition and circulating cytokines are warranted, to establish a better understanding of body composition, inflammation, insulin resistance and glycemic control, physical function and exercise capacity in relation to cognitive function within individuals with T2D.

5.6 CONCLUSIONS
Generally speaking, the health status of our cohort was worse than people with diabetes in Australia. They were more obese, and the prevalence of hypertension, raised triglycerides,
reduced HDL cholesterol and the use of insulin and oral diabetic medications were all higher than people with diabetes in Australia, substantiating the potential generalisability of our clinical trial outcomes to this cohort or other Caucasians or other international populations with T2DM (external validity).

The muscle strength and power of our cohort were higher than people in the same age group, which could be explained by the larger body weight and consequently large fat free mass. However, the overall exercise capacity, represented by 6MWD and physical function assessed by stair climb power, of our cohort was more limited than healthy people of a similar age.

Our results suggest the importance of lower exercise capacity and stair climb power for worse memory and information processing speed in older adults with T2DM. We have shown that the predictive value of sagittal adipose diameter was independent of, and stronger than that of visceral adipose tissue for memory in this cohort. Our data also demonstrate an association between increases in low-grade inflammation assessed by CRP and reductions in total adiponectin and HMW adiponectin relative to total adiponectin ratio and poorer cognitive function. Overall, these data expand evidence from animal models and healthy individuals, showing for the first time in older adults with T2DM that physical performance, body composition, inflammation, and adiponectin are related to cognitive function. Multiple regressions model included all of these factors showed that they were all independently and still significantly related to cognitive function adjusted for age, sex, education level, and physical activity level. Understanding how chronic exercise exposure may modify these factors is crucial to advance our understanding and optimisation of the physical activity prescription for cognitive health.
5.7 REFERENCES


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### TABLE 5.1 SAMPLE SIZE CALCULATIONS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Experimental Mean Change (SD)</th>
<th>Control Mean Change (SD)</th>
<th>Effect Size (ES)</th>
<th>Beta</th>
<th>Alpha</th>
<th>Sample Size Estimate (total study)</th>
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<tr>
<td>Insulin Sensitivity (HOMA2-IR)</td>
<td>-0.6(0.8)</td>
<td>0(0.8)</td>
<td>0.75</td>
<td>0.10</td>
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<tr>
<td>HbA1c (%)</td>
<td>-1.2(1.7)</td>
<td>0(0.2)</td>
<td>0.71</td>
<td>0.1</td>
<td>0.05</td>
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<tr>
<td>Cognition</td>
<td></td>
<td></td>
<td>0.59</td>
<td>0.2</td>
<td>0.05</td>
<td>94</td>
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</tbody>
</table>

HOMA2: Homeostasis Model Assessment 2

IR: Insulin Resistance

HbA1c: Glycosylated Haemoglobin A1c

Sample size estimates were driven by hypothesised differences between the experimental and control participants in the primary outcomes of the trial: insulin sensitivity and HbA1c, based on an average of published studies of in diabetes/obesity.80-83, 85, 116
### TABLE 5.2 BASELINE CHARACTERISTICS OF GREAT2DO PARTICIPANTS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n=103</th>
<th>Men n=52</th>
<th>Women n=51</th>
<th>p-value</th>
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<td><strong>Demographics</strong></td>
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<tr>
<td>Age (years)</td>
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<td>68.9±6.0</td>
<td>66.9±4.8</td>
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<td><strong>Education</strong></td>
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<tr>
<td>Primary School</td>
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<td>1 (1%)</td>
<td>2 (1.9%)</td>
<td>0.546</td>
</tr>
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<td>High School</td>
<td>46 (44.6%)</td>
<td>19 (18.4%)</td>
<td>27 (26.2%)</td>
<td>0.094</td>
</tr>
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<td>Tertiary</td>
<td>45 (43.7%)</td>
<td>25 (24.3%)</td>
<td>20 (19.4%)</td>
<td>0.365</td>
</tr>
<tr>
<td>Post-Graduate Study</td>
<td>9 (8.7%)</td>
<td>7 (6.8%)</td>
<td>2 (1.9%)</td>
<td>0.086</td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
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<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>99 (96.1%)</td>
<td>49 (47.6%)</td>
<td>50 (48.5%)</td>
<td>0.097</td>
</tr>
<tr>
<td>Asian</td>
<td>4 (3.9%)</td>
<td>2 (1.9%)</td>
<td>2 (1.9%)</td>
<td>0.984</td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Married/Defector</td>
<td>59 (57.3%)</td>
<td>35 (34.0%)</td>
<td>24 (23.3%)</td>
<td>0.038</td>
</tr>
<tr>
<td>Widowed</td>
<td>12 (11.7%)</td>
<td>4 (3.9%)</td>
<td>8 (7.8%)</td>
<td>0.206</td>
</tr>
<tr>
<td>Divorced</td>
<td>19 (18.5%)</td>
<td>8 (7.8%)</td>
<td>11 (10.7%)</td>
<td>0.419</td>
</tr>
<tr>
<td>Never Married</td>
<td>11 (10.7%)</td>
<td>5 (4.9%)</td>
<td>6 (5.8%)</td>
<td>0.750</td>
</tr>
<tr>
<td>Separated</td>
<td>2 (1.9%)</td>
<td>0 (0.0%)</td>
<td>2 (1.9%)</td>
<td>0.149</td>
</tr>
<tr>
<td><strong>Smoking-CURRENT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>25 (24.2%)</td>
<td>7 (6.7%)</td>
<td>18 (17.5%)</td>
<td>0.010</td>
</tr>
<tr>
<td>Once a Month</td>
<td>7 (6.8%)</td>
<td>1 (1%)</td>
<td>6 (5.8%)</td>
<td>0.047</td>
</tr>
</tbody>
</table>
### TABLE 5.2 BASELINE CHARACTERISTICS OF GREAT2DO PARTICIPANTS - CONTINUED

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n=103</th>
<th>Men n=52</th>
<th>Women n=51</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Two or Three Times a Month</td>
<td>11 (10.7%)</td>
<td>4 (3.9%)</td>
<td>7 (6.8%)</td>
<td>0.322</td>
</tr>
<tr>
<td>Once or Twice a Week</td>
<td>21 (20.4%)</td>
<td>11(10.7%)</td>
<td>10 (9.7%)</td>
<td>0.846</td>
</tr>
<tr>
<td>Three to Four Times a Week</td>
<td>13 (12.6%)</td>
<td>7 (6.8%)</td>
<td>6 (5.8%)</td>
<td>0.795</td>
</tr>
<tr>
<td>Almost Every Day</td>
<td>25 (24.2%)</td>
<td>21 (20.4%)</td>
<td>4 (3.9%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Health Status**

**Normal Weight**

- BMI: 18.5 – 24.9 kg/m²
  - Total: 3 (2.9%)  Men: 1 (1%)  Women: (1.9%)  p-value: 0.546

**Overweight**

- BMI: 25.0 – 29.9 kg/m²
  - Total: 33 (32.0%)  Men: 21(20.4%)  Women: 12(11.6%)  p-value: 0.067

**Obese**

- BMI ≥30kg/m²
  - Total: 67 (65.0%)  Men: 30 (29.1%)  Women: 37 (35.9%)  p-value: 0.114

- Cerebral Vascular Disease
  - Total: 3 (2.9%)  Men: 3 (2.9%)  Women: 0 (0.0%)  p-value: 0.082

- Depression Score >10
  - Total: 18 (17.5%)  Men: 5 (3.9%)  Women: 13 (12.6%)  p-value: 0.034

- Previous history of CVD
  - Total: 19 (18.4%)  Men: 14 (13.6%)  Women: 5 (4.9%)  p-value: 0.025

- Hypertension
  - Total: 76 (73.8%)  Men: 38 (36.9%)  Women: 38 (36.9%)  p-value: 0.869

- Hyperlipidaemia
  - Total: 45 (43.7%)  Men: 17 (16.5%)  Women: 28 (27.2%)  p-value: 0.003

- Diabetes Duration (years)
  - Total: 7.0 (28)  Men: 6.3 (25)  Women: 7.5 (28)  p-value: 0.047

**Metabolic Syndrome**

- Central Obesity
  - Total: 100 (97.1%)  Men: 50 (96.1%)  Women: 50 (98.0%)  p-value: 0.323

- Raised Triglycerides
  - Total: 81 (78.6%)  Men: 41 (39.8%)  Women: 40 (38.8%)  p-value: 0.950
TABLE 5.2 BASELINE CHARACTERISTICS OF GREAT2DO PARTICIPANTS - CONTINUED

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=103)</th>
<th>Men (n=52)</th>
<th>Women (n=51)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reduced HDL Cholesterol</td>
<td>77 (74.8%)</td>
<td>39 (37.9%)</td>
<td>38 (36.9%)</td>
<td>0.954</td>
</tr>
<tr>
<td>Hypertension</td>
<td>101 (98.0%)</td>
<td>50 (48.5%)</td>
<td>51 (49.5%)</td>
<td>0.157</td>
</tr>
<tr>
<td>Diabetes/Raised Fasting</td>
<td>103 (100 %)</td>
<td>52 (50.5%)</td>
<td>51 (49.5%)</td>
<td>0.982</td>
</tr>
<tr>
<td>Plasma Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDF Diagnosis of Metabolic Syndrome</td>
<td>100 (97.0%)</td>
<td>50 (48.5%)</td>
<td>50 (48.5%)</td>
<td>0.569</td>
</tr>
<tr>
<td>Sedentary (hour/day)</td>
<td>10.9±1.3</td>
<td>11.2±1.2</td>
<td>10.6±1.3</td>
<td>0.046</td>
</tr>
<tr>
<td>Number of Chronic Diseases (n)</td>
<td>5.1±1.9</td>
<td>5.1±2.1</td>
<td>5.1±1.7</td>
<td>0.560</td>
</tr>
<tr>
<td>Number of Medications (n)</td>
<td>6±3</td>
<td>6±3</td>
<td>5±3</td>
<td>0.187</td>
</tr>
<tr>
<td>Number on Insulin</td>
<td>16 (15.5%)</td>
<td>10 (9.7%)</td>
<td>6 (5.8%)</td>
<td>0.296</td>
</tr>
<tr>
<td>Metformin Users</td>
<td>74 (70%)</td>
<td>42 (19%)</td>
<td>32 (31%)</td>
<td>0.040</td>
</tr>
<tr>
<td>Metformin Dosage (mg/day)</td>
<td>1545±659</td>
<td>1504±651</td>
<td>1598±676</td>
<td>0.543</td>
</tr>
<tr>
<td>Glicazide</td>
<td>26 (25.2%)</td>
<td>11 (10.7%)</td>
<td>15 (14.5%)</td>
<td>0.335</td>
</tr>
<tr>
<td>Glicazide Dosage (mg/day)</td>
<td>85.1±61.2</td>
<td>74.5±42.9</td>
<td>92.9±82.7</td>
<td>0.509</td>
</tr>
<tr>
<td>Diet Controlled</td>
<td>18 (17.5%)</td>
<td>5 (4.9%)</td>
<td>13 (12.6%)</td>
<td>0.060</td>
</tr>
<tr>
<td>Exercise Capacity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Muscle Strength (N)</td>
<td>2533.5±854.2</td>
<td>2803.8±870.6</td>
<td>2236.7±702.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leg Press (N)</td>
<td>1616.4±464.7</td>
<td>1720.7±474.2</td>
<td>1499.5±428.7</td>
<td>0.459</td>
</tr>
<tr>
<td>Chest Press (N)</td>
<td>326.1±109.3</td>
<td>388.3±106.1</td>
<td>255.9±59.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Seated Row (N)</td>
<td>158.4±57.4</td>
<td>183.0±56.8</td>
<td>124.0±35.5</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>
TABLE 5.2 BASELINE CHARACTERISTICS OF GREAT2DO PARTICIPANTS - CONTINUED

<table>
<thead>
<tr>
<th>Variable</th>
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<th>Men n=52</th>
<th>Women n=51</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Knee Extension (Nm)</td>
<td>240.8±74.6</td>
<td>288.2±72.6</td>
<td>200.0±53.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Knee Flexion (Nm)</td>
<td>191.8±148.2</td>
<td>223.6±160.9</td>
<td>157.3±126.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Total Muscle Power (W)</td>
<td>1494.1±447.3</td>
<td>1790.8±796.2</td>
<td>1072.3±630.1</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Leg Press</td>
<td>528.0±237.1</td>
<td>675.0±352.9</td>
<td>378.1±243.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chest Press</td>
<td>191.0±114.1</td>
<td>253.5±115.9</td>
<td>127.5±68.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Seated Row</td>
<td>312.0±145.0</td>
<td>402.8±130.5</td>
<td>220.2±91.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Knee Extension</td>
<td>305.0±144.0</td>
<td>295.8±126.8</td>
<td>204.5±84.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Knee Flexion</td>
<td>158.1±16.1</td>
<td>173.7±170.1</td>
<td>141.9±154.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Six Minute Walk Distance (m)</td>
<td>545.9±93.2</td>
<td>569.3±92.6</td>
<td>523.0±89.1</td>
<td>0.030</td>
</tr>
</tbody>
</table>

Physical Performance

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n=103</th>
<th>Men n=52</th>
<th>Women n=51</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Gait Speed (m/sec)</td>
<td>1.2±0.2</td>
<td>1.2±0.2</td>
<td>1.2±0.2</td>
<td>0.210</td>
</tr>
<tr>
<td>Maximal Gait Speed (m/sec)</td>
<td>1.9±0.3</td>
<td>1.9±0.3</td>
<td>1.8±0.3</td>
<td>0.360</td>
</tr>
<tr>
<td>Chair Stand (sec)</td>
<td>12.1±2.7</td>
<td>11.7±1.9</td>
<td>12.0±3.0</td>
<td>0.350</td>
</tr>
<tr>
<td>Stair Climb Power (W)</td>
<td>370.4±126.6</td>
<td>430.0±129.3</td>
<td>314.9±96.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Static Balance Total Time (sec)</td>
<td>74.7±7.1</td>
<td>76.2±6.1</td>
<td>74.9±5.7</td>
<td>0.450</td>
</tr>
</tbody>
</table>

Body Composition

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n=103</th>
<th>Men n=52</th>
<th>Women n=51</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stretched Stature (m)</td>
<td>1.69±0.09</td>
<td>1.74±0.06</td>
<td>1.62±0.07</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body Mass Index (kg/m(^2))</td>
<td>31.6±5.4</td>
<td>30.3±4.4</td>
<td>32.9±6.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Wait Circumstance (cm)</td>
<td>107.2±11.9</td>
<td>109.1±11.4</td>
<td>105.1±12.2</td>
<td>0.092</td>
</tr>
<tr>
<td>Total Abdominal Adipose Tissue (cm(^2))</td>
<td>421.6±117.6</td>
<td>412.3±113.4</td>
<td>431.3±110.1</td>
<td>0.416</td>
</tr>
</tbody>
</table>
### TABLE 5.2 BASELINE CHARACTERISTICS OF GREAT2DO PARTICIPANTS - CONTINUED

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n=103</th>
<th>Men n=52</th>
<th>Women n=51</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visceral Adipose Tissue (cm²)</td>
<td>215.0±89.2</td>
<td>258.7±83.4</td>
<td>169.6±70.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Subcutaneous Abdominal Adipose Tissue (cm²)</td>
<td>206.7±90.4</td>
<td>153.6±62.4</td>
<td>261.8±82.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sagittal Abdominal Diameter (cm)</td>
<td>27.6±3.9</td>
<td>28.3±3.7</td>
<td>26.8±4.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mid-Thigh Cross Section Area (cm²)</td>
<td>109.4±24.1</td>
<td>127.6±16.8</td>
<td>90.5±13.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Thigh Subcutaneous Adipose Tissue (cm²)</td>
<td>84.4±47.4</td>
<td>56.8±20.0</td>
<td>113.1±50.5</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intermuscular Adipose Tissue (cm²)</td>
<td>13.3±6.5</td>
<td>14.0±6.8</td>
<td>12.5±6.2</td>
<td>0.262</td>
</tr>
<tr>
<td>Mid-Thigh Muscle Attenuation</td>
<td>84.1±2.3</td>
<td>84.0±2.2</td>
<td>84.3±2.4</td>
<td>0.480</td>
</tr>
<tr>
<td>Total Fat Mass (kg)</td>
<td>31.8±11.4</td>
<td>28.6±8.9</td>
<td>35.1±12.8</td>
<td>&lt;0.010</td>
</tr>
<tr>
<td>Free Fat Mass (kg)</td>
<td>57.0±10.0</td>
<td>63.3±7.7</td>
<td>50.7±7.8</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Skeletal Muscle Mass (kg)</td>
<td>30.4±4.1</td>
<td>32.0±3.8</td>
<td>28.7±3.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>35.7±7.2</td>
<td>30.6±5.7</td>
<td>40.0±6.6</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Muscle Mass (%)</td>
<td>34.6±4.0</td>
<td>35.1±3.4</td>
<td>34.2±4.5</td>
<td>0.258</td>
</tr>
</tbody>
</table>

**Habitual Physical Activity Level**

| PASE (score) | 116±60 | 121±70 | 112±48 | 0.480 |

**Quality of Life**

| SF-36 (0-100) | |
| SF-36 Physical Component Summary | 45.1±9.2 | 46.8±8.0 | 43.4±10.1 | 0.060 |
| SF-36 Mental Components Summary | 48.8±10.8 | 50.0±9.0 | 47.5±12.5 | 0.060 |
**TABLE 5.2 BASELINE CHARACTERISTICS OF GREAT2DO PARTICIPANTS - CONTINUED**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total</th>
<th>Men</th>
<th>Women</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=103</td>
<td>n=52</td>
<td>n=51</td>
<td></td>
</tr>
<tr>
<td><strong>Depressive symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Geriatric Depression Scale (0/30)</td>
<td>6.90 ± 5.3</td>
<td>6.3 ± 4.6</td>
<td>7.6 ± 6.0</td>
<td>0.204</td>
</tr>
<tr>
<td><strong>Cognitive Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word List Memory Score (0/20)</td>
<td>21.3±3.9</td>
<td>19.8±3.7</td>
<td>22.8±3.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Word List Recall Score (0/10)</td>
<td>7.0±1.8</td>
<td>6.5±1.8</td>
<td>7.6±1.7</td>
<td>0.002</td>
</tr>
<tr>
<td>Word List Recognition Score (0/10)</td>
<td>10.0 (4.0)</td>
<td>10.0 (4.0)</td>
<td>10.0 (3.0)</td>
<td>0.080</td>
</tr>
<tr>
<td>Trail Making Test A Score (sec)</td>
<td>40.6±12.6</td>
<td>41.4±12.8</td>
<td>39.8±12.5</td>
<td>0.540</td>
</tr>
<tr>
<td>Trail Making Test B Score (sec)</td>
<td>95.2±42.5</td>
<td>97.6±38.7</td>
<td>93.0±46.2</td>
<td>0.480</td>
</tr>
<tr>
<td>DIFFBA Score (sec)</td>
<td>45.1 (267.1)</td>
<td>45.4 (223.6)</td>
<td>44.1 (254.8)</td>
<td>0.750</td>
</tr>
<tr>
<td>Modified Mini-Mental State Score (0/100)</td>
<td>94.1 ± 4.8</td>
<td>92.2±5.2</td>
<td>95.0±4.0</td>
<td>0.058</td>
</tr>
<tr>
<td><strong>Glucose Metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fasting Glucose (mmol/L)</td>
<td>7.3±2.4</td>
<td>7.2±2.3</td>
<td>7.3±2.4</td>
<td>0.850</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.1±1.1</td>
<td>7.0±1.0</td>
<td>7.2±1.2</td>
<td>0.340</td>
</tr>
<tr>
<td>Fasting Insulin (mU/L)</td>
<td>9.4±4.9</td>
<td>8.7±3.5</td>
<td>10.0±6.0</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>(n=87)</td>
<td>(n=42)</td>
<td>(n=45)</td>
<td></td>
</tr>
<tr>
<td><strong>HOMA2-IR</strong></td>
<td>2.9±1.1</td>
<td>2.8±1.1</td>
<td>3.0±1.1</td>
<td>0.310</td>
</tr>
<tr>
<td>HOMA2-%Beta</td>
<td>110.8±4.5</td>
<td>106.9±39.4</td>
<td>114.5±50.7</td>
<td>0.440</td>
</tr>
<tr>
<td></td>
<td>(n=87)</td>
<td>(n=42)</td>
<td>(n=45)</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>4.4±11.1</td>
<td>4.1±0.8</td>
<td>4.7±1.2</td>
<td>&lt;0.010</td>
</tr>
</tbody>
</table>
TABLE 5.2 BASELINE CHARACTERISTICS OF GREAT2DO PARTICIPANTS - CONTINUED

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total n=103</th>
<th>Men n=52</th>
<th>Women n=51</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Triglycerides (mmol/L)</td>
<td>1.7±0.9</td>
<td>1.8±1.1</td>
<td>1.6±0.8</td>
<td>0.121</td>
</tr>
<tr>
<td>Serum High Density Lipoprotein (mmol/L)</td>
<td>1.2±0.3</td>
<td>1.1±0.3</td>
<td>1.3±0.4</td>
<td>0.016</td>
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<tr>
<td>Serum High Density Lipoprotein (mmol/L)</td>
<td>2.4±0.9</td>
<td>2.2±0.8</td>
<td>2.6±0.9</td>
<td>0.018</td>
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<tr>
<td>Low-Grade Systematic Inflammation</td>
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<tr>
<td>C - Reactive Protein (mg/L)</td>
<td>3.9±4.2</td>
<td>2.9±3.0</td>
<td>5.0±4.9</td>
<td>0.110</td>
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<tr>
<td>Adipokines</td>
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<tr>
<td>Serum HMW Adiponectin (ng/ml)</td>
<td>5020.6±4717.7</td>
<td>5346.6±6017.2</td>
<td>4660.1±2780.7</td>
<td>0.652</td>
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<tr>
<td>Serum Total Adiponectin (ng/ml)</td>
<td>6446.8 (18540.0)</td>
<td>6403.2 (16307.7)</td>
<td>6526.5 (16998.0)</td>
<td>0.193</td>
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<tr>
<td>Adiponectin Ratio</td>
<td>0.4 (4.3)</td>
<td>0.4 (4.3)</td>
<td>0.43 (2.9)</td>
<td>0.874</td>
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</table>

Normally distributed data presented as mean ± SD. Non-normally distributed data presented as median (range). Difference between men and women was assessed via one way ANOVA. Non-normally distributed data were log-transformed before use with parametric statistics. Categorical variables we assessed using a Chi-square. Participants taking insulin were excluded from analyses for HOMA2-IR and %Beta.

Participants taking insulin were excluded from analyses for fasting insulin, HOMA 2 Insulin Resistance and %Beta.

CVD: Cardiovascular disease including ischemic heart disease, myocardial infarction and angina

HOMA2-IR: Homeostatic Model of Assessment 2 of Insulin Resistance
HbA1c: Glycosylated haemoglobin

PASE: Physical Activity Scale for the Elderly

SF-36: The Short Form (36) Health Survey

DIFFBA: Difference score Trail Making Test B minus Trail Making Test A

HMW: High-molecular weight

% represents percentage

M: Metre

Sec: Second

N: Newton

W: Watt

Kg: Kilograms
### Tabela 5.3: Cognition vs. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM r (p value)</th>
<th>WLR r (p value)</th>
<th>WLRE r (p value)</th>
<th>TMTA r (p value)</th>
<th>TMTB r (p value)</th>
<th>DIFFBA r (p value)</th>
<th>3MS r(p value)</th>
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<tr>
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</tr>
<tr>
<td>Age (year)</td>
<td>-0.33 (&lt;0.01)</td>
<td>-0.34 (&lt;0.01)</td>
<td>-0.36 (&lt;0.01)</td>
<td>0.29 (&lt;0.01)</td>
<td>0.21 (0.03)</td>
<td>0.14 (0.15)</td>
<td>-0.24 (0.02)</td>
</tr>
<tr>
<td>Education (year)</td>
<td>0.18 (0.08)</td>
<td><strong>0.22 (0.03)</strong></td>
<td><strong>0.21 (0.03)</strong></td>
<td>-0.18 (0.07)</td>
<td>-0.18 (0.08)</td>
<td><strong>-0.25 (0.01)</strong></td>
<td>0.06 (0.55)</td>
</tr>
<tr>
<td>Duration of Diabetes (year)</td>
<td>0.05 (0.61)</td>
<td>0.07 (0.55)</td>
<td>0.04 (0.68)</td>
<td>0.06 (0.55)</td>
<td>0.21 (0.13)</td>
<td><strong>0.20 (0.04)</strong></td>
<td>0.15 (0.19)</td>
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<tr>
<td>Total no of Diseases</td>
<td>-0.05 (0.63)</td>
<td>0.18 (0.08)</td>
<td>0.19 (0.06)</td>
<td>0.01 (0.91)</td>
<td>-0.05 (0.61)</td>
<td>-0.05(0.62)</td>
<td>-0.10 (0.44)</td>
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<tr>
<td>Total no of Medications</td>
<td>-0.19 (0.06)</td>
<td><strong>-0.30 (&lt;0.01)</strong></td>
<td><strong>-0.31 (&lt;0.01)</strong></td>
<td>0.04(0.68)</td>
<td>-0.18 (0.11)</td>
<td>0.01 (0.63)</td>
<td>0.07 (0.42)</td>
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<td><strong>SF-36 (0-100)</strong></td>
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<td>Physical Component</td>
<td>0.02 (0.72)</td>
<td>0.16 (0.11)</td>
<td>0.17 (0.10)</td>
<td>-0.13 (0.26)</td>
<td>-0.04 (0.70)</td>
<td>0.05 (0.72)</td>
<td>0.03 (0.79)</td>
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<td>Summary Score (log)</td>
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<td>Mental Component</td>
<td>-0.11 (0.19)</td>
<td>0.06 (0.67)</td>
<td>0.07 (0.51)</td>
<td>-0.10 (0.39)</td>
<td>0.03 (0.71)</td>
<td>0.08 (0.55)</td>
<td><strong>0.20(0.04)</strong></td>
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<tr>
<td>Summary Score (log)</td>
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TABLE 5.3 COGNITION VS. BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM  r (p value)</th>
<th>WLR  r (p value)</th>
<th>WLRE r (p value)</th>
<th>TMTA r (p value)</th>
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<th>DIFFBA r (p value)</th>
<th>3MS r(p value)</th>
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<tr>
<td>Physical Activity Level</td>
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<td>Physical Activity Level</td>
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<td>PASE (score) (log)</td>
<td>0.15 (0.17)</td>
<td>0.01 (0.91)</td>
<td>0.01 (0.92)</td>
<td>0.04 (0.71)</td>
<td>0.14 (0.17)</td>
<td><strong>0.24 (0.03)</strong></td>
<td>0.01 (0.91)</td>
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<td>Depressive symptom</td>
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<tr>
<td>Depressive symptom</td>
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<td>Geriatric Depression Scale (0/30)</td>
<td>0.04 (0.71)</td>
<td>0.04 (0.67)</td>
<td>-0.03 (0.81)</td>
<td>0.16 (0.10)</td>
<td>0.07 (0.49)</td>
<td>0.11 (0.28)</td>
<td>-0.11 (0.27)</td>
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<td>Exercise capacity</td>
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<tr>
<td>Exercise capacity</td>
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<tr>
<td>Muscle Strength (kg)</td>
<td>-0.21 (0.07)</td>
<td>-0.20 (0.09)</td>
<td>0.17 (0.12)</td>
<td>-0.14 (0.18)</td>
<td>-0.01 (0.92)</td>
<td>-0.02 (0.85)</td>
<td>0.24 (0.13)</td>
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<tr>
<td>Muscle Power (W)</td>
<td>-0.19 (0.11)</td>
<td>-0.14 (0.17)</td>
<td>0.13 (0.25)</td>
<td>-0.13 (0.26)</td>
<td>-0.06 (0.53)</td>
<td>-0.02 (0.73)</td>
<td>0.09 (0.48)</td>
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<tr>
<td>6 Minute Walk Distance (m)</td>
<td>0.11 (0.29)</td>
<td><strong>0.21 (0.04)</strong></td>
<td>0.10 (0.37)</td>
<td><strong>-0.27 (&lt;0.01)</strong></td>
<td>-0.14 (0.22)</td>
<td>-0.04 (0.70)</td>
<td>0.03 (0.69)</td>
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<td>Physical Performance</td>
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<td>Physical Performance</td>
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<tr>
<td>Balance (sec)</td>
<td>0.11 (0.27)</td>
<td>0.12 (0.24)</td>
<td>0.11 (0.28)</td>
<td>0.13 (0.18)</td>
<td>-0.19 (0.61)</td>
<td>-0.14 (0.17)</td>
<td>0.16 (0.17)</td>
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<tr>
<td>Average Gait Speed (m/sec)</td>
<td>-0.01 (0.86)</td>
<td>0.04 (0.67)</td>
<td>0.06 (0.59)</td>
<td>0.01 (0.88)</td>
<td>0.07 (0.42)</td>
<td>0.12 (0.30)</td>
<td>0.07 (0.51)</td>
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<tr>
<td>Variable</td>
<td>WLM r (p value)</td>
<td>WLR r (p value)</td>
<td>WLRE r (p value)</td>
<td>TMTA r (p value)</td>
<td>TMTB r (p value)</td>
<td>DIFFBA r (p value)</td>
<td>3MS r(p value)</td>
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<tr>
<td>Maximal Gait Speed</td>
<td>0.11 (0.28)</td>
<td>0.17 (0.10)</td>
<td>0.12 (0.26)</td>
<td>-0.23 (&lt;0.01)</td>
<td>-0.21 (0.04)</td>
<td>-0.12 (0.23)</td>
<td>0.13 (0.19)</td>
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<tr>
<td>(m/sec)</td>
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<tr>
<td>Stair Climb Power (W)</td>
<td>0.02 (0.81)</td>
<td>0.02 (0.82)</td>
<td>0.04 (0.73)</td>
<td>-0.28 (&lt;0.01)</td>
<td>-0.11 (0.25)</td>
<td>-0.05 (0.61)</td>
<td>0.03 (0.78)</td>
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<tr>
<td>Chair Stand (sec)</td>
<td>0.05 (0.69)</td>
<td>0.01 (0.89)</td>
<td>0.05 (0.63)</td>
<td>0.38 (&lt;0.01)</td>
<td>0.14 (0.17)</td>
<td>-0.09 (0.39)</td>
<td>0.08 (0.44)</td>
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<td><strong>Body Composition</strong></td>
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<td>Body Mass Index</td>
<td>0.12 (0.27)</td>
<td>-0.03 (0.78)</td>
<td>0.05 (0.69)</td>
<td>0.15 (0.19)</td>
<td>-0.11 (0.27)</td>
<td>-0.10 (0.31)</td>
<td>0.19 (0.08)</td>
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<tr>
<td>(kg/m²)</td>
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<tr>
<td>Waist Circumstance(cm)</td>
<td>-0.20 (0.06)</td>
<td>-0.17 (0.08)</td>
<td>0.07 (0.52)</td>
<td>-0.03 (0.76)</td>
<td>-0.03 (0.76)</td>
<td>-0.04 (0.72)</td>
<td>0.12 (0.26)</td>
</tr>
<tr>
<td>Abdominal Total</td>
<td>-0.01 (0.88)</td>
<td>-0.15 (17)</td>
<td>0.12 (0.24)</td>
<td>-0.05 (0.65)</td>
<td>-0.04 (0.71)</td>
<td>-0.04 (0.70)</td>
<td>0.09 (0.39)</td>
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<tr>
<td>Adipose Tissue (cm²)</td>
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<tr>
<td>Visceral Adipose</td>
<td><strong>0.23 (0.02)</strong></td>
<td><strong>-0.26 (0.02)</strong></td>
<td>0.04 (0.71)</td>
<td>0.04 (0.67)</td>
<td>0.03 (0.75)</td>
<td>0.07 (0.47)</td>
<td>0.02 (0.89)</td>
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<tr>
<td>Abdominal Subcutaneous</td>
<td><strong>0.21 (0.04)</strong></td>
<td>0.06 (0.56)</td>
<td>0.10 (0.31)</td>
<td>0.10 (0.32)</td>
<td>-0.08 (0.42)</td>
<td>-0.02 (0.83)</td>
<td>0.01 (0.90)</td>
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<td>Adipose Tissue (cm²)</td>
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**TABLE 5.3 COGNITION VS. BASELINE CHARACTERISTICS**
## TABLE 5.3 COGNITION VS. BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM r (p value)</th>
<th>WLR r (p value)</th>
<th>WLRE r (p value)</th>
<th>TMTA r (p value)</th>
<th>TMTB r (p value)</th>
<th>DIFFBA r (p value)</th>
<th>3MS r(p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sagittal Adipose Diameter (cm)</td>
<td>-0.22 (0.02)</td>
<td>-0.28 (0.02)</td>
<td>0.22 (0.03)</td>
<td>-0.04 (0.67)</td>
<td>0.03 (0.75)</td>
<td>-0.07 (0.49)</td>
<td>0.01 (0.89)</td>
</tr>
<tr>
<td>Mid-thigh Muscular Area (cm²)</td>
<td>-0.13 (0.20)</td>
<td>-0.15 (0.16)</td>
<td>0.13 (0.25)</td>
<td>-0.05 (0.60)</td>
<td>0.02 (0.80)</td>
<td>0.07 (0.47)</td>
<td>0.03 (0.76)</td>
</tr>
<tr>
<td>Thigh Subcutaneous Adipose Tissue (cm²)</td>
<td>0.19 (0.05)</td>
<td>0.12 (0.19)</td>
<td>0.13 (0.19)</td>
<td>-0.07 (0.54)</td>
<td>0.02 (0.82)</td>
<td>0.03 (0.68)</td>
<td>0.05 (0.60)</td>
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<tr>
<td>Intermuscular Adipose Tissue (cm²)</td>
<td>-0.12 (0.18)</td>
<td>0.03 (0.74)</td>
<td>0.03 (0.76)</td>
<td>-0.02 (0.87)</td>
<td>-0.02 (0.89)</td>
<td>0.01 (0.92)</td>
<td>0.10 (0.29)</td>
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<tr>
<td>Mid-thigh Muscle Attenuation</td>
<td>-0.09 (0.35)</td>
<td>-0.10 (0.029)</td>
<td>0.11 (0.29)</td>
<td>0.04 (0.72)</td>
<td>0.11(0.31)</td>
<td>0.13 (0.19)</td>
<td>0.08 (0.55)</td>
</tr>
<tr>
<td>Body Fat (%)</td>
<td>0.05 (0.64)</td>
<td>0.13 (0.28)</td>
<td>0.12 (0.25)</td>
<td>0.04 (0.72)</td>
<td>0.06 (0.56)</td>
<td>0.01 (0.91)</td>
<td>0.05 (0.64)</td>
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<tr>
<td>Body Muscle (%)</td>
<td>0.18 (0.08)</td>
<td>0.13 (0.28)</td>
<td>-0.12 (0.24)</td>
<td>-0.03 (0.74)</td>
<td>-0.01 (0.90)</td>
<td>-0.01 (0.92)</td>
<td>0.09 (0.40)</td>
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<tr>
<td>Free Fat Mass (kg)</td>
<td>-0.15 (0.12)</td>
<td>0.13 (0.20)</td>
<td>0.08 (0.44)</td>
<td>-0.08 (0.44)</td>
<td>0.07 (0.49)</td>
<td>0.14 (0.17)</td>
<td>0.11 (0.30)</td>
</tr>
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</table>
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<th>TMTB r (p value)</th>
<th>DIFFBA r (p value)</th>
<th>3MS r (p value)</th>
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</thead>
<tbody>
<tr>
<td>Skeletal Muscle Mass</td>
<td>-0.03 (0.76)</td>
<td>-0.13 (0.20)</td>
<td>0.06 (0.55)</td>
<td>-0.11 (0.28)</td>
<td>0.02 (0.82)</td>
<td>0.09 (0.39)</td>
<td>0.09 (0.39)</td>
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<td>Mass (kg)</td>
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<tr>
<td>Total Fat Mass (kg) (log)</td>
<td>0.07 (0.48)</td>
<td>-0.08 (0.49)</td>
<td>0.02 (0.81)</td>
<td>-0.08 (0.49)</td>
<td>-0.06 (0.59)</td>
<td>-0.00 (0.96)</td>
<td>0.15 (0.12)</td>
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<td>Metabolism</td>
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<tr>
<td>Fasting Glucose (mmol/L) (log)</td>
<td>0.12 (0.24)</td>
<td>0.26 (0.01)</td>
<td>0.15 (0.18)</td>
<td>0.11 (0.30)</td>
<td>0.08 (0.43)</td>
<td>0.06 (0.55)</td>
<td>0.09 (0.40)</td>
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<td>HbA1c (%)</td>
<td>0.03 (0.76)</td>
<td>0.19 (0.07)</td>
<td>0.17 (0.10)</td>
<td>0.18 (0.08)</td>
<td>0.10 (0.20)</td>
<td>0.08 (0.49)</td>
<td>0.00 (0.96)</td>
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<tr>
<td>Fasting Insulin (uM/L) (log)</td>
<td>-0.05 (0.64)</td>
<td>0.01 (0.91)</td>
<td>0.08 (0.48)</td>
<td>0.04 (0.71)</td>
<td>-0.07 (0.48)</td>
<td>-0.05 (0.64)</td>
<td>0.03 (0.76)</td>
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<td>HOMA 2-IR</td>
<td>0.04 (0.71)</td>
<td>0.10 (0.20)</td>
<td>0.07 (0.48)</td>
<td>-0.04 (0.71)</td>
<td>-0.12 (0.18)</td>
<td>-0.06 (0.55)</td>
<td>0.07 (0.48)</td>
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<td>HOMA 2-%Beta</td>
<td>0.04 (0.70)</td>
<td>-0.06 (0.55)</td>
<td>0.09 (0.35)</td>
<td>0.10 (0.20)</td>
<td>-0.18 (0.09)</td>
<td>-0.14 (0.18)</td>
<td>0.08 (0.44)</td>
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<td>Inflammation</td>
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<td>C-Reactive Protein (mg/L) (log)</td>
<td>0.08 (0.48)</td>
<td>-0.07 (0.48)</td>
<td>0.12 (0.24)</td>
<td>0.23 (0.04)</td>
<td>-0.00 (0.96)</td>
<td>-0.05 (0.64)</td>
<td>0.00 (0.96)</td>
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TABLE 5.3 COGNITION VS. BASELINE CHARACTERISTICS

<table>
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<tr>
<th>Variable</th>
<th>WLM r (p value)</th>
<th>WLR r (p value)</th>
<th>WLRE r (p value)</th>
<th>TMTA r (p value)</th>
<th>TMTB r (p value)</th>
<th>DIFFBA r (p value)</th>
<th>3MS r(p value)</th>
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<tbody>
<tr>
<td>Adipokines</td>
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<tr>
<td>Serum HMW</td>
<td>-0.13 (0.25)</td>
<td>-0.17 (0.10)</td>
<td>0.11 (0.28)</td>
<td>-0.07 (0.48)</td>
<td>-0.09 (0.40)</td>
<td>-0.17 (0.10)</td>
<td>0.15 (0.12)</td>
</tr>
<tr>
<td>Adiponectin (ng/ml) (log)</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Serum Total Adiponectin</td>
<td>0.07 (0.50)</td>
<td><strong>0.34 (0.01)</strong></td>
<td>0.03 (0.76)</td>
<td>-0.17 (0.13)</td>
<td>-0.03 (0.76)</td>
<td>0.18 (0.09)</td>
<td>-0.07 (0.48)</td>
</tr>
<tr>
<td>(ng/ml) (log)</td>
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<td></td>
</tr>
<tr>
<td>Serum HMW/Total</td>
<td>0.01 (0.91)</td>
<td>-0.23 (0.91)</td>
<td>0.12 (0.26)</td>
<td>-0.06 (0.55)</td>
<td>-0.29 (0.13)</td>
<td><strong>-0.42 (0.01)</strong></td>
<td>0.12 (0.24)</td>
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<tr>
<td>Adiponectin Ratio (log)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
HOMA2-IR: Homeostatic model of assessment of insulin resistance 2

HbA1c: Glycosylated hemoglobin

WIM: Word List Memory score (0/20)

WLR: Word List Recall score (0/10)

WLRE: Word List Recognition score (0/10)

TMTA: Trail Making Test A score (sec)

TMTB: Trail Making Test B score (sec)

DIFFBA score (sec): Difference score between Trail Making Test B score minus Trail Making Test A score

3MS: Modified Mini Mental State score (0/100)

PASE: Physical Activity Scale for the Elderly

HMW: High-Molecular Weight

% represents percentage

M: Meter

Sec: Second

N: Newton

W: Watt

Kg: Kilograms
TABLE 5.4 MULTIPLE REGRESSION OF COGNITIVE TEST SCORES AND METABOLISM: SUB-STUDY OF GREAT2DO TRIAL

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM β (p value)</th>
<th>WLR β (p value)</th>
<th>WLRE β (p value)</th>
<th>TMTA β (p value)</th>
<th>TMTB β (p value)</th>
<th>DIFFBA β (p value)</th>
<th>3MS β (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting Glucose (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.22 (0.82)</td>
<td>0.17 (0.15)</td>
<td>-0.14 (0.40)</td>
<td>-0.07 (0.62)</td>
<td>0.05 (0.74)</td>
<td>0.03 (0.86)</td>
<td>-0.14 (0.33)</td>
</tr>
<tr>
<td>Women</td>
<td>0.15 (0.28)</td>
<td>0.26 (0.07)</td>
<td>0.18 (0.29)</td>
<td>0.33 (0.02)</td>
<td>0.19 (0.18)</td>
<td>0.00 (0.99)</td>
<td>-0.17 (0.25)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>0.06 (0.47)</td>
<td><strong>0.23 (0.02)</strong></td>
<td>0.03 (0.83)</td>
<td>0.17 (0.08)</td>
<td>-</td>
<td>0.09 (0.35)</td>
<td>0.09 (0.35)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Men</td>
<td>-0.13 (0.33)</td>
<td>0.16 (0.20)</td>
<td>0.14 (0.34)</td>
<td>0.04 (0.76)</td>
<td>-0.03 (0.86)</td>
<td>0.04 (0.79)</td>
<td>-0.12 (0.40)</td>
</tr>
<tr>
<td>Women</td>
<td>0.13 (0.38)</td>
<td>0.20 (0.18)</td>
<td>0.04 (0.82)</td>
<td>0.22 (0.13)</td>
<td>0.26 (0.07)</td>
<td>0.00 (0.35)</td>
<td>0.06 (0.71)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.02 (0.82)</td>
<td>0.16 (0.08)</td>
<td>0.10 (0.32)</td>
<td>0.14 (0.16)</td>
<td>0.13 (0.20)</td>
<td>0.08 (0.41)</td>
<td>0.04 (0.71)</td>
</tr>
<tr>
<td>HOMA-%Beta</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Men</td>
<td>0.06 (0.60)</td>
<td>-0.05 (0.72)</td>
<td>0.01 (0.99)</td>
<td>0.04 (0.98)</td>
<td>-0.19 (0.24)</td>
<td>-0.23 (0.17)</td>
<td>0.06 (0.70)</td>
</tr>
<tr>
<td>Women</td>
<td>-0.04 (0.75)</td>
<td>-0.09 (0.58)</td>
<td>0.06 (0.55)</td>
<td>-0.21 (0.19)</td>
<td>-0.15 (0.31)</td>
<td>-0.04 (0.75)</td>
<td>0.10 (0.51)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>0.01 (0.92)</td>
<td>0.06 (0.51)</td>
<td>0.06 (0.60)</td>
<td>0.05 (0.63)</td>
<td>-0.04 (0.72)</td>
<td>-0.00 (0.9)</td>
<td>-0.02 (0.89)</td>
</tr>
<tr>
<td>HOMA-IR</td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.02 (0.88)</td>
<td>0.01 (0.90)</td>
<td>0.26 (0.07)</td>
<td>-0.02 (0.87)</td>
<td>0.01 (0.94)</td>
<td>0.44 (0.78)</td>
<td>-0.07 (0.66)</td>
</tr>
<tr>
<td>Women</td>
<td>0.10 (0.49)</td>
<td>0.10 (0.53)</td>
<td>0.26 (0.07)</td>
<td>0.10 (0.52)</td>
<td>-0.08 (0.58)</td>
<td>-0.04 (0.78)</td>
<td>0.03 (0.87)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.02 (0.80)</td>
<td>-0.07 (0.51)</td>
<td>0.26 (0.07)</td>
<td>-0.15 (0.18)</td>
<td>-0.18 (0.09)</td>
<td>-0.12 (0.26)</td>
<td>-0.13 (0.25)</td>
</tr>
</tbody>
</table>
β-coefficients for relationship between cognitive test scores and metabolic variables after adjusting for age, sex, and years of education for combined men and Women: GREAT2DO-substudy

All baseline metabolism measures were stratified by sex after controlling age and highest years of education: in men and Women: GREAT2DO-substudy

HbA1c: Glycated hemoglobin

HOMA: The Homeostasis Model Assessment

IR: Insulin resistance

WIM: Word List Memory score (0/20)

WLR: Word List Recall score (0/10)

WLRE: Word List Recognition score (0/10)

TMTA: Trail Making Test A score (sec)

TMTB: Trail Making Test B score (sec)

DIFFBA score (sec): Difference score between Trail Making Test B score minus Trail Making Test A score

3MS: Modified Mini Mental State score (0/100)

% represents percentage
<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM $\beta$ (p value)</th>
<th>WLR $\beta$ (p value)</th>
<th>WLRE $\beta$ (p value)</th>
<th>TMTA $\beta$ (p value)</th>
<th>TMTB $\beta$ (p value)</th>
<th>DIFFBA $\beta$ (p value)</th>
<th>3MS $\beta$ (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Muscle Strength (N)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.17 (0.66)</td>
<td>-0.65 (0.06)</td>
<td>-0.67 (0.06)</td>
<td>0.33 (0.20)</td>
<td>0.17 (0.65)</td>
<td>0.15 (0.68)</td>
<td>-0.17 (0.65)</td>
</tr>
<tr>
<td>Women</td>
<td>-0.43 (0.10)</td>
<td>-0.14 (0.62)</td>
<td>-0.14 (0.64)</td>
<td>-0.33 (0.25)</td>
<td>0.24 (0.37)</td>
<td>0.31 (0.27)</td>
<td>-0.61 (0.06)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.31 (0.20)</td>
<td>-0.42 (0.09)</td>
<td>-0.40 (0.10)</td>
<td>-0.11 (0.62)</td>
<td>0.25 (0.26)</td>
<td>0.30 (0.19)</td>
<td>-0.41 (0.08)</td>
</tr>
<tr>
<td><strong>Total Muscle Power (W)</strong></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.03 (0.85)</td>
<td>0.01 (0.98)</td>
<td>0.03 (0.81)</td>
<td>-0.17 (0.19)</td>
<td>-0.05 (0.71)</td>
<td>0.02 (0.86)</td>
<td>0.20 (0.15)</td>
</tr>
<tr>
<td>Women</td>
<td>-0.18 (0.19)</td>
<td>-0.13 (0.34)</td>
<td>-0.13 (0.38)</td>
<td>-0.14 (0.33)</td>
<td>0.11 (0.42)</td>
<td>0.20 (0.16)</td>
<td>-0.18 (0.21)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.07 (0.47)</td>
<td>-0.04 (0.68)</td>
<td>-0.02 (0.88)</td>
<td>-0.18 (0.11)</td>
<td>&lt;0.01 (0.99)</td>
<td>0.09 (0.46)</td>
<td>0.12 (0.38)</td>
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<tr>
<td><strong>Six Minute Walk Distance (m)</strong></td>
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<tr>
<td>Men</td>
<td>0.14 (0.40)</td>
<td><strong>0.29 (0.049)</strong></td>
<td>0.20 (0.08)</td>
<td>-0.12 (0.49)</td>
<td>0.22 (0.21)</td>
<td>0.18 (0.25)</td>
<td>-0.03 (0.84)</td>
</tr>
<tr>
<td>Women</td>
<td>-0.00 (0.98)</td>
<td>0.11 (0.46)</td>
<td>0.03 (0.85)</td>
<td>-0.29 (0.06)</td>
<td>-0.24 (0.12)</td>
<td>-0.05 (0.72)</td>
<td>-0.04 (0.87)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>0.07 (0.51)</td>
<td><strong>0.22 (0.04)</strong></td>
<td>0.19 (0.12)</td>
<td><strong>-0.21 (0.05)</strong></td>
<td>-0.02 (0.88)</td>
<td>0.09(0.45)</td>
<td>0.01 (0.93)</td>
</tr>
</tbody>
</table>
### Table 5.5: Multiple Regression of Cognitive Test Scores and Exercise Capacity and Physical Performance: Sub-Study of GREAT2DO Trial - Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM β (p value)</th>
<th>WLR β (p value)</th>
<th>WLRE β (p value)</th>
<th>TMTA β (p value)</th>
<th>TMTB β (p value)</th>
<th>DIFFBA β (p value)</th>
<th>3MS β (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Static Balance (sec)</strong></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.00 (0.95)</td>
<td>0.04 (0.83)</td>
<td>0.13 (0.41)</td>
<td>0.11 (0.78)</td>
<td>0.11 (0.50)</td>
<td>0.13 (0.42)</td>
<td>-0.12 (0.45)</td>
</tr>
<tr>
<td>Women</td>
<td>-0.10 (0.52)</td>
<td>0.11 (0.51)</td>
<td>0.03 (0.83)</td>
<td>0.11 (0.51)</td>
<td>0.04 (0.78)</td>
<td>-0.07 (0.64)</td>
<td>0.31 (0.04)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.05 (0.60)</td>
<td>0.00 (0.95)</td>
<td>0.09 (0.41)</td>
<td>0.08 (0.49)</td>
<td>0.03 (0.80)</td>
<td>0.03 (0.82)</td>
<td>0.07 (0.55)</td>
</tr>
<tr>
<td><strong>Average Gait Speed (m/sec)</strong></td>
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</tr>
<tr>
<td>Men</td>
<td>-0.13 (0.43)</td>
<td>0.31 (0.02)</td>
<td>0.17 (0.24)</td>
<td>-0.05 (0.71)</td>
<td>-0.21 (0.19)</td>
<td>-0.24 (0.12)</td>
<td>0.00 (0.96)</td>
</tr>
<tr>
<td>Women</td>
<td>-0.15 (0.33)</td>
<td>-0.10 (0.53)</td>
<td>0.08 (0.85)</td>
<td>-0.12 (0.43)</td>
<td>0.01 (0.95)</td>
<td>0.14 (0.36)</td>
<td>0.17 (0.25)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>0.00 (0.97)</td>
<td>0.11 (0.26)</td>
<td>0.14 (0.19)</td>
<td>-0.09 (0.40)</td>
<td>-0.11 (0.31)</td>
<td>-0.05 (0.61)</td>
<td>0.07 (0.52)</td>
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<tr>
<td><strong>Maximal Gait Speed (m/sec)</strong></td>
<td></td>
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</tr>
<tr>
<td>Men</td>
<td>0.07 (0.62)</td>
<td>0.31 (0.02)</td>
<td>-0.14 (0.38)</td>
<td>-0.14 (0.35)</td>
<td>-0.13 (0.42)</td>
<td>0.10 (0.49)</td>
<td>0.03 (0.85)</td>
</tr>
<tr>
<td>Women</td>
<td>0.08 (0.62)</td>
<td>0.04 (0.81)</td>
<td>-0.05 (0.74)</td>
<td>-0.10 (0.59)</td>
<td>-0.08 (0.62)</td>
<td>-0.15 (0.93)</td>
<td>0.04 (0.81)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>0.07 (0.50)</td>
<td>0.17 (0.10)</td>
<td>-0.10 (0.37)</td>
<td>-0.12 (0.27)</td>
<td>-0.09 (0.84)</td>
<td>-0.08 (0.49)</td>
<td>0.04 (0.75)</td>
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</table>
### Table 5.5: Multiple Regression of Cognitive Test Scores and Exercise Capacity and Physical Performance: Sub-Study of GREAT2DO Trial - Continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM</th>
<th>WLR</th>
<th>WLRE</th>
<th>TMTA</th>
<th>TMTB</th>
<th>DIFFBA</th>
<th>3MS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chair Stand (sec)</td>
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</tr>
<tr>
<td>Men</td>
<td>0.06 (0.73)</td>
<td>-0.07 (0.68)</td>
<td>0.08 (0.65)</td>
<td>0.26 (0.13)</td>
<td>0.12 (0.52)</td>
<td>-0.22 (0.26)</td>
<td>0.02 (0.92)</td>
</tr>
<tr>
<td>Women</td>
<td>0.17 (0.26)</td>
<td>0.17 (0.31)</td>
<td>0.06 (0.51)</td>
<td><strong>0.51 (0.01)</strong></td>
<td>0.12 (0.47)</td>
<td>0.17 (0.31)</td>
<td>0.14 (0.31)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>0.10 (0.36)</td>
<td>0.06 (0.60)</td>
<td>0.10 (0.39)</td>
<td><strong>0.34 (0.00)</strong></td>
<td>0.13 (0.30)</td>
<td>-0.15 (0.22)</td>
<td>0.09 (0.43)</td>
</tr>
<tr>
<td>Stair Climb Power (w)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>0.20 (0.22)</td>
<td>0.08 (0.58)</td>
<td>0.08 (0.62)</td>
<td><strong>-0.29 (0.06)</strong></td>
<td>0.05 (0.79)</td>
<td>0.12 (0.49)</td>
<td>0.05 (0.80)</td>
</tr>
<tr>
<td>Women</td>
<td>-0.02 (0.87)</td>
<td>0.12 (0.46)</td>
<td>0.09 (0.69)</td>
<td>-0.21 (0.18)</td>
<td>-0.11 (0.50)</td>
<td>0.06 (0.70)</td>
<td>-0.00 (0.99)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>0.12 (0.32)</td>
<td>0.11 (0.36)</td>
<td>0.07 (0.62)</td>
<td><strong>-0.29 (0.02)</strong></td>
<td>-0.03 (0.80)</td>
<td>0.10 (0.45)</td>
<td>0.02 (0.85)</td>
</tr>
</tbody>
</table>

β-coefficients for relationship between cognitive test scores and exercise capacity and physical performance variables after adjusting for age, sex, and years of education for combined men and Women: GREAT2DO-substudy.

All baseline exercise capacity and physical performance measures were stratified by sex after controlling age and highest years of education in men and Women: GREAT2DO-substudy.

WLM: Word List Memory score (0/20)
WLR: Word List Recall score (0/10)
WLRE: Word List Recognition score (0/10)
TMTA: Trail Making Test A score (sec)
TMTB: Trail Making Test B score (sec)*
DIFFBA score (sec): Difference score between Trail Making Test B score minus Trail Making Test A score
3MS: Modified Mini Mental State score (0/100)
M: Meter
Sec: second
W: Watt
Min: Minute
**TABLE 5.6 MULTIPLE REGRESSION OF COGNITIVE TEST SCORES AND BODY COMPOSITION: SUB-STUDY OF GREAT2DO TRIAL**

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM β (p value)</th>
<th>WLR β (p value)</th>
<th>WLRE β (p value)</th>
<th>TMTA β (p value)</th>
<th>TMTB β (p value)</th>
<th>DIFFBA β (p value)</th>
<th>3MS β (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total Abdominal Adipose Tissue (cm²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.17 (0.29)</td>
<td>-0.16 (0.11)</td>
<td>0.05 (0.67)</td>
<td>-0.04 (0.74)</td>
<td>-0.16 (0.16)</td>
<td>-0.06 (0.58)</td>
<td>0.11 (0.33)</td>
</tr>
<tr>
<td>Women</td>
<td>0.10 (0.50)</td>
<td><strong>-0.04 (0.00)</strong></td>
<td>-0.01 (0.92)</td>
<td>-0.06 (0.69)</td>
<td>-0.05 (0.75)</td>
<td>0.03 (0.83)</td>
<td>0.22 (0.18)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.02 (0.85)</td>
<td><strong>-0.17 (0.06)</strong></td>
<td>0.05 (0.29)</td>
<td>0.01 (0.95)</td>
<td>-0.22 (0.14)</td>
<td>0.13 (0.42)</td>
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<tr>
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<tr>
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<td><strong>Subcutaneous Abdominal Adipose Tissue (cm²)</strong></td>
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TABLE 5.6 MULTIPLE REGRESSION OF COGNITIVE TEST SCORES AND BODY COMPOSITION: SUB-STUDY OF GREAT2DO TRIAL - CONTINUED

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<tr>
<th>Variable</th>
<th>WLM</th>
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<th>WLRE</th>
<th>TMTA</th>
<th>TMTB</th>
<th>DIFFBA</th>
<th>3MS</th>
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<tr>
<td>Women</td>
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<td>0.12(0.39)</td>
<td>-0.04 (0.76)</td>
<td>0.05 (0.74)</td>
<td>0.14 (0.35)</td>
<td>-0.09 (0.54)</td>
<td>0.07 (0.62)</td>
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<tr>
<td>Men and Women</td>
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<td>-0.21(0.03)</td>
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<td>Thigh Muscle Area (cm²)</td>
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<tr>
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<td>0.13 (0.41)</td>
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<td>0.04 (0.80)</td>
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<td>Subcutaneous Adipose Tissue (Thigh) (cm²)</td>
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<td>-0.13 (0.34)</td>
<td>0.04 (0.77)</td>
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<td>0.10 (0.96)</td>
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<td>Men and Women</td>
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<td>0.05 (0.67)</td>
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TABLE 5.6 MULTIPLE REGRESSION OF COGNITIVE TEST SCORES AND BODY COMPOSITION: SUB-STUDY OF GREAT2DO TRIAL - CONTINUED

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM β (p value)</th>
<th>WLR β (p value)</th>
<th>WLRE β (p value)</th>
<th>TMTA β (p value)</th>
<th>TMTB β (p value)</th>
<th>DIFFBA β (p value)</th>
<th>3MS β (p value)</th>
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<td>0.09 (0.51)</td>
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<td>0.09 (0.54)</td>
<td>0.23 (0.09)</td>
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<tr>
<td>Women</td>
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<td>-0.08 (0.58)</td>
<td>-0.23 (0.12)</td>
<td>&lt;0.01 (0.98)</td>
<td>0.06 (0.67)</td>
<td>0.11 (0.46)</td>
<td>-0.07 (0.63)</td>
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<tr>
<td>Men and Women</td>
<td>-0.04 (0.62)</td>
<td>0.12 (0.17)</td>
<td>-0.04 (0.72)</td>
<td>-0.01 (0.93)</td>
<td>-0.02 (0.86)</td>
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<td>Thigh Muscle Density</td>
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<td>-0.19 (0.28)</td>
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<td>Skeletal Muscle Mass (kg)</td>
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<td>Men</td>
<td>-0.23 (0.12)</td>
<td>0.00 (0.97)</td>
<td>-0.24 (0.15)</td>
<td>-0.06 (0.69)</td>
<td>0.06 (0.68)</td>
<td>0.10 (0.58)</td>
<td>0.16 (0.30)</td>
</tr>
<tr>
<td>Women</td>
<td>-0.23 (0.12)</td>
<td>0.00 (0.97)</td>
<td>0.09 (0.57)</td>
<td>-0.06 (0.69)</td>
<td>0.06 (0.68)</td>
<td>0.10 (0.58)</td>
<td>0.16 (0.30)</td>
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<tr>
<td>Men and Women</td>
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<td>0.11 (0.35)</td>
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<td>0.05 (0.66)</td>
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TABLE 5.6 MULTIPLE REGRESSION OF COGNITIVE TEST SCORES AND BODY COMPOSITION: SUB-STUDY OF GREAT2DO TRIAL - CONTINUED

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM β (p value)</th>
<th>WLR β (p value)</th>
<th>WLRE β (p value)</th>
<th>TMTA β (p value)</th>
<th>TMTB β (p value)</th>
<th>DIFFBA β (p value)</th>
<th>3MS β (p value)</th>
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</thead>
<tbody>
<tr>
<td>Free Fat Mass (kg)</td>
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<tr>
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<td>0.18 (0.28)</td>
<td>-0.08 (0.58)</td>
<td>-0.20 (0.21)</td>
<td>-0.20 (0.25)</td>
<td>0.19 (0.33)</td>
<td>0.07 (0.25)</td>
<td>0.03 (0.04)</td>
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<tr>
<td>Women</td>
<td>-0.09 (0.57)</td>
<td>-0.14 (0.38)</td>
<td>-0.04 (0.80)</td>
<td>-0.04 (0.80)</td>
<td>0.19 (0.23)</td>
<td>0.26 (0.09)</td>
<td>0.03 (0.84)</td>
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<tr>
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<td>-0.10 (0.37)</td>
<td>-0.16 (0.27)</td>
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<td>0.21 (0.15)</td>
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<tr>
<td>Total Fat Mass (kg)</td>
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<td>-0.18 (0.29)</td>
<td>-0.18 (0.30)</td>
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<td>0.36 (0.04)</td>
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<td>-0.12 (0.50)</td>
<td>-0.03 (0.85)</td>
<td>0.23 (0.14)</td>
<td>0.29 (0.06)</td>
<td>0.10 (0.54)</td>
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<tr>
<td>Men and Women</td>
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<td>0.00 (0.97)</td>
<td>-0.09 (0.41)</td>
<td>-0.06 (0.69)</td>
<td>0.06 (0.68)</td>
<td>0.10 (0.58)</td>
<td>0.16 (0.30)</td>
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<td>0.12 (0.38)</td>
<td>0.19 (0.12)</td>
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<td>-0.04 (0.79)</td>
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<tr>
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<td>0.06 (0.69)</td>
<td>0.07 (0.66)</td>
</tr>
<tr>
<td>Men and Women</td>
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<td>0.13 (0.14)</td>
<td>0.09 (0.37)</td>
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<td>0.06 (0.54)</td>
<td>0.01 (0.91)</td>
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**TABLE 5.6 MULTIPLE REGRESSION OF COGNITIVE TEST SCORES AND BODY COMPOSITION: SUB-STUDY OF GREAT2DO TRIAL - CONTINUED**

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM β (p value)</th>
<th>WLR β (p value)</th>
<th>WLRE β (p value)</th>
<th>TMTA β (p value)</th>
<th>TMTB β (p value)</th>
<th>DIFFBA β (p value)</th>
<th>3MS β (p value)</th>
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<tbody>
<tr>
<td><strong>Body Mass Index</strong></td>
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<td>Men</td>
<td>0.14 (0.33)</td>
<td>-0.15 (0.13)</td>
<td>0.02 (0.82)</td>
<td>-0.03 (0.77)</td>
<td>-0.11 (0.50)</td>
<td>-0.02 (0.88)</td>
<td>0.21 (0.25)</td>
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<tr>
<td>Women</td>
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<td>-0.16 (0.32)</td>
<td>0.03 (0.81)</td>
<td>0.10 (0.53)</td>
<td>0.11 (0.44)</td>
<td>0.07 (0.66)</td>
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<tr>
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<td>-0.10 (0.50)</td>
<td>0.14 (0.32)</td>
<td>0.20 (0.28)</td>
<td>0.01 (0.93)</td>
<td>0.05 (0.63)</td>
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<td><strong>Body Weight (kg)</strong></td>
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<tr>
<td>Men</td>
<td>-0.02 (0.87)</td>
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<td>0.22 (0.15)</td>
<td>0.17 (0.26)</td>
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<td>0.31 (0.04)</td>
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<td>0.04 (0.67)</td>
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<td>-0.04 (0.67)</td>
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<td>0.11 (0.29)</td>
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<td><strong>Waist Circumstance (cm)</strong></td>
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<td>Men</td>
<td>0.18 (0.19)</td>
<td>-0.28 (0.03)</td>
<td>-0.22 (0.14)</td>
<td>0.05 (0.72)</td>
<td>-0.03 (0.86)</td>
<td>0.02 (0.88)</td>
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<tr>
<td>Women</td>
<td>-0.09 (0.52)</td>
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<td>0.16 (0.12)</td>
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β-coefficients for relationship between cognitive test scores and exercise capacity and physical performance variables after adjusting for age, sex, and years of education for combined men and Women: GREAT2DO-substudy

All baseline body composition measures were stratified by sex after controlling age and highest years of education in men and Women: GREAT2DO-substudy

WIM: Word List Memory score (0/20)

WLR: Word List Recall score (0/10)

WLRE: Word List Recognition score (0/10)

TMTA: Trail Making Test A score (sec)

TMTB: Trail Making Test B score (sec)*

DIFFBA score (sec): Difference score between Trail Making Test B score minus Trail Making Test A score

3MS: Modified Mini Mental State score (0/100)
TABLE 5.7 MULTIPLE REGRESSION OF COGNITIVE TEST SCORES AND PSYCHO-SOCIAL, QUALITY OF LIFE, AND PHYSICAL ACTIVITY: SUB-STUDY OF GREAT2DO TRIAL

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM $\beta$ (p value)</th>
<th>WLR $\beta$ (p value)</th>
<th>WLRE $\beta$ (p value)</th>
<th>TMTA $\beta$ (p value)</th>
<th>TMTB $\beta$ (p value)</th>
<th>DIFFBA $\beta$ (p value)</th>
<th>3MS $\beta$ (p value)</th>
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<td>-0.16 (0.30)</td>
<td>-0.05 (0.71)</td>
<td>0.04 (0.81)</td>
<td>-0.09 (0.55)</td>
<td>0.23 (0.14)</td>
<td>0.30 (0.06)</td>
<td>-0.03 (0.85)</td>
</tr>
<tr>
<td>Women</td>
<td>0.05 (0.77)</td>
<td>0.12 (0.51)</td>
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<td>0.02 (0.89)</td>
<td>0.25 (0.11)</td>
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<td>0.09 (0.60)</td>
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<td>0.01 (0.93)</td>
<td>0.04 (0.74)</td>
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<td>Men</td>
<td>-0.16 (0.21)</td>
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<td>0.06 (0.60)</td>
<td>0.24 (0.08)</td>
<td>-0.04 (0.81)</td>
<td>-0.11 (0.46)</td>
<td>0.01 (0.98)</td>
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<tr>
<td>Women</td>
<td>0.10 (0.51)</td>
<td>-0.16 (0.30)</td>
<td>0.05 (0.77)</td>
<td>-0.09 (0.56)</td>
<td>-0.01 (0.51)</td>
<td>-0.08 (0.60)</td>
<td>0.04 (0.81)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.02 (0.85)</td>
<td>-0.13 (0.18)</td>
<td>0.06 (0.52)</td>
<td>0.07 (0.48)</td>
<td>0.07 (0.53)</td>
<td>0.10 (0.35)</td>
<td>0.02 (0.85)</td>
</tr>
<tr>
<td>SF-36 MCS (score) (log)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.06 (0.67)</td>
<td>-0.12 (0.36)</td>
<td>-0.22 (0.13)</td>
<td>0.17 (0.21)</td>
<td>0.19 (0.16)</td>
<td>0.17 (0.23)</td>
<td>-0.08 (0.58)</td>
</tr>
<tr>
<td>Women</td>
<td>0.12 (0.37)</td>
<td>0.20 (0.16)</td>
<td>0.16 (0.29)</td>
<td>0.11 (0.49)</td>
<td>0.17 (0.23)</td>
<td>0.25 (0.08)</td>
<td>0.09 (0.55)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>0.04 (0.63)</td>
<td>0.06 (0.50)</td>
<td>-0.04 (0.73)</td>
<td>0.13 (0.17)</td>
<td>0.01 (0.97)</td>
<td>0.07 (0.51)</td>
<td>-0.03 (0.78)</td>
</tr>
</tbody>
</table>
### Table 5.7: Multiple Regression of Cognitive Test Scores and Psycho-social, Quality of Life, and Physical Activity: Sub-study of GREAT2DO Trial - continued

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM β (p value)</th>
<th>WLR β (p value)</th>
<th>WLRE β (p value)</th>
<th>TMTA β (p value)</th>
<th>TMTB β (p value)</th>
<th>DIFFBA β (p value)</th>
<th>3MS β (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geriatric Depression Scale (0/30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.10 (0.47)</td>
<td>-0.11 (0.41)</td>
<td>-0.20 (0.17)</td>
<td>0.21 (0.12)</td>
<td>0.06 (0.65)</td>
<td>0.06 (0.92)</td>
<td>-0.17 (0.23)</td>
</tr>
<tr>
<td>Women</td>
<td>0.23 (0.10)</td>
<td>0.08 (0.58)</td>
<td>-0.20 (0.14)</td>
<td>0.09 (0.55)</td>
<td><strong>-0.30 (0.04)</strong></td>
<td><strong>-0.32 (0.03)</strong></td>
<td>-0.03 (0.87)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.04 (0.41)</td>
<td>-0.01 (0.99)</td>
<td>0.03 (0.78)</td>
<td>0.15 (0.14)</td>
<td>-0.12 (0.22)</td>
<td>-0.12 (0.09)</td>
<td>-0.10 (0.52)</td>
</tr>
</tbody>
</table>
β-coefficients for relationship between cognitive test scores and exercise capacity and physical performance variables after adjusting for age, sex, and years of education for combined men and Women: GREAT2DO-substudy

All baseline body composition measures were stratified by sex after controlling age and highest years of education in men and Women: GREAT2DO-substudy

WIM: Word List Memory score (0/20)
WLR: Word List Recall score (0/10)
WLRE: Word List Recognition score (0/10)
TMTA: Trail Making Test A score (sec)
TMTB: Trail Making Test B score (sec)*
DIFFBA score (sec): Difference score between Trail Making Test B score minus Trail Making Test A score
3MS: Modified Mini Mental State score (0/100)
SF-36: Short Form-36
PCS: Physical Component Summary
MCS: Mental Component Summary
TABLE 5.8 MULTIPLE REGRESSION OF COGNITIVE TEST SCORES AND INFLAMMATION AND ADIPOKINES: SUB-STUDY OF GREAT2DO TRIAL

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM β (p value)</th>
<th>WLR β (p value)</th>
<th>WLRE β (p value)</th>
<th>TMTA β (p value)</th>
<th>TMTB β (p value)</th>
<th>DIFFBA β (p value)</th>
<th>3MS β (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/L) (log)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.01 (0.91)</td>
<td>-0.24 (0.09)</td>
<td>0.10 (0.90)</td>
<td>0.27 (0.06)</td>
<td>0.05 (0.72)</td>
<td>-0.05 (0.72)</td>
<td>-0.08 (0.58)</td>
</tr>
<tr>
<td>Women</td>
<td>0.15 (0.38)</td>
<td>-0.02 (0.92)</td>
<td>-0.02 (0.92)</td>
<td>0.34 (0.05)</td>
<td>-0.09 (0.59)</td>
<td>-0.18 (0.28)</td>
<td>0.04 (0.60)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>0.02 (0.83)</td>
<td>-0.15 (0.15)</td>
<td>0.13 (0.44)</td>
<td><strong>0.30 (&lt;0.01)</strong></td>
<td>-0.02 (0.87)</td>
<td>-0.10 (0.35)</td>
<td>0.04 (0.71)</td>
</tr>
<tr>
<td>HMW Adiponectin (ng/ml)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.09 (0.66)</td>
<td>0.49 (0.02)</td>
<td>0.04 (0.84)</td>
<td>0.20 (0.33)</td>
<td>-0.15 (0.50)</td>
<td>0.10 (0.99)</td>
<td>0.02 (0.95)</td>
</tr>
<tr>
<td>Women</td>
<td>0.02 (0.94)</td>
<td>0.17 (0.51)</td>
<td>-0.25 (0.26)</td>
<td>-0.16 (0.52)</td>
<td>0.30 (0.22)</td>
<td>0.41 (0.10)</td>
<td>0.36 (0.15)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.04 (0.73)</td>
<td>0.04 (0.78)</td>
<td>0.06 (0.69)</td>
<td>-0.16 (0.27)</td>
<td>-0.17 (0.27)</td>
<td>0.08 (0.60)</td>
<td>0.19 (0.25)</td>
</tr>
<tr>
<td>Total Adiponectin (ng/ml) (log)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.07 (0.70)</td>
<td>0.12 (0.53)</td>
<td>0.04 (0.87)</td>
<td>-0.23 (0.26)</td>
<td>0.17 (0.41)</td>
<td>0.01 (0.99)</td>
<td>0.14 (0.53)</td>
</tr>
<tr>
<td>Women</td>
<td>0.05 (0.83)</td>
<td><strong>0.59 (&lt;0.01)</strong></td>
<td>-0.26 (0.25)</td>
<td>0.19 (0.44)</td>
<td>0.27 (0.26)</td>
<td>0.41 (0.10)</td>
<td>-0.41 (0.11)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.02 (0.85)</td>
<td><strong>0.25 (0.04)</strong></td>
<td>0.18 (0.11)</td>
<td>-0.21 (0.17)</td>
<td>-0.02 (0.91)</td>
<td>-0.20 (0.90)</td>
<td>0.10 (0.55)</td>
</tr>
</tbody>
</table>
TABLE 5.8 MULTIPLE REGRESSION OF COGNITIVE TEST SCORES AND INFLAMMATION AND ADIPOKINES: SUB-STUDY OF GREAT2DO TRIAL

<table>
<thead>
<tr>
<th>Variable</th>
<th>WLM β (p value)</th>
<th>WLR β (p value)</th>
<th>WLRE β (p value)</th>
<th>TMTA β (p value)</th>
<th>TMTB β (p value)</th>
<th>DIFFBA β (p value)</th>
<th>3MS β (p value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adiponectin Ratio (ng/ml) (log)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>-0.04 (0.83)</td>
<td>-0.15 (0.47)</td>
<td>0.27 (0.22)</td>
<td>0.05 (0.80)</td>
<td>-0.30 (0.15)</td>
<td><strong>-0.49 (0.02)</strong></td>
<td>0.31 (0.15)</td>
</tr>
<tr>
<td>Women</td>
<td>0.02 (0.93)</td>
<td>0.47 (0.05)</td>
<td>-0.14 (0.56)</td>
<td>0.17 (0.51)</td>
<td>-0.24 (0.36)</td>
<td>-0.44 (0.08)</td>
<td>0.01 (0.95)</td>
</tr>
<tr>
<td>Men and Women</td>
<td>-0.04 (0.77)</td>
<td>0.14 (0.15)</td>
<td>-0.16 (0.30)</td>
<td>0.06 (0.80)</td>
<td>-0.25 (0.11)</td>
<td><strong>-0.43 (0.01)</strong></td>
<td>0.06 (0.70)</td>
</tr>
</tbody>
</table>
β-coefficients for relationship between cognitive test scores and CRP variables after adjusting for age, sex, and years of education for combined men and women: GREAT2DO-substudy

All baseline CRP and adiponectin measures were stratified by sex after controlling age and highest years of education in men and women: GREAT2DO-substudy

WIM: Word List Memory score (0/20)

WLR: Word List Recall score (0/10)

WLRE: Word List Recognition score (0/10)

TMTA: Trail Making Test A score (sec)

TMTB: Trail Making Test B score (sec)*

DIFFBA score (sec): Difference score between Trail Making Test B score minus Trail Making Test A score

3MS: Modified Mini Mental State score (0/100)

CRP: C-reactive protein

HMW: High Molecular Weight
TABLE 5.9 MULTIPLE REGRESSIONS OF WORD LIST RECALL AND SERUM GLUCOSE FASTING

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Co-efficient</th>
<th>p-value</th>
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</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.23</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.30</td>
<td>0.001</td>
</tr>
<tr>
<td>Years of Education</td>
<td>0.24</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum Glucose Fasting (log unit)</td>
<td>0.23</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Word List Recall</strong></td>
<td><strong>r²=0.26</strong></td>
<td><strong>p&lt;0.0001</strong></td>
</tr>
</tbody>
</table>
TABLE 5.10 MULTIPLE REGRESSIONS OF WORD LIST RECALL AND SIX MINUTE WALK DISTANCE

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.35</td>
<td>0.09</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.24</td>
<td>0.01</td>
</tr>
<tr>
<td>Years of Education</td>
<td>0.24</td>
<td>0.01</td>
</tr>
<tr>
<td>6 Minute Walk Distance</td>
<td>0.22</td>
<td>0.04</td>
</tr>
<tr>
<td>Word List Recall</td>
<td>r²=0.29</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>Variable</td>
<td>Standard Co-efficient</td>
<td>p-value</td>
</tr>
<tr>
<td>--------------------------</td>
<td>-----------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Age</td>
<td>0.21</td>
<td>0.051</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.03</td>
<td>0.80</td>
</tr>
<tr>
<td>Years of Education</td>
<td>0.19</td>
<td>0.052</td>
</tr>
<tr>
<td>6 Minute Walk Distance</td>
<td>-0.21</td>
<td>0.052</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>$r^2=0.15$</td>
<td>p=0.003</td>
</tr>
</tbody>
</table>
TABLE 5.12 MULTIPLE REGRESSIONS OF TRAIL MAKING TEST A AND STAIR CLIMB POWER

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.19</td>
<td>0.08</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.15</td>
<td>0.20</td>
</tr>
<tr>
<td>Years of Education</td>
<td>0.15</td>
<td>0.13</td>
</tr>
<tr>
<td>Stair Climb Power</td>
<td>-0.29</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Trail Making Test A</strong></td>
<td><strong>r²=0.17</strong></td>
<td><strong>p=0.001</strong></td>
</tr>
</tbody>
</table>
# Table 5.13 Multiple Regressions of Trail Making Test A and Chair Stand

<table>
<thead>
<tr>
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<th>Standard Co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.21</td>
<td>0.04</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.02</td>
<td>0.84</td>
</tr>
<tr>
<td>Years of Education</td>
<td>0.20</td>
<td>0.05</td>
</tr>
<tr>
<td>Chair Stand</td>
<td>0.34</td>
<td>0.001</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>$r^2=0.24$</td>
<td>$p=0.0002$</td>
</tr>
</tbody>
</table>
### TABLE 5.14 MULTIPLE REGRESSIONS OF TRAIL MAKING TEST A AND C-REACTIVE PROTEIN

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.30</td>
<td>0.006</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.02</td>
<td>0.88</td>
</tr>
<tr>
<td>Years of Education</td>
<td>0.19</td>
<td>0.07</td>
</tr>
<tr>
<td>C - reactive Protein (log units)</td>
<td>-0.30</td>
<td>0.006</td>
</tr>
<tr>
<td>Trail Making Test A</td>
<td>$r^2=0.18$</td>
<td>$p=0.003$</td>
</tr>
</tbody>
</table>
TABLE 5.15 MULTIPLE REGRESSIONS OF WORD LIST RECALL AND SERUM TOTAL ADIPONECTIN

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.22</td>
<td>0.16</td>
</tr>
<tr>
<td>Sex</td>
<td>-0.24</td>
<td>0.36</td>
</tr>
<tr>
<td>Years of Education</td>
<td>-0.26</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum Total Adiponectin (log)</td>
<td>-0.59</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Word List Recall</strong></td>
<td><strong>r²=0.33</strong></td>
<td><strong>p=0.01</strong></td>
</tr>
</tbody>
</table>
TABLE 5.16 MULTIPLE REGRESSIONS OF DIFFBA AND SERUM ADIPONECTIN RATIO

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.08</td>
<td>0.52</td>
</tr>
<tr>
<td>Sex</td>
<td>0.59</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Years of Education</td>
<td>0.26</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum Total Adiponectin (log)</td>
<td>-0.43</td>
<td>0.01</td>
</tr>
<tr>
<td>DIFFBA</td>
<td>( r^2=0.33 )</td>
<td>( p&lt;0.0001 )</td>
</tr>
</tbody>
</table>

DIFFBA: Difference score between Trail Making Test B minus Trail Making Test A
### TABLE 5.17 MULTIPLE REGRESSIONS OF DIFFBA AND PHYSICAL ACTIVITY SCALE FOR THE ELDERLY

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.67</td>
<td>0.51</td>
</tr>
<tr>
<td>Sex</td>
<td>0.07</td>
<td>0.95</td>
</tr>
<tr>
<td>Years of Education</td>
<td>0.26</td>
<td>0.08</td>
</tr>
<tr>
<td>Serum Total Adiponectin (log)</td>
<td>-0.38</td>
<td>0.006</td>
</tr>
<tr>
<td>Scores of PASE</td>
<td>( r^2 = 0.210 )</td>
<td>( p=0.002 )</td>
</tr>
</tbody>
</table>

PASE: Physical Activity Scale for the Elderly
### TABLE 5.18 MULTIPLE REGRESSIONS OF WORD LIST RECALL AND SAGITTAL ABDOMINAL DIAMETER

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standard Co-efficient</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>-0.30</td>
<td>0.00</td>
</tr>
<tr>
<td>Sex</td>
<td>0.23</td>
<td>0.02</td>
</tr>
<tr>
<td>Years of Education</td>
<td>0.23</td>
<td>0.01</td>
</tr>
<tr>
<td>Sagittal Abdominal Diameter</td>
<td>-0.21</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Word List Recall</strong></td>
<td><strong>r^2=0.22</strong></td>
<td><strong>p&lt;0.0001</strong></td>
</tr>
</tbody>
</table>
FIGURE LEGENDS

Figure 5.1: Study Recruitment Flow Chart
n=sample size

Figure 5.2: The Relationship between Glucose Fasting and Word List Recall.
Simple linear regression between glucose fasting and word list recall was analysed. Low glucose fasting was significantly associated with worse Word List Recall. Cognitive function was significantly associated with age, years of education, and men had lower cognitive function on immediate and delayed memory, information processing speed, executive function, pure executive function, and global cognitive function than women. Age, years of education, and sex were added to the model. This relationship remained after for age, sex, and years of education in a multiple regression model (r=0.26; p<0.0001). r and p values were calculated by linear regression analysis.

Figure 5.3: The Relationship between Six-Minute Walk Distance and Word List Recall. Simple linear regression between six-minute walk distance and word list recall was analysed. Low six-minute walk distance was significantly associated with worse Word List Recall. Cognitive function was significantly associated with age, years of education, and men had lower cognitive function on immediate and delayed memory, information processing speed, executive function, pure executive function, and global cognitive function than women, age, years of education, and sex.
were added to the model. This relationship remained after for age, sex, and years
of education in a multiple regression model (r=0.54; p<0.0001). r and p values
were calculated by linear regression analysis.

Figure 5.4: The Relationship between Sagittal Abdominal Diameter and Word
List Recall. Simple linear regression between sagittal abdominal diameter and
word list recall was analysed. Low sagittal abdominal diameter was significantly
associated with higher delayed memory (word list recall). Cognitive function was
significantly associated with age, years of education, and men had lower cognitive
function on immediate and delayed memory, information processing speed, executive
function, pure executive function, and global cognitive function than women, age,
years of education, and sex were added to the model. This relationship remained after for age, sex, and years of
education in a multiple regression model (r=-0.47; p<0.0001). r and p values were
calculated by linear regression analysis.

Figure 5.5: The Relationship between Six-Minute Walk Distance and
Information Processing Speed. Simple linear regression between six-minute walk
distance and information processing speed was analysed. Low six-minute walk
distance was significantly associated with decreased information processing speed.
Cognitive function was significantly related to age, years of education, and men had
lower cognitive function on immediate and delayed memory, information processing
speed, executive function, pure executive function, and global cognitive function than
women, age, years of education, and sex were added to the model. This relationship remained after for age, sex, and years of education in a multiple regression model (r=-0.39; p=0.003). r and p values were calculated by linear regression analysis.

Figure 5.6: The Relationship between Stair Climb Power and Information Processing Speed. Simple linear regression between stair climb power and information processing speed was analysed. Low stair climb power was significantly associated with decreased information processing speed. Cognitive function was significantly associated with age, years of education, and men had lower cognitive function on immediate and delayed memory, information processing speed, executive function, pure executive function, and global cognitive function than women, age, years of education, and sex were added to the model. This relationship remained after for age, sex, and years of education in a multiple regression model (r=-0.41; p=0.001). r and p values were calculated by linear regression analysis.

Figure 5.7: The Relationship between Chair Stand and Information Processing Speed. Simple linear regression between chair stand and information processing speed was analysed. Fast chair stand was significantly associated with higher information processing speed. Cognitive function was significantly associated with age, years of education, and men had lower cognitive function on immediate and delayed memory, information processing speed, executive function, pure executive function, and global cognitive function than women, age, years of education, and sex
were added to the model. This relationship remained after for age, sex, and years of education in a multiple regression model (r=0.49; p=0.0002). r and p values were calculated by linear regression analysis.

**Figure 5.8: The Relationship between C-reactive Protein and Information Processing Speed.**  Simple linear regression between C-reactive protein and information processing speed was analysed. High C-reactive protein was significantly associated with decreased information processing speed. Cognitive function was significant associated with age, years of education, and men had lower cognitive function on immediate and delayed memory, information processing speed, executive function, pure executive function, and global cognitive function than women, age, years of education, and sex were added to the model. This relationship remained after for age, sex, and years of education in a multiple regression model (r=0.42; p=0.003). r and p values were calculated by linear regression analysis.

**Figure 5.9: The Relationship between Serum Total Adiponectin and Word List Recall.**  Simple linear regression between serum total adiponectin and Word List Recall was analysed. Lower serum total adiponectin was significantly associated with decreased Word List Recall scores. Cognitive function was related to age, years of education, and men had lower cognitive function on immediate and delayed memory, information processing speed, executive function, pure executive function, and global cognitive function than women, age, years of education, and sex were added to the model. This relationship remained after for age, sex, and years of
education in a multiple regression model (r=0.57; p=0.01). r and p values were calculated by linear regression analysis.

**Figure 5.10: The Relationship between serum HMW Adiponectin Relative to Total Adiponectin Ratio and Pure Executive Function.** *Simple linear regression between serum HMW adiponectin relative to total adiponectin ratio and pure executive function was analysed.* Lower serum total adiponectin was significantly associated with worse pure executive function. Cognitive function was associated with age, years of education, and men had lower cognitive function on immediate and delayed memory, information processing speed, executive function, pure executive function, and global cognitive function than women, age, years of education, and sex were added to the model. This relationship remained after for age, sex, and years of education in a multiple regression model (r=0.57; p<0.0001). r and p values were calculated by linear regression analysis.

**Figure 5.11: The relationship between Physical Activity Scale for the Elderly and pure executive function.** *Simple linear regression between Physical Activity Scale for the Elderly and pure executive function was analysed.* Higher s Physical Activity Scale for the Elderly was significantly associated with worse pure executive function. Cognitive function was associated with age, years of education, and men had lower cognitive function on immediate and delayed memory, information processing speed, executive function, pure executive function, and global cognitive function than women, age, years of education, and sex were added to the model.
This relationship remained after for age, sex, and years of education in a multiple regression model ($r=0.45; p=0.002$). $r$ and $p$ values were calculated by linear regression analysis.

A lower score in word list memory, word list recall, Trail making Test A, Trail Making test B, Trail Making test B minus Trial Making Test A, and global cognitive function equals poorer function
FIGURE 5.1 STUDY RECRUITMENT FLOW CHART

Assessed for eligibility (n=427)

Excluded (n=324)
Not meeting included criteria (n=285)

Randomised (n=103)

Allocated to intervention (n=49)
Allocated to intervention (n=54)

Lost to follow (n=8)
Lost to follow (n=5)

Analysed (n=49)
Analysed (n=54)
FIGURE 5.2 SERUM GLUCOSE FASTING VERSUS WORD LIST RECALL

n=102, r=0.52, r^2=0.26, p<0.0001
FIGURE 5.3 SIX MINUTE WALK DISTANCE VERSUS WORD LIST RECALL

\[ n=100, r=0.54, r^2=0.29, p<0.0001 \]
FIGURE 5.4 SAGITTAL ABDOMINAL DIAMETER VERSUS WORD LIST RECALL

\[ n=101, r=-0.47, r^2=0.22, p<0.0001 \]
FIGURE 5.5 SIX MINUTE WALK DISTANCE VERSUS TRAIL MAKING TEST A

n=100, r=-0.39, r^2=0.15, p=0.003
FIGURE 5.6 STAIR CLIMB POWER VERSUS TRAIL MAKING TEST A

n=97, r=-0.41, r^2=0.17, p=0.001
FIGURE 5.7 CHAIR STAND VERSUS TRAIL MAKING TEST A

n=84, r=0.49, \( r^2 = 0.24 \), p=0.0002
FIGURE 5.8 CRP VERSUS TRAIL MAKING TEST A

n=88, r=0.42, r²=0.18, p=0.003

CRP: C-reactive protein
FIGURE 5.9 SERUM TOTAL ADIPONECTIN VERSUS WORD LIST RECALL

n=39, r=0.57, \( r^2 = 0.33 \), p=0.01
FIGURE 5.10 SERUM HMW ADIPONECTIN RELATIVE TO TOTAL ADIPONECTIN RATIO VERSUS PURE EXECUTIVE FUNCTION

HMW: High–Molecular Weight

DIFFBA: Trail Making Test B minus Trail Making Test A

n=39, r=0.57, r²=0.33, p<0.0001
FIGURE 5.11 PHYSICAL ACTIVITY SCALE FOR THE ELDERLY VERSUS PURE EXECUTIVE FUNCTION

n=77, r=0.45, r^2=0.21, p=0.002
CHAPTER 6

THE EFFECTS OF POWER TRAINING ON COGNITION IN OLDER ADULTS WITH TYPE 2 DIABETES MELLITUS: A RANDOMISED SHAM EXERCISE CONTROLLED, DOUBLE-BLIND TRIAL
6.1 ABSTRACT

Objectives - T2DM has been associated with an increased risk of cognitive impairment and dementia. Our aim of this GREAT2DO sub-study was therefore to assess whether 12 months of high intensity, high velocity, progressive resistance training (POWER training) could slow cognitive decline in older adults with T2DM. Our secondary aim was to identify potential mechanisms linking POWER training with improved cognitive function in this at-risk group of older adults, including changes in metabolic profile, body composition, physical activity levels, psychological status, or other clinical characteristics.

Methods - One-hundred and three participants were randomised to receive either supervised POWER training or SHAM exercise 3 days per week for 12 months. The primary cognitive outcomes of this sub-study included measures of memory performance (Word List Memory, Word List Recall, and Word List Recognition), information processing speed (Trail Making Test A), executive function (Trail Making Test B), pure executive function (Difference scores between Trail Making Test B minus Trail Making Test A), and global cognitive function (3MS), analysed via repeated measures mixed models adjusted for age, sex, years of education, duration of diabetes, Short Form-36 (SF-36) MCS, HbA1c, and cognitive function. The potential mediators/correlates of the hypothesised cognitive changes included measures of insulin resistance and glucose homeostasis obtained via Homeostatic Model of Assessment 2 (HOMA2-IR) and glycosylated haemoglobin (HbA1c), total fat mass and skeletal muscle mass assessed using bioelectrical impedance (BIA), total abdominal adipose tissue, subcutaneous abdominal adipose tissue, visceral adipose tissue, sagittal diameter, thigh muscle area, thigh subcutaneous adipose area, intramuscular adipose area, and thigh muscle density quantified using computed tomography, serum levels of adiponectin and C-reactive protein (CRP), physical performance, depressive symptoms via Geriatric Depression Scale (GDS) and physical activity levels via Physical Activity Scale for the Elderly (PASE).
Results: There were improvements over time in immediate and delayed memory (Word List memory and Word List Recall); information processing speed, attention/executive function, and global cognitive function. No significant improvements were found in Word List Recognition or pure executive function. Unexpectedly, POWER training did not significantly improve the scores for any cognitive outcomes relative to the SHAM exercise condition. Instead, SHAM exercise significantly improved executive function (TMT-B; p=0.03) and global cognitive function (3MS; p=0.04) compared to POWER training. As hypothesised, but only within the POWER group, changes in skeletal muscle mass and thigh muscle area were positively related to better scores in Word List Memory and information processing speed (β=0.36, p=0.04, β=−0.34, p<0.05, respectively) while no body composition relationships with cognition change were found in Word List Recognition, information processing speed, executive function, or global cognitive function. Again as expected, increasing serum levels of adiponectin were associated with better global cognitive function (β=0.57, p=0.03) in the POWER group, but not in the SHAM group (β=0.10, p=0.59). Measurements of HOA2-IR tended to be associated with information processing speed (β=−0.36, p=0.06) in POWER group, and were significantly associated with global cognitive function (β=−0.40, p<0.01) in SHAM group, as hypothesized. Measurements of glucose fasting, HbA1c, fasting insulin, and HOMA 2 beta function were not associated with any tests of cognition in our cohorts. Improved physical performance, including static balance, chair stand time, stair power and gait speed were all significantly related to cognitive improvements, but not in the POWER group, and may have been linked to a common mediator or potentially even a result of improved cognition after exercise.

Conclusions - Contrary to our expectations, the results of our study suggest that 12 months of POWER training is not better than low intensity SHAM exercise for cognitive outcomes in older adults with T2DM. In fact, both types of exercise significantly improved memory, information processing speed, executive function, and global function, and low intensity SHAM exercise was
superior to high intensity POWER training for executive function and global function. Improvements in cognitive function were associated with skeletal muscle mass, thigh muscle area, and physical performance as hypothesised, but only in the POWER group. Adiponectin increases and improved insulin sensitivity were related to better cognition in some domains in both groups. Unexpectedly, changes in visceral adiposity did not predict cognitive improvements. Future studies enrolling adults with more cognitive impairment at baseline and non-exercise control groups are needed to identify the precise roles of exercise modality and intensity, as well as body composition and metabolic adaptations to exercise, on cognitive function in T2DM.
6.2 INTRODUCTION

The prevalence of diabetes mellitus is rising with age, and this condition is projected to affect 435 million adults globally by 2030.\textsuperscript{1} T2DM is the most common type of diabetes and represents 90-95\% of all diabetes mellitus.\textsuperscript{2} Especially in conjunction with obesity, T2DM is characterized by resistance to the actions of insulin in target tissues, including skeletal muscle, adipose tissue and liver. Older adults with T2DM have an increased risk of cognitive decline and dementia.\textsuperscript{3} Evidence from prospective studies indicates that cognitive function and insulin resistance are closely associated.\textsuperscript{4, 5} Relationships between high HbA1c and cognitive dysfunction have been demonstrated in older\textsuperscript{6} and middle aged\textsuperscript{7} individuals. Also, in older patients with T2DM, acute deficits in working memory and attention have been observed in the hyperglycaemic state during a glucose clamp.\textsuperscript{8}

Many physiological abnormalities associated with T2DM may play a role in the higher risk of cognitive impairment in this cohort. For example, skeletal muscle, the largest reservoir for glucose disposal, is important for the maintenance of cognitive function,\textsuperscript{9} and muscle mass is lower in T2DM compared to age-matched controls.\textsuperscript{10} A previous study in older diabetes adults has shown that central obesity is linked to risk of cognitive decline in late life,\textsuperscript{11} and central obesity is a key feature of T2DM. In addition, anti-inflammatory mediators such as adiponectin are secreted from adipose tissue,\textsuperscript{12} and are known to be lower than normal in T2DM.\textsuperscript{13} Adiponectin plays a role as a regulator of glucose homeostasis and insulin signaling\textsuperscript{14, 15} Previous findings have shown that insulin resistance increases the risk of Alzheimer’s disease (AD), amyloid plaques, neurofibrillary tangles and brain atrophy.\textsuperscript{15-19} By enhancing insulin sensitivity, adiponectin might reduce brain pathology and AD risk. Furthermore, at the cellular level, Chan et al\textsuperscript{20} reported that high concentrations of adiponectin (10 \(\mu\)g/ml) were protective against amyloid beta-induced neurotoxicity in Sw-APP transfected SH-SY5Y cells exposed to oxidative stress conditions,
further supporting putative cognitive protection related to adiponectin. Thus, many pathways exist for modulation of cognitive function in T2DM.

Exercise is recommended by all consensus panels as central to the treatment of T2DM.\textsuperscript{21-24} The benefits of exercise in T2DM include improved glycaemic control, increased insulin sensitivity, decreased adiposity, decreased inflammation, decreased blood pressure, decreased blood lipids, physical function (gait speed and balance), and treatment of many common comorbidities, including peripheral vascular disease, osteoarthritis, sarcopenia, depression, and cognitive impairment.\textsuperscript{24-27} Thus, it is important to understand and optimise adaptations to exercise in T2DM, as well as to identify the physiological mechanisms linking exercise adaptation with improved cognitive function in this cohort.

Resistance exercise offers a unique and relatively novel approach to the exercise treatment of T2DM and metabolic syndrome. Progressive resistance training (PRT) is an anabolic form of exercise, differing substantially from aerobic exercise in its ability to induce muscle hypertrophy and associated metabolic and functional changes.\textsuperscript{26, 27} Skeletal muscle hypertrophy is thought to mediate the metabolic benefits of PRT, by increasing the quality and quantity of skeletal muscle available for glucose storage. It has been shown in randomised controlled trials (RCTs) to improve insulin sensitivity, glucose homeostasis, blood pressure, dyslipidaemia, adiponectin, markers of inflammation and catabolism, muscle mass, and visceral obesity, which are important factors in T2DM that have been associated with a reduced risk of cognitive decline.\textsuperscript{28-30} Our systematic review of the limited evidence available (Chapter 2 and Chapter 3) has shown that aerobic exercise has positive cognitive benefits in animals and humans with diabetes mellitus, and that improvements in insulin resistance after aerobic exercise were inversely related to improved cognitive function in older adults with T2DM. However, we identified no previous studies
investigating the role of anabolic exercise such as PRT on cognitive function in older adults with T2DM.

In Chapter 5, we have shown cross-sectional relationships between body composition and cognitive function. Specifically, we have shown that sagittal abdominal diameter best predicted cognitive impairment in our older adults with T2DM, while visceral adipose tissue, subcutaneous abdominal fat and waist circumference were also inversely related to various cognitive domains in men. In addition, higher fat-free mass was positively related to better cognition in women. Given that sarcopenia has been related to both T2DM\textsuperscript{31} and cognitive impairment,\textsuperscript{32} and that we reported in Chapter 5 better cognition in those with better functional performance partially dependent on muscle mass and function (stair climb power, chair stand time, and 6MWD), further study of the role of muscle mass and function, as well as central obesity and cognitive decline in T2DM is warranted. Additionally, we showed in Chapter 5 that higher inflammatory marker C-reactive protein (CRP) and lower adiponectin was related to worse cognitive performance. Thus, identification of potential pro- and anti-inflammatory mediators of cognitive adaptation to exercise is needed. For example, adiponectin improves insulin sensitivity\textsuperscript{14,15} and vascular function,\textsuperscript{29} and has anti-atherogenic, anti-inflammatory actions\textsuperscript{30} and cardio-protective effects.\textsuperscript{33} Thus, reduced adiponectin in obesity and diabetes could indirectly influence AD risk through modulation of several interrelated systemic factors.

Although recent reports suggest that PRT can attenuate normal age-related cognitive changes and deficits associated with mild cognitive impairment\textsuperscript{34, 35} and dementia,\textsuperscript{36-38} it has not been established whether PRT improves cognition for cognitively normal or near-normal older adults with T2DM who are at increased risk of cognitive decline. The purpose of this report was to investigate the effects of a 12-month high velocity PRT program (POWER training) on cognitive
function, and the relationship of changes in physical performance, body composition, psychosocial status, physical activity, metabolic profile, and inflammatory milieu to changes in cognitive function in older adults with T2DM.

6.3 METHODS

6.3.1 Study Design

The GREAT2DO study is an ongoing double blind randomised, SHAM-exercise controlled clinical trial on the insulin resistance and glucose homeostasis effects of 12 months of power training versus SHAM exercise, with 5 years of follow-up after the RCT phase. This GREAT2DO sub-study was designed to investigate the effects of power training on cognitive function. Between July 2006 and December 2009, 103 participants were randomised to receive 12 months of high-intensity, high-velocity power training (POWER) or low intensity, non-progressive exercise (SHAM training) in addition to usual care. Study personnel involved in collection of outcome measures were unaware of each participant’s assigned group, and participants were presented with both forms of exercise as potentially beneficial for health outcomes. Written informed consent was obtained from all participants and Study protocol (Ethics Committee Protocol No: X04-0096) was approved by the Sydney South West Area Health Service and the University of Sydney Human Research Ethics Committees. The trial was registered with the Australian Clinical Trials Registry (ACTR) (ACTR No: ACTRN12606000436572). The assessments were conducted at Cumberland Campus of the University of Sydney in Lidcombe New South Wales (NSW) Australia. Computerised Tomography (CT) Scans were performed at the Radiology Department of RPAH in Camperdown NSW Australia. The exercise training was conducted at Freshwater Rehabilitation in Manly NSW Australia or the Centre for STRONG Medicine, Balmain Hospital in Balmain NSW.
Australia by research staff at each site.

6.3.2 **Inclusionary and Exclusionary Criteria**

Inclusionary criteria were for the GREAT2DO study required participants to be community dwelling, 60 years of age or above and sedentary (no progressive resistance training; structured exercise ≤ 1/week; less than 150 min/week low or moderate intensity walking or other aerobic exercise), and to have been diagnosed with both T2DM and metabolic syndrome. Participants could be treated with diet alone, oral medications, insulin or combination at the time of enrolment, without recent changes in medication (<3 months). Exclusionary criteria for the study were the presence of unstable chronic diseases or significant cognitive impairment (defined as diagnosed dementia or inability to understand study protocols and sign informed consent), or any contraindications to PRT, or being un-willing to commit to a 12-month exercise training program, 3 times per week.

6.3.3 **Recruitment**

Participants were recruited from July 2006 until December 2009 from publicity in media, advertisements in local newspapers, General Practitioner (GP) lists, Diabetes Australia newsletters and pamphlets, completing the 12-month RCT phase in 2011.

6.3.4 **Sample Size Estimates**

Sample size estimates were driven by hypothesised differences between the experimental and control participants in the primary outcomes of the trial: insulin sensitivity and glycosylated hemoglobin A1c (HbA1c), based on an average of published studies of progressive resistance training in diabetes/obesity.\(^{39-43}\) Sample size was also sufficient for testing secondary hypotheses.
regarding all components of metabolic syndrome as well, with > 90% power, alpha of 0.05, assuming 10% loss to follow-up (See Table 5.1). Largest available standard deviations (SDs) were used for conservative estimates of effect size (ES). In our experience in fully supervised training of older adults with frailty/chronic disease, dropout averages 10-15% over 12 months. Therefore, we inflated sample size needs for approximately 10% drop out rate to account for anticipated attrition (n =103).

6.3.5 Screening Procedure

Potential participants underwent initial telephone interview and screening using a questionnaire as well as a complete physician history and physical examination. If eligible after physician screening, the remainder of the baseline physical performance testing was completed, followed by baseline cognitive tests and CT scan. If following screening a participant was excluded for an abnormal stress test or other acute illness, he or she entered the study following appropriate treatment and medical review. Participants were randomised at the completion of all baseline assessments.

6.3.6 Randomisation/Allocation/Concealment

Randomisation was at the level of the individual patient, stratified by sex and use or non-use of insulin, in blocks of 4 via a computer-generated randomisation scheme (www.randomization.com). Opaque sealed envelopes were prepared by an independent researcher, containing sequential treatment assignments. Envelopes were opened by each participant after completion of all baseline testing or read to participant via telephone.
6.3.7 Assessments

Participants were randomised using a 1:1 ratio to a high-intensity resistance exercise (POWER) or low-intensity SHAM exercise control group. Cognitive testing occurred between 8 am and 10 am at baseline and at 6 and 12 months. Study personnel involved in collection of outcome measures were blinded to randomisation assignment at 0, 6 and 12 months.

6.3.8 Demographics, Health Status, Medications and Treatment Plan

Participants were asked routine questions to obtain demographic information, as well as their current health status relating to the presence of other chronic diseases. Participants also provided a list of all their current medication and dosages. Each participant’s individual treatment plan was then determined and scored as either diet only, oral hypoglycemic only, insulin only or oral hypoglycemic and insulin.

6.3.9 Intervention

Experiment intervention protocol: power training

The POWER group trained 3 days per week under supervision using pneumatic resistance equipment (Keiser Sports Health Equipment, Ltd, Fresno, CA, USA) at two sites. A version of PRT known as power training was used, in which the concentric contraction (lifting) was performed as quickly as possible, whereas the eccentric contraction (lowering) was performed over 4 seconds. Participants in the POWER group exercised for approximately 45-60 minutes per session.

The exercises targeted large symmetrical muscle groups of the arms, legs, and trunk: seated row, chest press, leg press, knee extension, hip flexion, hip extension, and hip abduction. For each
exercise, participants performed three sets of eight repetitions (two sets of eight on each leg for hip flexion, hip extension, and hip abduction). The intensity was set at 80% of the most recently determined one repetition maximum (1RM), reassessed every 4 weeks. When 1RM testing was not feasible, resistances were increased by targeting a Borg scale rating of perceived exertion between 15 and 18, which approximates 80% of the 1RM.

*Control group intervention: SHAM exercise*

SHAM exercise participants were supervised by the same trainers in the same facility, but at different hours to avoid contamination and unblinding. The exercises were presented as potentially beneficial and participants were blinded to the investigators’ hypotheses regarding efficacy. These participants performed 3 sets of 8 repetitions on the same machines, but with no loading beyond the bar of the machine, using 1-2 second concentric and eccentric contraction speed. No interim 1RM testing and no progression took place. This regimen has been shown to produce minimal changes in muscle function or mass, functional status, mobility, depression, aerobic capacity, or other clinical outcomes.\(^4^3\) Low intensity power training has also been shown to have no effect on visceral fat, adiponectin, glucose homeostasis, insulin sensitivity, blood pressure or bone density, thus providing an ideal SHAM exercise control condition.\(^4^4, 4^5\)

6.3.10 *Usual Care*

Participants in both groups were given no dietary or pharmacological treatment or counseling, but continued to be under the care of their own GPs and consultant physicians for the duration of the study. Any abnormalities uncovered during study assessments were communicated to these physicians, but recommendations for treatment adjustments were not made.
6.3.11 Adverse Events

Monitoring of adverse events were achieved by weekly questionnaire/interview and proxy information was obtained whenever necessary to minimise missing data. Adverse events included any exacerbation of underlying disease, or new onset musculoskeletal, cardiovascular, or metabolic abnormality attributed directly to study protocols. Specific adverse events which were routinely monitored included: falls, cardiac events during physical testing and exercise training (angina, arrhythmias, blood pressure excursions, clinically significant electrocardiogram changes); fatigue, muscle soreness or musculoskeletal injury after resistance or SHAM physical training; anxiety during CT scan; pain, bruising, or infection at the venipuncture and biopsy site. In addition, participants were asked to report all changes in medications, health care professional visits, new diagnoses, acute illnesses, or any new symptoms throughout the 12 months.

6.3.12 Outcome Measures

All outcome measures at baseline were administered by blinded assessors. Each test was chosen because of excellent psychometric properties and minimal sensitivity to practice effects of aging or early neurodegenerative disease. Cognitive testing took place in a fed state (after breakfast), and before any physical testing on that day to standardize known effects of fasting and acute exercise on cognitive performance. If a participant was acutely ill, the assessment was delayed until health stabilised.

Primary Outcomes

Assessment of global cognitive score

Global cognition was evaluated using the Modified Mini-mental State Examination (3MS). The 3MS retains the brevity, ease of administration, and objective scoring of the MMS but
broadens the range of items and scores from 0-30 to 0-100; a higher score indicates better function.

**Assessment of processing speed, attention, and executive function**

The Trail Making Test (TMT)\(^{47}\) is extensively used in neuropsychological assessment of visual attention and task switching. It can provide information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning.\(^1\) It is also sensitive to detecting brain damage and several cognitive impairments such as Alzheimer's disease and dementia.\(^{48}\)

The test consists of two parts (A and B)\(^{46}\) that must be performed as quickly and accurately as possible. Trail Making Test A (TMT-A) assesses attention and information processing speed, and requires the examinee to draw a line connecting the numbers 1 through 25 in order. Trail Making Test B (TMT-B) consists of encircled numbers and letters; participants were instructed to draw a line as quickly and as accurately as possible from 1 to A, A to 2, 2 to B, and so on, until they completed the task. It is considered to assess elements of attention, information processing speed, and executive function. The score on each part represents the amount of time required to complete the task. We recorded the amount of time (s) required to complete each task; a higher score indicates worse function.

Apart from these two direct scores, other studies have proposed additional indexes to better describe the cognitive skills required to complete the Trail Making Test. The Trail Making Test index score, subtracting Trail Making Test A time from Trail Making Test B time, is meant to remove the speed component from the test evaluation\(^{49}\) as an indicator of pure executive function.

**Assessment of memory**
Immediate and delayed memory were assessed using the Consortium to Establish a Registry for Alzheimer’s disease (CERAD) neuropsychological tests.\textsuperscript{50, 51} Word List Memory tests the ability to recall immediately learned lists of words. Ten printed words are presented to the participant who reads them, and afterwards recalls as many as possible. Three trials are given with alternate order of words. Scores is the total number of correctly recalled words after all three trials. Administration time is approximately 5 minutes. Word List recall is a test of delayed recall. After a 5-minute distracting cognitive task, participants are asked to recall as many words as possible from previously presented ten word memory task, within a maximum period of 90 seconds, with a maximum score of 10 points. Finally, the Word List Recognition test was performed as an additional test of delayed memory. This is a test of ability to recognize previously presented words from distractor words presented at same time. The 10 original words were randomly presented visually, mixed with 10 new words. Participants were asked to identify the words they had seen before. Score consists of the number of correct “yes” responses and “no” responses, with a maximum score of 10 points. A higher score indicates better function. Administration time requires approximately 5 minutes.

Insulin sensitivity and glucose homeostasis

We tested HbA1c, C-peptide levels, fasting glucose, and fasting insulin levels in the morning after a 12 hour fast. The Homeostatic Model Assessment 2 computer model\textsuperscript{52} was used to calculate beta cell function (%Beta), insulin sensitivity (IS, %S), and insulin resistance. C-peptide was used for Homeostatic Model Assessment 2 calculations due to the use of long-acting insulin in 16 participants. However, ultimately the sixteen participants were omitted from Homeostatic Model Assessment 2 calculations because of insulin therapy, because it has not yet been validated in this cohort. Blood samples were taken at Cumberland Campus of University of Sydney in Lidcombe NSW Australia, and sent to Douglass Hanly Moir Pathology (DHM) (Macquarie Park, NSW,

**Secondary Outcomes**

The secondary outcomes for this cognitive sub-study included serum results for physical performance, body composition, as well as glucose homeostasis, insulin sensitivity, systemic inflammation, and adiponectin levels. These factors were chosen for inclusion based on relationships in published literature as well as in our cross-sectional analyses (Chapter 5) with cognitive performance.

**Physical Performance**

**Static Balance**

Six-position static balance test, performed according to Rossiter-Fornoff and colleagues\(^5^3\) was used to assess both static and dynamic balance. The series of static balance stands were done in the following order: (1) Wide Stance, (2) Narrow Stance, (3) Semi-tandem Stance, (4) Tandem Stance, (5) One Leg, Eyes Open, (6) One Leg, Eyes Closed. The number of seconds to the nearest 0.01 seconds was recorded for each position, up to a maximum of 15 seconds, and the sum of all 6 stances was used in analyses.

**Gait Velocity**

Gait velocity was performed using an Ultra-timer (DCPB Electronics, Glasgow, Scotland, UK). Participants were asked to walk with any habitual assistive devices at their self-selected normal and maximal speed for 2-3 trials. Gait velocity was defined as the mean of the 2 closest trials.

**Walking Endurance**

Six-minute walk distance is used to assess the walking endurance to the nearest 0.1m. The better
of 2 trials 10 days apart was recorded. The six minute walk test is a proxy for predicting overall cardiovascular endurance capacity (aerobic capacity) and in the elderly participant it may be determined by muscle strength and endurance, balance, orthopaedic or neurologic abnormalities, and other problems.\textsuperscript{54}

\textit{Stair Climber}

Maximal stair climb\textsuperscript{55} was used as a proxy for lower extremity power. Two trials were conducted of the 9-step stair climb with 30-60 seconds rest between each trial. The best of the 2 test results was used.

\[
\text{Power (W)} = \text{Body Weight (N)} \times \text{Height of Stairs (m)} / \text{Ascent Time (s)}
\]

\textit{Chair stand}

The five chair stand (sit to up) test, performed according to Guralnik\textsuperscript{56} and colleagues was used as an index for lower extremity power/balance. Time taken, as well as numbers of stands completed were recorded.

\textbf{Body Composition}

\textit{Anthropometry}

Morning fasting stretch stature (wall-mounted Holtain stadiometer, Holtain Limited, Crymych Pembs., UK) and naked weight [weight in gown (kg)–weight of gown (kg)] were measured in triplicate to the nearest 0.1cm and 0.01kg respectively. Body mass index (BMI) was calculated from fasting naked weight and stretched stature measurements.\textsuperscript{57}

\textit{Waist Circumference}

Waist Circumference was obtained with a Lufkin (W606PM) flexible steel tape measure by a
number of methods for data collection and the ISAK protocol\textsuperscript{57} was used for this analysis. Measures were recorded by an experienced anthropometrist with technical measurement errors $<$1%.

**Bioelectrical Impedance Assessment (BIA)**

All participants were fasting and BIA was performed at a similar time of day for all participants. Skeletal muscle mass was determined using the following equation.\textsuperscript{58}

\[
\text{Skeletal muscle mass} = [0.401 \times \text{height2/BIA} + (3.825 \times \text{sex}) + (0.071 \times \text{age})] + 5.102 \text{ with height in cm, BIA resistance in ohms (average of 3 measures), sex coded 1 for men and 0 for women, and age in years. Total fat mass was determined by using BIA by subtracting lean body mass from total mass to determine total fat mass. Lean body mass was determined using the following equation.}^{59}
\]

\[
\text{Lean Body Mass} = -4.03 + 0.734(\text{Ht2/BIA}) + 0.116(\text{BW}) + 0.096(\text{Xc}) + 0.984(\text{sex}) \text{ with height (Ht) in cm, BIA resistance in ohms (average of 3 measures), body weight (BW) in kg, X}
\]

**Computed tomography (CT)**

Scanning (GE High Speed CTI Scanner, Milwaukee, WI) was carried out at the Royal Prince Alfred Hospital, Sydney) to quantify total abdominal adipose tissue (cm\textsuperscript{2}) (TAAT), visceral adipose tissue (cm\textsuperscript{2}) (VAT), mid-thigh muscle cross sectional area (cm\textsuperscript{2}) (CSA), and mid-thigh muscle attenuation (an index of intramyocellular lipid content).

**CT scans of the abdomen**

A 1-mm thick slice was taken at the mid-point between the iliac crest and lowest rib (determined with the participant supine). This scan location is concordant with the standing waist circumference measurement site used by the International Diabetes Federation (IDF), which is a
criteria used by the IDF to classify metabolic syndrome.\textsuperscript{60} Settings were kV: 100 and mA: 170 with a displayed field of view (DFOV) 45 – 48, depending on participant size.

\textit{CT scans of the mid-thigh}

A 1-mm slice was performed at the mid-point between the inguinal crease and the proximal pole of the patella (measured with the participant supine and hip and knee flexed). The non-dominant leg was then scanned with the leg fully extended and relaxed. Settings were kV: 100 and mA: 170 with a field of view (DFOV) optimised to the size of each leg.

\textit{Image analysis}

Scan images were analysed according to optical density by a blinded investigator using NIH Image software (Version 1.63, National Institutes of Health) programmed with specific macros to quantify regional cross-sectional adipose tissue, and muscle area and muscle density. To determine VAT, macros were programmed to select the outer perimeter extending from the paraspinal muscles to the anterior abdominal muscles. The program calculated this measure by summing the area within the selected perimeter occupied by pixels with optical density in the range of 140 to 240. Mid-thigh muscle density (unitless measure) was calculated according to a specific optical density range (10-113) chosen to best discriminate muscle from fat and bone. Bland-Altman coefficient of repeatability, determined using a high level of reliability for intra-tester and inter-tester analyses using these protocols with no evidence of systematic bias (Chapter 4).

\textbf{Assessment of inflammatory markers and adipokines}

High-sensitivity CRP was measured in duplicate by enzyme-linked immunosorbent assay (ELISA) (eBIOSCIENCE, Camarillo, CA), with the average value used in statistical analyses. The lowest
detectable concentration was 0.01mg/L, and the intraassay co-efficient of variation was 6.4%. CRP analysis was available in 89 participants.

Adiponectin

During blood sampling, extra blood was sampled and the serum stored for future analysis of serum adiponectin. Serum adiponectin was measured in duplicate by enzyme-linked immunosorbent assay (ELISA) (eBIOSCIENCE, Camarillo, CA), with the average value used in statistical analyses. The lowest detectable concentration was 0.01mg/L. Co-efficient of variation was required to be less than 15%, otherwise a third measurement was performed. The average intra-assay co-efficient of variation was 7.2%.

Questionnaires

All questionnaires were interviewer-administered by a trained interviewer, in a private room using visual prompts. All questionnaires were widely used, previously validated questionnaires in cohorts similar to this one. Habitual physical activity levels were assessed using the Physical Activity Scale for the Elderly (PASE) questionnaire, where higher scores reflect increasing amounts of habitual structured and unstructured physical activity. Depressive symptoms were assessed by the Geriatric Depression Scale. Health-related quality of life was assessed using Version 2 of the Medical Outcome Survey 36-item Short-Form (SF-36) questionnaire.

6.3.13 Covariates

Covariates specified a priori for inclusion in models of cognitive outcomes were age, sex, educational history, as these have been linked to cognitive performance in published literature. Additional covariates were identified from baseline comparisons between treatment groups, with
factors that were different between groups by a statistical or clinically relevant amount, and potentially related to the dependent cognitive outcome of interest selected for inclusion in cognitive outcome models as potential confounders.

6.3.14 Statistical Analyses

Normally distributed data are presented as mean ± SD; non-normally distributed data as median (range) or frequencies. Non-normally distributed data were transformed for use with parametric statistics. Comparisons of baseline characteristics between groups were made using Chi Square tests for categorical data and unpaired t-tests for normally distributed continuous data. For primary outcomes, the effect of intervention (POWER vs. SHAM) over time on the cognitive functions was investigated in intention-to-treat (ITT) analyses.

Repeated measures mixed models of 6- and 12-month outcomes adjusted for baseline cognitive values, age, sex and educational level, and any potential confounders identified were constructed to test our primary hypotheses. We tested for main effects of time and a group × time interaction. The post hoc analyses were made between times and groups using the Bonferroni method. Relationships of interest and risk factors for changes in cognitive function and other secondary outcomes were analysed with simple and multiple linear regression models as appropriate.

All available data from participants who were randomised and received at least one dose of the intervention, regardless of compliance, were used for analysis, resulting in an n of 100 for the assessment of cognitive changes over time. The 3 participants who withdrew prior to the first intervention session were not included in mixed models, as is the protocol for pharmacological studies. Participants with missing cognitive data were included as long as one cognitive
assessment was available, as the mixed models allow for inclusion of these participants without imputation. For regression models, only participants who had data from both of the variables in the regression were included, resulting in variable numbers for these analyses, as indicated in Tables and Figures.

Relative effect sizes (ES) were calculated as:

Effect Size = Δ Treatment – Δ Control/Pooled (Treatment + Control) Baseline SD. Calculations of ES were adjusted via Hedges’ bias-corrected effect size for small sample sizes using Coe’s online calculator.\(^{65}\) Effect sizes were interpreted according to Cohen’s interpretation of ‘trivial’ (<0.20), ‘small’ (≥0.20 <0.50), ‘moderate’ (≥0.50 <0.80), and ‘large’ (≥0.80) effect size.\(^{66}\) Ninety-five percent confidence intervals (CIs) for the relative ES were calculated. For non-normally distributed data, median was substituted for mean, and range/4 was substituted for SD.\(^{67}\) The statistical analyses were conducted using SPSS software (Version 21; SPSS Inc., Chicago, IL, USA). All statistical significance tests were two-sided, and an alpha-level of 0.05 was considered statistically significant.

### 6.4 RESULTS

Figure 6.1 with Consolidated Standards of Reporting Trials (CONSORT) flowchart shows the flow of participants from the time of screening to study completion at 12 months. A total of 427 people were assessed for eligibility, and 103 (24.1%) of those were eligible for randomisation. Reasons for exclusion were not meeting study criteria (5.6%), medical reasons (2.1%), too young (1.2%), too physically active (16.4%), too far to travel (8.2%), inability to commit to the study protocol (33.3%), no longer interested in participating (3.5%), work commitments (2.6%) and other (3.0%). As shown in Figure 6.1, among 103 study participants, 100 began the intervention, 86 completed
their 12-month follow-up, and 14 dropped out (defined as not completing their 12-month assessment).

6.4.1 Adverse Events

There were eight adverse events in five participants adjudicated to be related to study procedures, seven in the POWER training group and one in SHAM exercise group. These included three syncopal episodes in a man with known syncope, one hamstring strain, one back pain leading to dropout, one exacerbation of pre-existing umbilical hernia requiring surgical repair, one subscapularis tear in a woman with pre-existing grade IV osteoarthritis/rotator cuff disease requiring surgery and partial thickness tear of a rotator cuff muscle managed conservatively. Three of the four participants in the POWER group who experienced adverse events did not change their training mode and the POWER group had higher attendance than the SHAM group overall. No significant difference between the POWER training and the SHAM group in terms of number of adverse events was observed (p=0.25). In addition, data analysis in these participants with adverse events did not show an significant differences with any cognitive outcomes compared to participants without adverse events (Word List Memory: 3.0±3.6 vs 2.9±3.5, p=0.96, Word List Recall: 1.2±1.7 vs 0.98±1.5, p=0.25, Word List Recognition 1.0±0.02 vs 1.0±0.03, p=0.56, Trail Making Test A: 1.3±0.21 vs 1.4±0.17, p=0.53, Trail Making Test B: -24.8±25.5 vs 0.7±30.8, p=0.26, DIFFBA: -22.8±25.3 vs -2±29.8, p=0.18, 3MS: 1.67±2.08 vs 2.35±4.21, p=0.78). Moreover, there were no significant differences in any cognitive domains within the POWER group with or without adverse events (Word List Memory: 2.0±3.6 vs 3.0±3.8, p=0.23, Word List Recall: 2.0±1.7 vs 1.3±1.5, p=0.46, Word List Recognition: 1.0±0.02 vs 1.0±0.03, p=0.14, Trail Making Test A: 1.24±1.78 vs 1.36±1.78, p=0.28, Trail Making Test B: 15.9±22.4 vs 6.0±30.3, p=0.23, DIFFBA: -17.7±28.4 vs 10.4±30.0, p=0.13, 3MS: 1.67±2.08 vs 0.78±3.09, p=0.63).
There is no evidence that the small number of adverse events observed were related the outcomes of the study.

6.4.2 Baseline Characteristics and Adherence

Participant characteristics are reported in Table 6.1. Baseline relationships among metabolic profile, body composition, exercise and functional performance, inflammation and cognition have been previously reported in Chapter 5. There were no statistically significant or clinically meaningful differences between the two groups at baseline for homeostatic model assessment - insulin resistance (p=0.14) or any body composition parameters (p=0.30-0.99). The SHAM group had a higher income (p=0.01), and tended to have older age (p=0.09), higher HbA1c (p<0.05), higher F-36 Mental Component Summary (p=0.06), and longer duration of T2DM (p=0.07). Conversely, the POWER group had a significantly higher Modified 3MS score (p=0.02), and tended to have higher GDS (p=0.10) and higher chest press (muscle strength) (p=0.06). Overall, annual median and range of training adherence for the POWER group (including dropouts) was 77.8% (11.2-97.2%), while the median adherence for the SHAM group was 83.2% (14.6-98.6%), tending to be higher in the SHAM group (p = 0.09). Adherence was not related to any domains of cognition at baseline (p=0.19-0.99).

6.4.3 Change in Cognitive Function

Results of the repeated-measures mixed-effect models across the seven neuropsychological assessments are shown in Table 6.2, with significance levels indicated for time effect or time-by-group interactions. Contrary to our hypotheses, 3MS increased significantly in the SHAM group compared to the POWER group (p=0.04). In the post hoc analysis, the POWER group showed no significant increase in the 3MS score at 12 months compared to at baseline and 6 months
(p>0.05) and the SHAM group showed significant increase at 6 months and 12 months compared to at baseline (p<0.05) (Figure 6.2). At 6 months and 12 months, the between-group difference in 3MS scores was not significant. Between-group effect size showed a trivial effect between POWER and SHAM group [Effect size -0.06 (-0.45, 0.33)]. Trail Making Test B score improved in the SHAM compared to the POWER groups (p=0.03) adjusted for age, sex, education, SF-36 MCS, and HbA1c. SHAM group decreased Trail Making Test B score at 6 months and 12 months compared to at baseline with post-hoc analysis revealing a significant difference (Figure 3), but no difference in the POWER group between baseline, 6 months, and 12 months. There was a significant difference between the groups at 12 months (p<0.05). Effect size was small between POWER and SHAM groups [Effect size 0.44 (0.05, 0.84)].

Contrary to our hypotheses, there were no differences between the POWER and SHAM group for changes in Word List Memory, Word List Recall, Word List Recognition, Trail Making Test A, or DIFFBA (p=0.19-0.73) (Table 6.2). In the post hoc analysis, the POWER group showed significant increase in the Word List Memory score at 12 months compared to at baseline and 6 months (p<0.05) and the SHAM group showed significant increase at 6 months and 12 months compared to at baseline (p<0.05). There were no significant differences between the groups at each timepoints (Table 6.2). The POWER group improved Word List Recall at 6 months and 12 months compared to at baseline (p<0.05) and SHAM group improved at 6 months compared at baseline. There were no significant differences between the groups at each time points. Again, SHAM group showed a significant decreased Trail Making Test A score at 6 months and 12 months compared to at baseline, but no significant difference between at baseline, 6 months, and 12 months.
6.4.4 Changes in Metabolic Profile

Metabolic profile changes are shown in Table 6.3. Contrary to our hypotheses, there were no significant differences in fasting serum glucose, HbA1c, fasting insulin, HOMA2 beta cell function, or HOMA2-IR in the POWER group compared to the SHAM group (p=0.13-0.99). In the post hoc analysis, both groups showed similar, significant reductions in HbA1c level at 6 months and 12 months compared to at baseline (p<0.05). There were no significant differences between the groups at each time points.

6.4.5 Changes in Physical Performance

Results are presented in Table 6.4. Using a mixed model, as expected, total muscle strength significantly increased in the POWER group compared to the SHAM group (p=0.000). Over time, total muscle strength significantly increased at 6 months and 12 months in POWER group compared to at baseline. There had a significant difference in total muscle strength in POWER group compared to SHAM group at 6- and 12- months. Contrary to our hypotheses, there were no differences in any physical performance variables between groups (p=0.11-0.86). Over time, however, there were similar, significant improvements in total strength, habitual gait speed, maximal gait speed, chair stand time and stair climb power in both groups. In the post hoc analysis, the POWER group showed significant increase in the habitudinal gait speed at 6 months and 12 months compared to at baseline (p<0.05) and the SHAM group showed significant increase at 12 months compared to at a baseline (p<0.05). There were no significant differences between the groups at each time points. SHAM group improved maximal gait speed at 6 months and 12 months compared to at baseline (p<0.05). Stair climb power significantly increased in POWER group at 12 months compared to at baseline. At each time points, no between-group difference in stair climb power approached statistical significance. SHAM group also significantly
increased in chair stand at 6 months and 12 months compared to at baseline (p<0.05) (Table 6.4). In the post hoc analysis, chair stand time significantly declined in both treatment groups at 6 months compared to at baseline, but there was no difference between POWER and SHAM at each time points. The POWER group increased 6 minute walk distance at 12 months compared to at baseline, and SHAM group increased 6 minute walk distance at 6 months compared to at baseline (p<0.05). There were no consistent group differences by POWER and SHAM for either 6 minute walk distance at each time points.

6.4.6 Changes in Body Composition

Results are shown in Table 6.5. As expected, thigh muscle area significantly increased in the POWER group compared to the SHAM group (p=0.03), which was the only significant group difference in body composition, and was one of our primary hypotheses in this regard. However, there was a trend for a reduction in total abdominal adipose tissue in the POWER group compared to the SHAM group (p=0.10), and a similar pattern for reductions in visceral adipose tissue (p=0.16) was also present, again suggesting that POWER training may be beneficial as we hypothesised, although the study may have been underpowered to show a statistically significant difference.

No differences were seen between the POWER and SHAM group for changes in body mass index, body weight, skeletal muscle mass, total fat mass, percent muscle mass, subcutaneous thigh adipose tissue, sagittal abdominal diameter, subcutaneous thigh fat area, intermuscular fat area, or thigh muscular density (p=0.10-0.92). In post hoc analysis, POWER group showed significant increase in the mid-thigh muscle at 6 months and 12 months compared to at baseline (p<0.05). There were no significant difference between the groups at each timepoints (Table 6.5).
Moreover, POWER group showed significant decline in visceral adipose tissue and abdominal subcutaneous adipose tissue at 6 months compared to at baseline (p<0.05). Similarly, POWER group also improved total abdominal adipose tissue at 6 months and 12 months compared to at baseline (p<0.05). There was no difference between treatments at each time points. In post hoc analysis, Total fat mass declined significant in the POWER group, but there was no difference between treatments at each time points (Table 6.5). POWER and SHAM groups significantly decreased body mass index at 6 months compared to at baseline (p<0.05). There were no significant differences between the groups at each time points. In post hoc analysis, Waist circumstance significantly declined in both treatment groups at 12 months compared to at baseline (p<0.05), the between-group difference in waist circumstance did not approach statistical significance at each time point (Table 6.5).

6.4.7 Changes in Quality of Life, Psychosocial Function and Physical Activity Level

Results are shown in Table 6.6. Using a mixed model, no significant group differences were found for changes in SF-36 MCS (p=0.41), PASE (p=0.30) or GDS (p=0.88), while a trend for increases in SF-36 PCS was present, unexpectedly favoring the SHAM group (p=0.06). In post hoc analysis, depressive scores declined in the POWER group at 6 months compared to at baseline (p<0.01). Depressive scores decreased in SHAM group at 6 months and 12 months compared to at baseline. By contrast, there were no significant differences between the groups at each time points (p>0.05).

6.4.8 Changes in Adiponectin and Systematic Marker of Inflammation

Results are shown in Table 6.7. There were no significant differences in the change in HMW adiponectin, total adiponectin, ratio of HMW-to-total adiponectin, or CRP in the POWER group
compared to the SHAM group (p=0.40, p=0.54, p=0.91, p=0.82, p=0.14, respectively), and all ESs were negligible to small. Neither were there time effects for HMW adiponectin (p=0.66), total adiponectin (p=0.54), nor adiponectin ratio (p=0.51), while SHAM group improved CRP at 6 months compared to at baseline CRP (p<0.05). There were no consistent group differences by POWER and SHAM at each time points.

### 6.4.9 Relationships between Changes in Body Composition Variables

Results are shown in Table 6.8. Changes in total abdominal adipose tissue and changes in thigh muscle area were not related in the POWER group (n=37, r=0.26, p=0.13), but were significantly related in the SHAM group (n=43, r=0.35, p=0.02), with both muscle and fat depositions changing in direct proportion to each other. Such a direct relationship might be expected due to generalised weight gain from increased dietary intake, for example, whereas an inverse relationship would be hypothesised if the changes were related to exercise exposure. Changes in thigh muscle area were not related to changes in subcutaneous abdominal adipose tissue in the POWER group (n=37, r=0.25, p=0.11) nor in the SHAM group (n=43, r=0.25, p=0.11). Finally, total abdominal adipose tissue was positively related to changes in subcutaneous abdominal adipose tissue in the POWER group (n=37, r=0.67, p<0.0001) and in the SHAM group (n=44, r=0.74, p<0.0001).

### 6.4.10 Changes in Metabolic Profile and Changes in Cognition

Results are presented in Table 6.9. Findings were mixed. Using multiple regression models, higher HOMA2-IR tended to be related to worse information processing speed in the POWER (n=32, β=0.34, p=0.07), and in the SHAM group (n=36, β=-0.28, p=0.11). Also, higher HOMA2-IR was associated with worse global cognitive function in the SHAM group (n=37, β=-0.40, p<0.01), but not in the POWER group (n=32, β=-0.10, p=0.55) adjusted for age, sex, years
of education, duration of diabetes, SF-36 MCS, cognitive score, and HbA1c.

6.4.11 Changes in Physical Performance and Changes in Cognition

Results are presented in Table 6.10. Using multiple regression models, as expected, there was a direct relationship between increases in total static balance and better global cognitive function within the POWER group ($\beta=0.27$, $p=0.03$) (Figure 6.10.1) but this was not present in the SHAM group ($\beta=0.02$, $p=0.89$) (Figure 6.10.2), after controlling for age, gender, education, SF-36 MCS score, duration of diabetes, and HBA1c. Similarly, changes in habitual gait speed also tended to be directly related to changes in Word List Recall in the POWER group ($\beta=0.35$, $p=0.06$), but again, no relationship was present in the SHAM group ($n=48$, $\beta=-0.09$, $p=0.54$). Higher stair climb power also tended to be related to better pure executive function ($n=33$, $\beta=0.16$, $p=0.09$) in the POWER group ($n=37$, $\beta=0.12$, $p=0.50$), but not in the SHAM. By contrast, increased total static balance tended to related to better information processing speed in the SHAM group only ($n=45$, $\beta=-0.32$, $p=0.06$), and not in the POWER group ($n=35$, $\beta=-0.24$, $p=0.16$). Chair stand time was also unexpectedly related to better delayed memory in the SHAM group ($n=38$, $\beta=0.39$, $p=0.02$) (Figure 6.11.2), but again, no relationship was present in the POWER group ($n=30$, $\beta=0.16$, $p=0.53$) (Figure 6.11.2). Finally, higher total muscle strength was related to better information processing speed in the POWER group ($n=35$, $\beta=-0.41$, $p=0.03$) (Figure 6.28.1), no relationships was found in SHAM group ($n=44$, $\beta=-0.06$, $p=0.73$) (Figure 6.28.2).

Unexpectedly, higher maximal gait speed tended to be associated with worse Word List Recognition in the POWER group ($\beta=-0.36$, $p=0.08$). No 6MWD changes were related to changes in any cognitive domains in either the POWER or SHAM group. Moreover, our data did not find any associations physical performance with and executive function in both POWER
and SHAM exercise groups (p>0.05).

6.4.12 Changes in Body Composition and Changes in Cognition

Results from multiple linear regression models testing explanatory body composition variables on cognitive function changes, adjusted for age, sex, educational level, duration of diabetes, HbA1c, and cognitive function, are presented in Tables 6.1. Most muscle compartment changes exhibited hypothesised relationships with better cognitive outcomes in the POWER group. Higher skeletal muscle mass was positively related to better Word List Memory in the POWER group (β=0.36, p=0.03; Figure 6.12.1). Furthermore, in the POWER group, better information processing speed was directly related to higher thigh muscle area (β=-0.34, p<0.05; Figure 6.13.1), also as hypothesised. Similarly, increased free fat mass tended to be related to better Word List Memory and Word List Recall (n=36, β=0.32, p=0.08; n=36, β=0.38, p=0.06, respectively) in the POWER group. The only significant relationship in the SHAM group was that skeletal muscle mass was directly related to better global cognitive function (n=44, β=0.20, p<0.05; Figure 6.14.2).

Relationships between changes in adiposity and changes in cognition were contrary to our hypotheses. Unexpectedly, decreased total abdominal adipose tissue area was significantly related to worse attention/executive function in the POWER group (TMT- B: n=36, β=-0.40, p=0.04; Figure 6.15.1) but not in the SHAM group (TMT- B: n=36, β=-0.40, p=0.04; Figure 6.15.2). Similarly, total abdominal adipose tissue area tended to be inversely related to changes in pure executive function in the POWER group (n=36, β=-0.34, p=0.09), but again, no relationship was present in the SHAM group (n=41, β=-0.05, p=0.78). Similarly, worse Word List Recall was related to decreased subcutaneous abdominal adipose tissue, weight, and body mass index in the POWER group (n=37, β=0.39, p=0.03; n=36, β=0.48, p=0.03; n=36, β=0.44,
p=0.01, respectively; Figure 6.16.1-6.18.1), but again, no such relationships were present in the SHAM group (n=44, β=-0.04, p=0.76; n=46, β=-0.20, p=0.13; n=46, β=-0.19, p=0.16, respectively; Figure 6.16.2-6.18.2). Finally, lower total abdominal adipose tissue, visceral adipose tissue, body weight, and body mass index were directly related to worse Word List Memory (n=42, β=0.35, p=0.01; n=44, β=0.31, p=0.01; n=45, β=0.34, p=0.01; n=46, β=0.38, p=0.03; n=47, β=0.41, p=0.03, respectively; Figure 6.19.2-6.22.2) in the SHAM group, but no relationships were present in the POWER group (n=37, β=-0.12, p=0.51; n=37, β=0.14, p=0.44; n=37, β=-0.22, p=0.26; n=36, β=-0.11, p=0.56; n=36, β=0.07, p=0.72, respectively; Figure 6.19.1-6.22.1). No other body composition relationships with any tests of cognition were observed.

Given the observed correlations between individual body composition parameters (see sections above); we identified the body composition outcomes (BMI, total abdominal adipose tissue, visceral adipose tissue, abdominal subcutaneous adipose tissue, sagittal abdominal diameter, thigh muscle area, and skeletal muscle mass that were related to cognitive outcomes of memory and information processing speed in multiple regression models. To do this, separate multiple regression models were constructed with cognitive function (memory and information processing speed) as the dependent variable, and with skeletal muscle mass, thigh muscle area and either total abdominal adipose tissue, sagittal abdominal diameter, visceral adipose tissue, BMI or abdominal subcutaneous adipose tissue as the second independent variable, to investigate whether portion of the variance in cognitive function attributed to skeletal muscle mass was independent of BMI, total abdominal adipose tissue, abdominal subcutaneous adipose tissue, sagittal abdominal diameter, and visceral adipose tissue.

When individual body compartment parameters were added into these multiple regression models, change in skeletal muscle mass explained a significant portion of the variance in the change in
memory, independently of changes in total abdominal adipose tissue (p=0.66), visceral adipose tissue (p=0.35), subcutaneous abdominal adipose tissue (p=0.73), sagittal abdominal diameter (p=0.59), and body mass index (p=0.80), none of which retained their original relationship to memory observed in univariate regression models. Thus, the unexpected direct relationships between adipose tissue gain and cognitive improvements appeared to have been a spurious finding due to the fact that changes in muscle and fat depots were directly associated, and it was only the increase in muscle mass that explained the improvement in cognition.

6.4.13 Relationships between Changes in Psychosocial, Quality of Life, and Physical Activity Change in Cognition

Results are presented in Table 6.12 Contrary to our hypotheses, no clear relationships of the cognitive scores to either SF-36 MCS and PCS or GDS were observed (p=0.17-0.97).

6.4.14 Relationships between Changes in Adiponectin and Inflammation and Changes in Cognition

Results are presented in Table 6.13. As hypothesised, higher serum total adiponectin concentrations were directly related to better global cognitive function, in the POWER group (β=0.57, p=0.03; Figure 6.23.1), adjusted for age, sex, years of education, duration of diabetes, SF-36 MCS, and HbA1c. Also in the POWER group, increased total adiponectin expression tended to be associated with better Word List Recall (β=0.66, p=0.09). Results for the SHAM group were mixed however. Increased HMW adiponectin was related to better attention/executive function (TMT-B) and pure executive function (n=16, β=-0.65, p=0.03; n=16, β=-0.68, p=0.04, respectively; Figure 6.24.2-6.25.2) in the SHAM group. Unexpectedly; however, increased adiponectin ratio was associated with worse Word List Memory in the SHAM
group (n=16, $\beta=-0.33$, p=0.01; Figure 6.26.2).

Systemic inflammation was also inconsistently related to cognitive changes. Increased CRP was related to worsened Word List Recognition in the SHAM group only (n=36, $\beta=0.35$, p=0.02; Figure 6.27.2), but this relationship was not present in the POWER group (n=29, $\beta=-0.17$, p=0.51; Figure 6.27.1).

6.5 DISCUSSION

To our knowledge, this sub-study of GREAT2DO is the first RCT in older people with T2DM to test the effect of high intensity, high velocity POWER training compared with low intensity SHAM exercise on cognitive function. Overall, there was no evidence in this cohort that POWER training provided additional benefit to cognitive function over that of SHAM exercise, as both groups improved over 12 months in most cognitive outcomes. Unexpectedly, in fact, SHAM exercise resulted in significantly greater benefits than POWER training for executive function and global cognition. We have also shown that clinically relevant improvements in cognition in older adults with T2DM were predicted by improvements in muscle mass, primarily if achieved via high intensity POWER training. Additionally, increases in adiponectin levels achieved via POWER training were related to better cognition, but mixed results were seen for SHAM exercise. Reduced inflammation did not improve cognitive outcomes, and in fact was related to worse memory in the SHAM group. The relationship of insulin resistance changes to cognitive improvements was inconsistent.

6.5.1 ROLE OF POWER TRAINING ON COGNITION

A large body of evidence indicates that aerobic training and resistance training enhance healthy
brain aging, including cognition, among healthy older adults.\textsuperscript{68, 69} Previous studies observed that 12 months of twice-weekly resistance training were strongly associated with better cognitive function in cognitively healthy women aged 65–75 years old.\textsuperscript{70} In contrast to these earlier studies, we show no significant improvements in any cognitive domains associated with POWER at 12 months which were greater than those seen after SHAM exercise. However, all of the previous studies included only young and healthy people,\textsuperscript{68, 71, 72} and there were no studies looking at the cognitive changes after exercise of any type in older adults with or without T2DM.

Several factors might have attenuated intervention differences in cognitive scores in our study groups. Trends for higher baseline quality of life (mental health score), and higher study exercise adherence may have contributed to controls performing better than expected. Most importantly, baseline cognition was higher for Word List Memory, Word List Recognition, Trail Making Test, and 3MS values in the POWER group compared with SHAM, and that may have limited the ability to increase cognitive scores in this group and minimised the difference between groups.

However, we agree that even stability would have been better than what might have been predicted from an older cohort with T2DDM and multiple other risk factors for cognitive decline. Age has been related to cognitive function on Word List Memory (\(r=-0.33\), \(p<0.001\)), Word List Recall (\(r=-0.32\), \(p<0.001\)), Trail Making Test A (\(r=0.29\), \(p<0.003\)), Trail Making Test B (\(r=0.22\), \(p=0.028\)), and the Modified Mini-mental State Exam (\(r=-0.24\), \(p=0.02\)), as reported on page 323 of Chapter 5. A statistically significant association was observed between age and the score on all seven cognitive tests. Compared to other previous studies in cognitively intact healthy older individuals, the reported cognitive deterioration per year varies from -0.56 to -0.9 for 3MS score,\textsuperscript{144} 0.55 to 1.56 for Trail Making Test A score (seconds),\textsuperscript{145} 1.1 to 3.2 for Trail Making Test B score (seconds),\textsuperscript{145} -1.3 to -2.5 for Trail Making: B-A Difference score (seconds),\textsuperscript{145} -1.6 to -1.9 score
for CERAD Word List Memory score,\textsuperscript{50} -0.15 to -0.7 scores for CERAD Word List Recall score,\textsuperscript{50,70} -0.3 to 1 score for Word List Recognition score.\textsuperscript{50}

Therefore, in a 12-month study of persons with clinically diagnosed T2DM, we might have expected this degree of decline in performance. Instead, after 12 months of either low intensity SHAM exercise or high intensity POWER training, the performance on these tests improved by 0.90 to 0.3.4 in 3MS score, -4.30 to -5.55 in Trail Making Test A score (seconds), -0.03 to -0.05 in Trail Making Test B score (seconds), 0.04 to -0.04 in Trail Making: B-A Difference score (seconds), 0.87-1.45 in Word List Memory score, 0.31 to 0.78 in Word List Recall score, 0.01 to 0.04 in Word List Recognition score. It has been shown that in randomised controlled trials that improvements in cognitive function may delay onset of cognitive impairment and dementia.\textsuperscript{146} Therefore, improvements in cognitive scores in 3MS, Trail Making Test A score (seconds), Trail Making Test B score (seconds), Trail Making: B-A Difference score (seconds), Word List Memory score, Word List Recall score, Word List Recognition score in our study corresponds to a reduction of cognitive ageing of approximately 1 to 3 years.

6.5.2 ASSOCIATIONS OF METABOLIC PROFILE AND COGNITIVE FUNCTION

It was expected in the context of previous metabolic research, that metabolic profile changes would be prominently related to cognitive outcomes. Regression analyses (Figure 6.9), notably, show that higher insulin resistance tended to be related to worse information processing speed within the POWER group only (β=0.34, p=0.07). Similar findings were reported by Yanagawa et al\textsuperscript{73} who found that improvements in HOMA-insulin resistance were related to better cognitive function in those who participated in aerobic training (p<0.0.5), with no relationship observed in those randomised to a non-exercise control group. Interestingly, both groups in that trial showed
similar significant improvements in global cognitive function ($\beta=-0.32$). This is in agreement with our data, which suggest that maintaining, or improving insulin resistance through the use of high or low intensity power training may be related to improved cognitive health of older adults with T2DM. These findings suggest that improvements in cognitive function are dependent on the improvements in hepatic insulin resistance. As HOMA2-IR is a measure of hepatic insulin resistance, reductions in HOMA2-IR seem to play a modulator role in synaptic transmission, and animal models have found insulin to be linked to feeding behavior as well as learning and memory.\textsuperscript{74} In an experimental animal model, rats, after training in a water maze, had increased insulin mRNA levels in the hippocampus, as well as increased accumulation of insulin receptor proteins.\textsuperscript{75, 76} There is evidence that insulin plays a role in cerebral glucose utilisation.\textsuperscript{77, 78} Insulin may also function as a neuromodulator directing the secretion and reuptake of neurotransmitters and affecting learning and memory.\textsuperscript{79,80} It is thought that impairments in the insulin signaling pathway play a role in AD and aging overall. The HOMA index is clinically relevant as it has been shown to reflect whole body insulin sensitivity as measured in clamp studies\textsuperscript{81, 82} and insulin resistance is predictive of cognitive impairments.\textsuperscript{83} Therefore, further investigations into the mechanism by which increases in insulin resistance lead to reductions in any tests of cognitive function are needed. Insulin resistance has been shown to directly cause a decrease in insulin degrading enzyme (IDE) in AD,\textsuperscript{84} potentially contributing to the development degradation of amyloid beta, a major part of the AD process, which generates neurofibrillary plaques in an animal model, while improvement in insulin resistance through exercise has been shown to ameliorate insulin degrading enzyme associated with a greater extent of cerebral amyloid beta.\textsuperscript{83-85} However, we found no associations between HOMA2-%beta function and fasting insulin in our participants. Although our data were widely distributed for most variables, both groups were generally near normal for both cognitive function and metabolic values of fasting insulin and %Beta function (floor effects), which may have weakened any potential associations.
Unexpectedly, insulin sensitivity did not change over time or between groups. However, glucose homeostasis did improve significantly and similarly in both groups over time. Insulin resistance index and glycosylated haemoglobin at baseline were relatively well controlled compared to previous studies, which may have attenuated any possible benefits of the intervention on metabolic profile (floor effect). These relationships may be clarified by including a broader range of participant characteristics including leaner, obese, inflammation, and adipokines.

There were some other physiological changes in this study which may be beneficial for cognition and deserve further exploration. Specifically, POWER training increased skeletal muscle mass and adiponectin levels over 12 months. We have previously reported that skeletal muscle mass plays a significant role in insulin resistance, glucose homeostasis and systemic inflammation. Improvement in insulin sensitivity ($r=-0.38$, $p=0.04$) and glucose hemostasis may be in part mediated by increasing skeletal muscle mass achieved via high intensity power training, as described in this GREAT2DO substudy. In addition, we are the first to show (in this thesis, see p 478) a relationship between increases in total adiponectin level and reductions in glucose control ($r=-0.35$, $p<0.05$) after exercise exposure.

Thus, POWER training may improve insulin sensitivity, adiponectin, and glucose level in older adults with T2DM. However, these benefits are not uniform in the intervention group, but appear to be associated with robust adaptations of skeletal muscle mass. Importantly, we have shown for the first time that improved executive function was related to increased skeletal muscle mass. As not all individuals exposed to POWER increased skeletal muscle mass to the extent required to see associated improvements in metabolic profile and cognitive function, there was no group difference in cognitive outcomes. Future studies with a non-exercise control group would likely magnify the group differences in muscle mass over time, and potentially result in greater 476
improvements in other physiological factors (e.g., adiponectin, insulin resistance, glucose homestasis) which could contribute to better cognition as well.

In contrast to earlier studies, our data demonstrated that neither fasting glucose nor HbA1c were related to cognitive changes over 12 months in our cohort, despite the fact had considerably lower baseline HbA1c values (7.11%; 54mmol/mol) compared to previous investigations (7.8%; 62 mmol/mol\textsuperscript{45} and 8.5%; 69 mmol/mol\textsuperscript{40, 86}), which may have precluded our ability to assess relationships between improvements in glucose control and cognitive benefits.

6.5.3 Role of Physical Performance and Cognition

It has been reported that poorer physical fitness and low physical activity are related to cognitive impairment in people at risk for diabetes.\textsuperscript{87} We showed many changes in physical performance in both groups, but relationships with cognition were predominantly seen within the POWER group. Regression analyses in our study (Figure 6.10.1) showed that increases in total static balance time were related to improvements in global cognitive function within the POWER group only ($\beta=0.27$, $p=0.03$), while this relationship was not significant in the SHAM group (Figure 6.10.2). Moreover, Higher total physical strength and power was associated the better information processing speed and delayed memory ($\beta=0.41$, $p=0.03$) (Figure 6.28.1), but not for the SHAM group ($\beta=-0.06$, $p=0.73$). To our knowledge, this is the first evidence to show that improving cognitive function in older people who have already developed type T2DM is associated with improved physical performance. The physical performance tasks which were related to better cognition are composite measures of mobility, lower extremity, strength and power, balance, and aerobic capacity, underlining the potentially clinically important impact of cognitive function on ability to function independently in this cohort.
It is not precisely known how these domains of physical performance and cognition are linked. T2DM and its common complication, peripheral neuropathy, may lead to sensory and motor deficits, which can result in mobility-related dysfunction, alterations in gait characteristics and balance impairments.\(^8\) Patients with diabetes and peripheral neuropathy have lower gait velocity, decreased cadence, shorter stride length, increased stance time and higher step to step variability compared to healthy controls.\(^8\) Additionally, cardiorespiratory fitness was an independent predictor of balance and cognitive performance in that study. Similar findings were reported by Yoo et al\(^8\) who found that an intervention combining cognitive training with physical exercise improved balance, which was related to memory. After the 12-week intervention, the group showed significant improvement, compared to the control group, in all the measures studied. Furthermore, other studies found that a high level of physical activity during life reduces the risk of dementia.\(^9\) Since physical activity also increases physical performance, such as muscle strength, gait speed, functional mobility, and balance,\(^9\) it is not surprising that there is a positive relationship between physical performance and cognition.\(^\)\(^2\) More specifically, older people with better physical performance levels, for example, mobility,\(^9\) balance,\(^6\) strength,\(^9,\)\(^4\) and aerobic fitness,\(^9\) have better cognitive functions, such as cognitive flexibility or global cognition. Moreover, similar to physical activity, better physical performance, such as balance\(^9\) and strength,\(^9,\)\(^4\) also decreases the risk of dementia.\(^1\)\(^0\)

This longitudinal data extends the baseline cross-sectional associations reported in Chapter 5, and suggests that the physical and cognitive benefits change in proportion to each other. This could be because the improved cognition contributes to the improved physical performance. However, it could also be that both adaptations are related to another underlying factor, such as anabolic hormone profile or reduction in inflammatory cytokines after POWER training. Future studies are needed to explore the mechanisms underlying this relationship between cognitive and physical
function improvements after exercise.

6.5.4 ROLE OF SKELETAL MUSCLE MASS AND COGNITION

This investigation was also the first to examine the relationships between changes in the expression of skeletal muscle bulk and change in cognitive domains. Multiple regression analyses, notably, showed that increases in skeletal muscle mass and thigh muscle area were related to better scores in Word List Memory ($\beta=0.38$, $p=0.03$; Figure 6.12.1) and information processing speed ($\beta=-0.34$, $p<0.05$; 6.13.1) within the POWER group, respectively. Similar findings were reported by Nourhashemiet al$^{96}$ who found an association between cognitive impairment and reduced muscle mass in women without dementia. Our data suggest that cognition-related improvements in body composition may be predominantly related to the amount of increase in skeletal muscle mass.

Our findings also suggest that skeletal muscle mass may be a more sensitive measure to relate body composition to cognitive outcomes than measures of adiposity. Skeletal muscle mass was increased in individuals compared with sham controls and was associated with cognition. Thus, our data present the importance of assessing specific measures of body composition and suggest the hypothesis that change in skeletal muscular mass and thigh muscle area may underlie previous relationships of specific measures of body composition (lean muscle) with cognitive decline.$^{103}$ It should be noted that there was a direct relationship between skeletal muscle mass change and global cognitive change in the SHAM group as well, but these muscle-cognitive relationships were more extensive in the POWER trainers.

Sarcopenia in the normal ageing process is most strongly linked with age-related reductions in muscle mass and physical activity.$^{97, 98}$ Physical inactivity results in a chronic elevation of
inflammatory biomarkers, which are also observed in patients with dementia and T2DM. Additionally, lower physical activity level is associated with less lean mass. Skeletal muscle mass is the primary site for glucose disposal, and thus it is possible that decreases in skeletal muscle simply decrease the available storage depot for glucose and increased insulin resistance, suggesting that behavioral changes associated with AD may result in loss of lean mass.

On the other hand, the benefits of exercise in cohorts with T2DM may include improved structural and functional changes such as glycaemic control, increased insulin sensitivity, decreased body fat content, decreased inflammation, decreased blood pressure, and decreased blood lipids, and treatment of many common comorbidities associated with cognitive impairment and ageing. Even after controlling for physical activity levels, however, skeletal muscle mass remained independently associated with cognition, suggesting that the decline in physical activity observed in our cohort is unlikely to fully explain our results.

An alternative explanation for our observations is that cognitive improvements and muscle hypertrophy share common underlying mechanisms. Cognitive impairment is associated with systemic inflammatory abnormalities that are also implicated in sarcopenia. Although our measures of inflammatory processes are limited in this study, we observed an independent relationship between skeletal muscle mass and insulin (p<0.05), a well-known anabolic hormone that may have neurotrophic and neuroprotective properties. A previous study has reported that insulin levels are associated with cognition in early AD. Muscle is our largest metabolically active organ, thus improving skeletal muscle mass through anabolic exercise may improve the metabolic health of older adults with T2DM, and thereby cognition. Exercise enhances insulin sensitivity, an effect which tended to be related to improvements in cognition in our POWER group. Thus, our observation that skeletal muscular mass and insulin levels are
interrelated suggests that increased anabolic support to both the muscle and brain may be a potential mechanism underlying cognitive benefits.

Progressive resistance training may boost the activity of antioxidant enzymes within skeletal muscle and thus be an anti-inflammatory stimulus through this process, enhancing defense against damage caused by oxygen reactive specimens and CRP, in the long run, modify the function of central systems, particularly the hippocampus, amygdala, medial septum, and entorhinal cortex (important regions related to memory processed such as consolidation, storage, and recall), as inflammation is known to be damaging to neuronal structure and metabolism.

Skeletal muscle is the primary site for glucose disposal, and thus it is possible that increases in skeletal muscle mass after POWER training simply increased the available storage depot for glucose in our study, which could ultimately lead to improved brain plasticity and cognition. In addition, part of the hypertrophic stimulus resulting from PRT or POWER training is attributable to increases in IGF-1. Mechanical stimulation of skeletal muscle results in the local production of two isoforms of IGF-1; IGF-1E, which is similar to that derived from hepatocytes and contributes to increases circulating IGF-1. IGF-1 management may play a role in cognitive function. It is therefore possible that a potential link between augmentation of skeletal muscle mass and better cognitive function exists.

6.5.5 Role of Adipose Tissue on Cognitive Performance

This investigation was also the first to examine the relationships between detailed measurements of adiposity and relative deficits in cognitive function after resistance training in older people with T2DM. We unexpectedly found that decreased total abdominal adipose tissue subcutaneous
abdominal adipose tissue were significantly associated with worse executive function and Word List Recall within the POWER group. Reductions in total abdominal adipose tissue (Figure 6.19.2), visceral adipose tissue (Figure 6.20.2), and sagittal diameter were also related to worse Word List Memory within the SHAM group. It is likely that this was mediated through reduction in body mass index within the POWER and SHAM group. This probably reflects the fact that our participants with higher BMI also had higher amounts of muscle in addition to higher amounts of fat, either from the increased thigh muscle required to support increased weight, or from fatty infiltration of muscle. Supporting this hypothesis, we found no associations between total abdominal adipose, visceral adipose tissue, and sagittal diameter and memory when controlling for BMI or skeletal muscle mass. To our knowledge no other studies have examined these relationships in such detail between regional and whole body adiposity, skeletal muscle and cognitive function in older adults with T2DM, and these findings require replication and further investigation.

6.5.6 Relationship between Psychosocial Status, Physical Activity Level and Cognition

Unexpectedly, reductions depressive symptoms were not related to improvements in cognitive function. Others have shown that depression may be associated with cognitive deficits. Depression has also been reported to result in greater cognitive impairment in individuals with diabetes than in participants without diabetes, with the greatest differences in attention/information processing speed and executive functioning. Our cohort had normal scores on the GDS on average, likely precluding such relationships however.

Changes in SF-36 MCS were not related to changes in cognitive function, and did not change significantly over time or between groups. This is contradictory to previous cross-sectional data
showing a direct relationship between SF-36 MCS and cognition in older adults with T2DM, suggesting that reductions in SF-36 MCS could either lead to, or result from, cognitive dysfunction. It is likely that in our study, as quality of life was close to normal at baseline, it may have not improved or been linked to cognition due to ceiling effects. Similarly, changes in SF-36 PCS were not associated with changes in cognitive function, likely for similar reasons.

A large body of evidence indicates that higher physical activity levels are associated with healthy brain ageing, including cognition, among healthy older adults. In a previous study, greater levels of physical activity, including walking, were strongly associated with better cognitive function in 18,000 Nurses’ Health Study participants who were generally healthy. However, we did not find positive effects of our interventions on physical activity level or relationships to cognitive function in either study group of GREAT2DO. It is possible that the self-report PASE tool was insufficiently sensitive to change or precise enough to delineate such changes or relationships, particularly in a cohort as sedentary as ours. Accelerometry data would be better suited to testing these hypotheses in longitudinal studies of older adults, particularly if memory impairment may cause recall bias in the cohort. Therefore, additional studies are needed to investigate the potentially bi-directional relationship between physical activity levels and cognitive function, and define the mechanistic pathways linking these two domains.

6.5.7 Relationship between Adiponectin and CRP Levels and Cognition

This is the first report of increased circulating levels of adiponectin after power training in older people with T2DM. Multiple regression models showed that higher circulating levels of total adiponectin independently predicted better global cognitive scores within the POWER group ($\beta=0.57$, $p=0.03$). This is in agreement with cross-sectional data, showing strong positive
relationships between total adiponectin levels and cognition. Increases in HMW adiponectin also predicted improvements in executive function. This is contradictory to a previous cross-sectional data showing a relationship between higher HMW adiponectin and worse cognition in older adults with mild cognitive impairment. However, consistent with our data, previous investigations into the effects of exercise in older adults have shown adiponectin to have positive effects on neurogenesis and cognitive function. Several mechanisms could explain our observations. Adiponectin has a neuroprotective effect on hippocampal neurons. Treatment with adiponectin preserves the integrity of the blood–brain barrier and has a neuroprotective effect on hippocampal neurons. Moreover, adiponectin plays a direct protective role against atherosclerotic vascular change, and loss of effects enhances endothelial dysfunction in the brain. Circulating adiponectin is strongly linked to protection against endothelial cell damage. In addition, adiponectin plays a role in the pathogenesis of multiple sclerosis and AD. Taken together, these findings suggest that the brain, vascular factors, and adiponectin interact and reinforce each other through mechanisms that may be associated with neural and vascular protective effects related to cognitive function.

Adiponectin is a protein hormone secreted predominantly by adipose tissue and modulates insulin-sensitizing, glucose control, anti-inflammatory and anti-oxidant properties. Our data showed that the change in serum circulating levels of total adiponectin in the POWER groups tended to be associated with improved executive function (p=0.09). Increase in total adiponectin levels was associated with improved %β cell (r=0.3, p<0.05) and reduced HbA1c (r=-0.35, p<0.05) in our cohort. Insulin resistance in particular has been studied and may mediate, cognitive function through modulation of hippocampal synaptic plasticity, neuroinflammation and subsequent protein deposition. Insulin resistance has been implicated in cognitive dysfunction in neurologically normal older adults, even in the absence of silent microvascular
In addition, we are the first to show a relationship between increases in total adiponectin level and reductions in glucose control ($r=-0.35$, $p<0.05$) and increase in $\%$ beta cell ($r=0.3$, $p<0.05$) after exercise exposure, as well as between increases in adiponectin and improvements in cognition ($\beta=0.57$, $p=0.03$). In our study, those in the POWER group who increased skeletal muscle mass increased their total adiponectin compared to those who decreased their skeletal muscle mass in the SHAM group ($p=0.10$). It appears to be associated with robust adaptations of skeletal muscle mass although there were no significant difference between change in skeletal muscle mass and adiponectin. Adaptations of skeletal muscle mass may potentially mediate metabolic profile and adiponectin which contribute to better cognition as well.

Another potential mediating factor is that POWER can result in a decrease in adiposity. Adipose tissue is a metabolically active tissue and source of a variety of hormones, such as leptin and adiponectin. Adiponectin is an effective insulin sensitizer; and circulating levels are inversely correlated to insulin resistance, metabolic syndrome, obesity, type 2 diabetes, cardiovascular, and inflammation. BMI is inversely related to circulating adiponectin. Reducing adiposity may increase adiponectin levels, thus mediating effects of insulin, inflammation, and glucose control on cognitive function. In agreement with this, as shown in our own data, increases in adiponectin were related to reductions in HbA1c.

It is possible that decreased adiponectin level in T2DM is a mediator of cognitive decline in this cohort therefore. Thus, increase in total adiponectin and HMW adiponectin through exercise may be a promising therapeutic target to alleviate Alzheimer's disease pathologies such as apoptosis and cognitive decline and dysfunctional brain insulin system. In our study, adiponectin was not improved significantly by exercise, although other studies have been positive in this regard. Future studies should compare the relative efficacy of different modes, intensities, and doses of
exercise on this factor which may provide a strong link between central obesity, insulin resistance, and cognition in the older adult.

After 12 months, no significant relationship between reduced CRP and better cognitive function was observed after controlling for potential confounding factors. Some previous literature has shown PRT to be an effective mode of exercise to reduce systemic inflammation, and this is also true in adults with T2DM, and may be related to cognitive processes. However, there is also a report of no reduction in systemic inflammation in response to PRT, reviewed here. Although some longitudinal studies have found associations specifically between increased CRP level and incident cognitive decline, others have revealed conflicting results, including minimal or no overall association with incident decline in memory, dementia, or neuropsychological test performance. Figure 7.1.1 shows that improvements in Word List Recognition following POWER training were related to reductions in CRP. Compared with other studies of cognition and CRP, our median CRP level at baseline within participants in the POWER group of 2.5 mg/L was much higher than in some other studies of dementia and memory, suggesting its potential relevance in high risk cohorts with cardiovascular disease, for example. Our findings support the utility of further refining an anti-inflammatory intervention to reduce overall cardiovascular risk and cognitive decline within individuals with T2DM. This possibility requires further exploration.

6.5.8 LIMITATIONS AND FUTURE DIRECTIONS

Contrary to our expectations, power training did not result in beneficial changes in any cognitive domains relative to the SHAM group. Similarly, glucose homeostasis, insulin sensitivity, physical performance, psychosocial status, physical activity, and systemic inflammation and
adipokines did not change between groups. It remains unclear why participants randomised to the SHAM group had significantly greater improvements in executive function and global cognitive performance compared to POWER training. It is possible that unprescribed dietary restrictions, higher SF-36 Mental Component Summary, higher adipokine levels (higher serum HMW adiponectin), lower depression score, and/or changes in habitual levels of physical activity outside of the study interventions may explain these findings. While data regarding changes in dietary intake and habitual physical activity by accelometry were collected, these data were not available at the time of writing, and were thus beyond the scope of the present analyses.

Another factor might have attenuated treatment differences in cognitive scores. Higher training intensity and velocity were the only differences between the POWER training and SHAM exercise control group, and not all participants in POWER training group reached the intended high intensity training range. Thus, the differences in training modality between the two groups were not quite as distinct as planned, and adherence was high and equivalent in both groups. This could have minimised the group differences observed. Our SHAM exercise control design, although more robust and ethically justified than if a waitlist control group or advice-only control group had been used instead, may have led to an actual underestimation of POWER training efficacy. Future trials may need to include a non-exercise control group as well, although this raises ethical concerns of clinical equipoise in a year-long trial of T2DM, as exercise is considered part of the standard care of this cohort, as reported on page 479 of Chapter 6.

Sample size limitations could have contributed to Type II errors for some analyses, however, in our study, this cohort was a random sample of the population. Sample size estimates were determined for differences between participants randomised to receive high intensity POWER training, compared to those randomised to receive SHAM exercise for the primary and secondary outcomes of the study. All participants (47 in the POWER group and 53 in the SHAM group)
were included in the statistical models, we have sufficient power to detect a statistically significant difference in secondary outcomes. Moreover, effect size were all negligible and small, suggesting that Type II error was not a major case of negative findings. On a population level, even small changes in cognition may be very relevant to the prevention of dementia over time however. Therefore, future larger studies should be powered to detect changes in cognition of this magnitude.

The most interesting finding from this investigation is that despite similar changes in skeletal muscle mass and thigh muscle area in the participants within the POWER groups, improvements in Word List Memory and information processing speed were only present in those randomised to the POWER group. Similarly, improvement 3MS scores were seen in the SHAM. The low intensity exercise within the SHAM group was likely sufficient to promote hypertrophy, and so gains in skeletal muscle mass within these participants would be attributed to cognitive improvement. Increase in lean mass and decrease in adiposity may be sensitive measure to relate body composition to cognitive outcomes and dementia. Higher skeletal muscle had better cognitive function in the POWER group and the SHAM group. In addition, increase in adiposity may resulted in cognitive improvement. Thus, favorable alterations in both skeletal muscle mass and adiposity mediated through low and high intensity power training can result in improvements in the metabolic health of individuals with T2DM contributed to the observed cognitive benefits.

The data presented within this report clearly show that increasing adipokine level and improving physical performance result in improvements in serum total adiponectin level and total static balance, respectively, and consequently, improvements in global cognitive function in the POWER and the SHAM group. Additionally, it remains unclear why participants randomised to the SHAM group with low intensity, who reductions in insulin resistance showed improvements in
global cognitive function but not in the POWER group (Figure 6.9.2). Serum adiponectin could be another important mediator. High serum adiponectin has been reported to mediate insulin resistance and cognition.\textsuperscript{136-138} In the present study, insulin resistance was independently associated with cognitive function adjusted age, sex, years of education, duration of diabetes, SF-36 Mental Component Summary, cognitive function, and HbA1c. However, the relationships between insulin resistance and global cognitive function was attenuated after controlled for age, sex, years of education, duration of diabetes, SF-36 MCS, cognitive function, HbA1c, and High Molecule Mass adiponectin / total adiponectin ratio. It is possible that un-prescribed dietary restrictions, and/or changes in habitual levels of physical activity and mental activity outside of the study interventions may explain these findings. While data regarding changes in dietary intake and habitual physical activity were collected, the data was not available at the time of writing, and were thus beyond the scope of the present analyses. However, the mechanistic pathways require further examination and were beyond the scope of this investigation. An alternative explanation for our observations is that cognitive function and sarcopenia (loss of lean tissue) share common underlying mechanisms. Alzheimer’s disease is associated with systemic anabolic and inflammatory abnormalities that are also implicated in sarcopenia.\textsuperscript{139} Although our measures of inflammatory processes are limited in this study, we observed an independent relationship between lean mass and insulin, a well-known anabolic hormone\textsuperscript{140} that may have neurotrophic\textsuperscript{141} and neuroprotective properties.\textsuperscript{141} Previous study reported that insulin levels are associated with cognition and brain volume in early Alzheimer’s disease. Lean mass and insulin levels are interrelated suggests that reduced anabolic support to both the muscle and brain may be a potential mechanism underlying the observed relationships. Additionally, adiponectin stimulates glucose utilisation, fatty acid oxidation, and inhibits intramuscular fat lipid deposition, finally improves insulin resistance contributed to glucose control, thus both improved insulin resistance and glucose level may predict cognitive changes.
Furthermore, balance is also significantly associated with global cognitive function in the present study. Balance is dependent on the functioning of the frontocerebellar and frontostriatal connections, connections between, respectively, the cerebellum and the striatum and the frontal cortex, for example, dorsolateral prefrontal cortex (DLPFC). Since the DLPFC is also involved in cognitive function, it is not surprising that in older people with T2DM, balance is significantly related to global cognitive function, because both performances appeal to the same neural circuits.

The mechanism behind the reductions in total abdominal adipose tissue and abdominal adipose tissue within the POWER group, and why this was associated with worse score in cognition is unclear. It is possible that the association of high adiposity to cardiovascular risk factor (triglyceride) is attenuated in older age groups. Adipose tissue produces (adipokines) many mediated insulin resistance and inflammation linked to structural brain abnormalities and cognitive impairments. In addition, leptin was associated with improved cognitive deficits and inflammation in the brain.

Due to funding constraints and equipment availability, exercise-induced improvements in insulin resistance, cytokines (Tumor Necrosis Factor-α and Interlukines-6), neurotropic, and other metabolic parameters (Aβ42) related to cognitive decline were not measured. Furthermore, IR was determined using HOMA2-IR, reflective of hepatic IR as opposed to being a whole body measure. Appropriately powered studies of similar design should be employed that utilize more direct measures of whole-body composition (such as dual-energy X-ray absorptiometry), IR (hyperinsulinaemic-euglycaemic clamp), and cognition. In addition, there is lack of control group without exercise because exercise intensity in SHAM is too higher than expect. Finally, exercise-induced cognitive benefits may relate to the type of tests administered or the specific task demands that rely more heavily on brain regions. Future controlled trials of resistance exercise
that include brain imaging measures of glucose metabolism and blood flow and other cognitive-related biomarkers will likely help to identify specific mechanisms to account for cognition-enhancing effects in older adults with T2DM.

In conclusion, this clinical trial in 103 older adults with intact cognition, a mean HbA1c level of 7.1%, and long-term T2DM shows no overall reduction of the rate of T2DM-related cognitive decline though high intensity resistance training compared to low intensity resistance training. However, increases in skeletal muscle mass and free fat mass, adiponectin level, and total static balance achieved through high intensity power training improved cognition in a cohort of older adults with T2DM.
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## TABLE 6.1 BASELINE CHARACTERISTICS OF STUDY COHORT

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<td>Almost every day</td>
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<td>Two to Three Times a Week</td>
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<td>Once or Twice a Week</td>
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<td>Two or Three Times a Month</td>
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<td>Once a Month</td>
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<td><strong>Health Status</strong></td>
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<td>Number of Chronic Diseases (n)</td>
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<td>Duration of Diabetes (years)</td>
<td>8.0 ± 6.0</td>
<td>7.0 ± 5.0</td>
<td>9.0 ± 7.0</td>
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<td>Hypertension (n)</td>
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<td>History of Stroke (n)</td>
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<td>Peripheral Neuropathy (n)</td>
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<td>Peripheral vascular disease (n)</td>
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<td>Sleep Apnoea (n)</td>
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<td><strong>Metabolic Syndrome (n)</strong></td>
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<td>Central Obesity</td>
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<td>Raised Triglycerides</td>
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<td><strong>IDF Diagnosis of Metabolic</strong></td>
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<td>Syndrome</td>
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<td><strong>Medication</strong></td>
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<td>Total No. of Medications/Day (n)</td>
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<td>Insulin Users (n)</td>
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<td>Metformin Users (n)</td>
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<td>Metformin Dosage (mg/day)</td>
<td>1544.6±659.0</td>
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<td>Glibenclamide Users (n)</td>
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<td>2</td>
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<td>Glicazide Users (n)</td>
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<td>Glicazide Dosage (mg/day)</td>
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<td>Acarbose Users (n)</td>
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<td>Diet control Users (n)</td>
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<td>7</td>
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<td><strong>Obesity Categories (n)</strong></td>
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<td>Normal (18.5&lt;BMI&lt;24.9)</td>
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<td>Overweight (25&lt;BMI&lt;29.9)</td>
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<td>Obese I (30&lt;BMI&lt;34.9)</td>
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<td>19</td>
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<td>Obese II (35&lt;BMI&lt;39.9)</td>
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<td>Obese III (BMI≥40)</td>
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<td>Quality of Life</td>
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<td>SF-36 (0-100)</td>
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<td>SF-36 Physical Component Summary</td>
<td>46.3 (61.7)</td>
<td>47.3 (61.8)</td>
<td>46.0 (41.6)</td>
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<td>SF-36 Mental Component Summary</td>
<td>0.8 (65.3)</td>
<td>50.5 (60.2)</td>
<td>52.2 (38.7)</td>
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<td>Habitual Physical Activity Level</td>
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<td>Physical Activity Scale for the Elderly (score)</td>
<td>574.4 (7891.0)</td>
<td>556.7 (7803.0)</td>
<td>601.2 (6344.0)</td>
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<td>Cardiovascular Profile</td>
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<td>Systolic Blood Pressure (mm Hg)</td>
<td>146.1±17.8</td>
<td>147±17.9</td>
<td>145±17.9</td>
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<td>Diastolic Blood Pressure (mm Hg)</td>
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<td>78.9±7.5</td>
<td>77.3±10.1</td>
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<td>Physical Performance</td>
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<tr>
<td>Physical Function</td>
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<td>Static Balance Total Time (sec)</td>
<td>74.8±7.1</td>
<td>75.1±7.4</td>
<td>74.5±7.0</td>
<td>0.70</td>
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<tr>
<td>Normal Gait Velocity (m/s)</td>
<td>1.20±0.19</td>
<td>1.18±0.19</td>
<td>1.21±0.18</td>
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<tr>
<td>Maximal Gait Velocity (m/s)</td>
<td>1.86±0.31</td>
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<td>1.85±0.32</td>
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<td>Six-Minute Walk (m)</td>
<td>544.7±95.7</td>
<td>552.8±95.7</td>
<td>539.3±96.2</td>
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<td>Fastest Chairstand (sec)</td>
<td>12.1±2.7</td>
<td>12.2±2.8</td>
<td>11.9±2.6</td>
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<tr>
<td>Stair Climb Power (W)</td>
<td>364.4±126.7</td>
<td>367.8±137.0</td>
<td>361.6±118.6</td>
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<tr>
<td>Muscle Strength</td>
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<tr>
<td>Leg Press (N)</td>
<td>1605.5±456.1</td>
<td>1655.8±479.9</td>
<td>1569.4±44</td>
<td>0.95</td>
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### TABLE 6.1 BASELINE CHARACTERISTICS OF STUDY COHORT - CONTINUED

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<th>Total (n=100)</th>
<th>POWER (n=47)</th>
<th>SHAM (n=53)</th>
<th>p-value</th>
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<tr>
<td>Chest Press (N)</td>
<td>332.3±108.5</td>
<td>349.0±130.8</td>
<td>302.7±84.7</td>
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<tr>
<td>Knee Extension (Nm)</td>
<td>157.0±56.9</td>
<td>167.1±65.3</td>
<td>148.4±47.7</td>
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<tr>
<td>Seated Row (N)</td>
<td>239.1±74.7</td>
<td>243.9±86.3</td>
<td>234.7±63.0</td>
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<tr>
<td>Knee Flexion (Nm)</td>
<td>141.0 (715)</td>
<td>141.0 (713)</td>
<td>143.0 (565)</td>
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*Power (W)*

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<th>SHAM (n=53)</th>
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<tr>
<td>Leg Press</td>
<td>515.7±330.6</td>
<td>473.0±337.8</td>
<td>553.4±332.6</td>
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<tr>
<td>Chest Press</td>
<td>155.7±76.8</td>
<td>170.4±88.9</td>
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<tr>
<td>Knee Extension</td>
<td>310.6±143.0</td>
<td>307.6±169.1</td>
<td>313.2±116.7</td>
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<tr>
<td>Seated Row</td>
<td>295.2±160.3</td>
<td>316.2±18.5</td>
<td>276.5±138.9</td>
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<tr>
<td>Knee Flexion</td>
<td>116.2±53.5</td>
<td>109.4±49.3</td>
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*Overall Body Composition*

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<tbody>
<tr>
<td>Stretched Stature (m)</td>
<td>1.68±0.89</td>
<td>1.68±0.94</td>
<td>1.67±0.85</td>
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<tr>
<td>Naked Body Weight (kg)</td>
<td>89.0±17.3</td>
<td>89.5±15.3</td>
<td>88.6±18.9</td>
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<tr>
<td>Body Mass Index (BMI (kg/m²))</td>
<td>31.5±5.4</td>
<td>31.3±4.6</td>
<td>31.6±6.1</td>
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<tr>
<td>Skeletal Muscle Mass (kg)</td>
<td>30.4±4.1</td>
<td>30.7±4.3</td>
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<tr>
<td>Fat Free Mass (kg)</td>
<td>56.1±10.7</td>
<td>56.7±11.3</td>
<td>55.6±10.1</td>
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<tr>
<td>Fat Mass (kg)</td>
<td>31.8±11.6</td>
<td>31.8±10.0</td>
<td>31.8±12.9</td>
<td>0.99</td>
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<tr>
<td>Body Fat (%)</td>
<td>36.4±8.4</td>
<td>36.5±8.2</td>
<td>36.3±8.7</td>
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*Regional Body Composition*

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<tr>
<td>Waist Circumference</td>
<td>107.2±11.9</td>
<td>107.9±10.8</td>
<td>106.6±12.9</td>
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(ISAK) (cm) 512
**TABLE 6.1 BASELINE CHARACTERISTICS OF STUDY COHORT - CONTINUED**

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<th>Total (n=100)</th>
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<td><strong>Regional Body Composition</strong></td>
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<tr>
<td>Sagittal Abdominal Diameter</td>
<td>26.8±3.5</td>
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<tr>
<td>Total Abdominal Adipose Tissue (Without Skin) (cm²)</td>
<td>418.9±118.36</td>
<td>428.3±112.2</td>
<td>410.5±124.1</td>
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<tr>
<td>Visceral Fat Area (cm²)</td>
<td>212.6±88.0</td>
<td>220.7±84</td>
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<td>0.38</td>
</tr>
<tr>
<td>Subcutaneous Abdominal Adipose</td>
<td>206.4±90.6</td>
<td>207.6±92.9</td>
<td>205.3±89.5</td>
<td>0.90</td>
</tr>
<tr>
<td><strong>Adipose tissue (cm²)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thigh Muscle Density</td>
<td>84.2±2.3</td>
<td>84.2±2.2</td>
<td>84.1±2.4</td>
<td>0.79</td>
</tr>
<tr>
<td>Total Thigh Fat Area (cm²)</td>
<td>97.5±50.0</td>
<td>92.5±42.9</td>
<td>102.2±55.5</td>
<td>0.42</td>
</tr>
<tr>
<td>Subcutaneous Thigh Fat Area (cm²)</td>
<td>84.3±47.6</td>
<td>78.6±40.2</td>
<td>89.5±53.3</td>
<td>0.30</td>
</tr>
<tr>
<td><strong>Cognitive Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word List Memory (0/30)</td>
<td>21.3 ± 3.9</td>
<td>21.4±3.5</td>
<td>21.2±4.2</td>
<td>0.68</td>
</tr>
<tr>
<td>Word List Recall (0/10)</td>
<td>7.0 ± 1.8</td>
<td>6.9±1.4</td>
<td>7.2±2.1</td>
<td>0.46</td>
</tr>
<tr>
<td>Word List Recognition (0/10)</td>
<td>10 (4)</td>
<td>10 (4)</td>
<td>10 (2)</td>
<td>0.64</td>
</tr>
<tr>
<td>Trial Making Test A (s)</td>
<td>40.7 ± 12.6</td>
<td>40.4±12.2</td>
<td>41.0±13.3</td>
<td>0.84</td>
</tr>
<tr>
<td>Trial Making Test B (s)</td>
<td>85.1 (254.7)</td>
<td>82.7 (241.0)</td>
<td>85.9 (254.8)</td>
<td>0.44</td>
</tr>
</tbody>
</table>
TABLE 6.1 BASELINE CHARACTERISTICS OF STUDY COHORT - CONTINUED

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=100)</th>
<th>POWER (n=47)</th>
<th>SHAM (n=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cognitive Function</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DIFFBA (s)</td>
<td>45.1 (267.1)</td>
<td>42.7 (267.1)</td>
<td>47.5 (208.9)</td>
<td>0.43</td>
</tr>
<tr>
<td>Modified Mini-mental State Examination (0/100)</td>
<td>94.2 ± 4.7</td>
<td>95.3± 3.9</td>
<td>93.3± 5.2</td>
<td>0.02</td>
</tr>
<tr>
<td>Depression Score (0/30)</td>
<td>6.8±5.3</td>
<td>7.7±4.9</td>
<td>6.1±4.6</td>
<td>0.13</td>
</tr>
<tr>
<td><strong>Metabolism</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol (mmol/L)</td>
<td>4.3±1.1</td>
<td>4.5±1.1</td>
<td>4.2±1.0</td>
<td>0.28</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.5 (4.4)</td>
<td>1.5 (4.4)</td>
<td>1.5 (4.1)</td>
<td>0.62</td>
</tr>
<tr>
<td>High Density Lipoprotein</td>
<td>1.22±0.54</td>
<td>1.21±0.29</td>
<td>1.23±0.38</td>
<td>0.84</td>
</tr>
<tr>
<td>Low Density Lipoprotein (mmol/L)</td>
<td>2.2(4.7)</td>
<td>2.3(3.9)</td>
<td>2.0 (4.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>Fasting Glucose Levels (mmol/L)</td>
<td>6.5 (13.4)</td>
<td>6.4 (13.0)</td>
<td>6.6 (12.2)</td>
<td>0.49</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.1±1.1</td>
<td>6.9±0.9</td>
<td>7.3±1.3</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Fasting Insulin (mU/L)</td>
<td>9.8 (34.1)</td>
<td>9.1 (33.3)</td>
<td>10.0(34.0)</td>
<td>0.20</td>
</tr>
<tr>
<td>(n=87)</td>
<td>(n=42)</td>
<td>(n=45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA2-%B</td>
<td>110.0±48.0</td>
<td>105.0±37.9</td>
<td>114.5±55.7</td>
<td>0.49</td>
</tr>
<tr>
<td>(n=87)</td>
<td>(n=42)</td>
<td>(n=45)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA2-IR</td>
<td>2.9±1.1</td>
<td>2.6±1.0</td>
<td>3.0±1.2</td>
<td>0.14</td>
</tr>
<tr>
<td>(n=87)</td>
<td>(n=42)</td>
<td>(n=45)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TABLE 6.1 BASELINE CHARACTERISTICS OF STUDY COHORT - CONTINUED

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=100)</th>
<th>POWER (n=47)</th>
<th>SHAM (n=53)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>C-reactive Protein (CRP) (mg/L)</td>
<td>2.5 (21.1)</td>
<td>2.4 (13.0)</td>
<td>2.8 (21.1)</td>
<td>0.98</td>
</tr>
<tr>
<td>Serum HMW Adiponectin (ng/ml)</td>
<td>3781.1 (23121.1)</td>
<td>4026.6 (13690.6)</td>
<td>3448 (23121.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>Serum Total Adiponectin (ng/ml)</td>
<td>7969.5±4738.7</td>
<td>7174.7±4114.4</td>
<td>8061.1±5230</td>
<td>0.54</td>
</tr>
<tr>
<td>Serum Adiponectin Ratio</td>
<td>0.40 (4.27)</td>
<td>0.45 (1.19)</td>
<td>0.37 (1.29)</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Normally distributed data presented as mean ± SD.
Non-normally distributed data presented as median (range).
Difference between groups was assessed via one-way ANOVA continuous data.
Non-normally distributed data were log-transformed before use with parametric statistics.
Non-normally distributed data after log-transformation were analyzed using Mann-Whitney U test of raw data.
Categorical variables we assessed using a Chi Square tests for categorical data.
Word list subset of the **Consortium to Establish a Registry for Alzheimer’s disease** is a measure immediate memory and delayed memory, higher score indicates better memory function.  Trail Making Test A is a measure of information processing speed, higher score (second) indicates worse information processing speed.  Trail Making Test B is a measure of executive function, higher score (second) indicates worse executive function.  DIFFBA (Trial Making Test B minus Trail Making Test A) (second) is a measure of pure executive function.  High score indicates worse executive function.  Modified Mini-mental State Examination (3MS) is used to assess general cognitive function; higher score indicates better global cognitive function.
16 participants were excluded from HOMA2-IR analyses due to insulin therapy.

HbA1C = Hemoglobin A1c

HOMA2 = Homeostasis Model Assessment 2

HMW: High-Molecule Weight

N: Newtons

Nm: Newton Meters
TABLE 6.2 COMPARISON OF COGNITIVE FUNCTIONS BETWEEN POWER AND SHAM GROUPS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mean Difference (95% CI) between baseline and 6 months</th>
<th>Mean Difference (95% CI) between baseline and 12 months</th>
<th>Relative ES (95% CIs)</th>
<th>T</th>
<th>p value</th>
<th>T×G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POWER (n=47)</td>
<td>SHAM (n=53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>POWER (n=47)</td>
<td>SHAM (n=53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cognitive Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Word List Memory (/30)</td>
<td>1.35 (0.17, 1.53)</td>
<td>2.07 (0.95, 3.19)</td>
<td>-0.04 (-0.43, 0.35)</td>
<td></td>
<td>0.000</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>2.80 (1.51, 4.08)</td>
<td>2.94 (1.71, 4.16)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.51 (-0.01, 1.03)</td>
<td>0.47 (-0.80, 1.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.29 (0.65, 193)</td>
<td>0.78 (0.27, 1.30)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.02 (-0.24, 0.23)</td>
<td>0.01 (-0.21, 0.22)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.02 (0.10, 0.50)</td>
<td>0.02 (-0.23, 0.28)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.01 (-4.48, 4.29)</td>
<td>0.23 (-3.85, 4.32)</td>
<td></td>
<td></td>
<td>0.000</td>
<td>0.73</td>
</tr>
<tr>
<td></td>
<td>-4.31 (-9.03, 0.41)</td>
<td>-5.78 (-9.12, -2.45)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.01 (-0.05, 0.05)</td>
<td>-0.02 (-0.06, 0.05)</td>
<td></td>
<td></td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>-0.02 (-0.06, 0.02)</td>
<td>-0.07 (-0.11, 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>-0.01 (-1.01, 0.12)</td>
<td>-0.03 (-0.12, 0.06)</td>
<td></td>
<td></td>
<td>0.83</td>
<td>0.43</td>
</tr>
<tr>
<td></td>
<td>0.03 (-0.09, 1.44)</td>
<td>-0.07 (-0.16, 0.03)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.004 (-0.004, 0.011)</td>
<td>0.009 (0.003, 0.016)</td>
<td></td>
<td></td>
<td>0.000</td>
<td>0.04</td>
</tr>
<tr>
<td>State Examination (0/100) (log)</td>
<td>0.004 (-0.002, 0.010)</td>
<td>0.015 (0.008, 0.023)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Non-normally distributed data were transformed before use with parametric statistics. Calculations of effect size were adjusted via Hedges’ bias-corrected effect size for small sample sizes. Ninety-five percent confidence intervals (CIs) for the relative ES were calculated. Effect Size = \((\Delta \text{Treatment} – \Delta \text{Control}) / \text{Pooled (Treatment + Control) Baseline SD}\).

Time effect and group and time interaction between groups were both adjusted for age, sex, and educational levels, SF-36 mental component score, HbA1c, and baseline cognitive score of the dependent cognitive outcome of interest.

Word List Memory, Word List Recall, and Word List Recognition are measures of immediate memory and delayed memory; higher score indicates better immediate memory and delayed memory. Trail Making Test A is a measure of attention/information processing speed; higher score (seconds) indicates worse attention/information processing speed. Trail Making Test B is a measure of attention/information processing speed and executive function; higher score (seconds) indicates worse attention/information processing speed and executive function. DIFFBA (seconds) is calculated by subtracting Trail Making Test A from Trail Making Test B, and is considered a purer measure of executive function; higher score indicates worse executive function. 3MS is a measure of global cognitive function; higher score indicates better global cognitive function.

\(^a P<0.05\); significant differences between baseline and 6 months in the POWER group, \(^b p<0.05\); significant differences between baseline and 12 months in the POWER group, \(^c P<0.05\); significant differences between 6 months and 12 months in the POWER group, \(^d P<0.05\); significant differences between baseline and 6 months in the SHAM group, \(^e P<0.05\); significant differences between baseline and 12
months in the SHAM group, \( f P<0.05 \); significant differences between 6 months and 12 months in the SHAM group, \( g P<0.05 \); significant differences between the POWER and SHAM groups at 6 months, \( h P<0.05 \); significant differences between the POWER and SHAM groups at 12 months.

Models are adjusted for age, gender, years of education, duration of diabetes, SF-36 Mental Component Summary, HbA1c, and cognitive score.

ES: Effect Size

POWER: Power training group

SHAM: Control group

CIs: Confidence intervals

T: Time

G×T: Group and time interaction

Sec: Second
### TABLE 6.3 COMPARISON OF METABOLISM BETWEEN POWER AND SHAM GROUPS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mean Difference (95% CI) between baseline and 6 months</th>
<th>Mean Difference (95% CI) between baseline and 12 months</th>
<th>Relative ES (95% CIs)</th>
<th>T</th>
<th>T×G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POWER (n=47) SHAM (n=53)</td>
<td>POWER (n=47) SHAM (n=53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose Homeostasis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-0.42 (-1.15, 0.30)</td>
<td>-0.30 (-0.83, 0.23)</td>
<td>-0.01 (-0.04, 0.38)</td>
<td>0.14</td>
<td>0.83</td>
</tr>
<tr>
<td>Fasting (mmol/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>-0.18 (-0.37, 0.01)</td>
<td>-0.19 (-0.4, 0.01)</td>
<td>-0.10 (-0.30, 0.49)</td>
<td>0.04</td>
<td>0.85</td>
</tr>
<tr>
<td>Serum Insulin</td>
<td>0.69 (-0.64, 2.02)</td>
<td>0.59 (-0.84, 2.02)</td>
<td>0.39 (-0.01, 0.79)</td>
<td>0.29</td>
<td>0.13</td>
</tr>
<tr>
<td>Fasting (mU/L)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA2-Beta</td>
<td>0.03 (-0.03, 0.09)</td>
<td>0.07 (-0.04, 0.18)</td>
<td>-0.21 (-0.60, 0.19)</td>
<td>0.17</td>
<td>0.99</td>
</tr>
<tr>
<td>Cell Function (%Beta)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOMA2-IR</td>
<td>-0.15 (-0.40, 0.10)</td>
<td>-0.10 (-0.43, 0.23)</td>
<td>-0.10 (-0.50, 0.29)</td>
<td>0.15</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Non-normally distributed data were log-transformed before use with parametric statistics.

Calculations of effect size were adjusted via Hedges’ bias-corrected effect size for small sample sizes. Ninety-five percent confidence intervals (CIs) for the relative ES were calculated.

Effect Size = (Δ Treatment – Δ Control) / Pooled (Treatment + Control) Baseline.
16 participants were excluded from HOMA2-IR analyses due to insulin therapy.

\[ a \] P<0.05; significant differences between baseline and 6 months in the POWER group, \[ b \] P<0.05; significant differences between baseline and 12 months in the POWER group, \[ c \] P<0.05; significant differences between 6 months and 12 months in the POWER group, \[ d \] P<0.05; significant differences between baseline and 6 months in the SHAM group, \[ e \] P<0.05; significant differences between baseline and 12 months in the SHAM group, \[ f \] P<0.05; significant differences between 6 months and 12 months in the SHAM group, \[ g \] P<0.05; significant differences between the POWER and SHAM groups at 6 months, \[ h \] P<0.05; significant differences between the POWER AND SHAM groups at 12 months.

ES: Effect Size

HOMA 2-IR: Homeostatic Model of Assessment 2

POWER: power training group

SHAM: Control group

IR: Insulin resistance

HbA1c: Glycosylated hemoglobin

CI: Confidence interval

T: Time

G×T: Group and time interaction
# TABLE 6.4 COMPARISON OF PHYSICAL PERFORMANCE BETWEEN POWER AND SHAM GROUPS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mean Difference (95% CI) between baseline and 6 months</th>
<th>Mean Difference (95% CI) between baseline and 12 months</th>
<th>Relative ES (95% CIs)</th>
<th>T</th>
<th>T×G</th>
<th>p value</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>POWER (n=47)</td>
<td>SHAM (n=53)</td>
<td>POWER (n=47)</td>
<td>SHAM (n=53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Physical Function and Exercise Capacity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total Muscle strength (N)</td>
<td>536.5 (105.2, 967.8) 43 (-251.2, 337.2)</td>
<td>860.5 (413.8, 1307.2) 18.4 (-277.8, 314.5)</td>
<td>0.62 (0.20, 1.03)</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
<td>0.000</td>
</tr>
<tr>
<td>Total Muscle Power (W)</td>
<td>216.6 (-103.4, 536.6) -112.7 (-437.4212.0)</td>
<td>205.3 (-516, 6106.0) -207.3 (-134.0, 548.7)</td>
<td>0.44 (-0.01, 0.90)</td>
<td>0.74</td>
<td>0.11</td>
<td>0.06</td>
<td>0.33</td>
</tr>
<tr>
<td>Statics Balance (sec)</td>
<td>0.01 (-0.02, 0.03)</td>
<td>0.00 (-0.00, 0.02)</td>
<td>0.01 (-0.02, 0.00)</td>
<td>0.05</td>
<td>0.06</td>
<td>0.06</td>
<td>0.33</td>
</tr>
<tr>
<td>Habitual Gait Speed</td>
<td>0.10 (0.02, 0.17)</td>
<td>0.04 (-0.01, 0.09)</td>
<td>0.10 (0.02, 0.18)</td>
<td>0.07</td>
<td>0.28</td>
<td>0.000</td>
<td>0.28</td>
</tr>
<tr>
<td>(m/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximal Gait Speed</td>
<td>0.08 (-0.04, 0.19)</td>
<td>0.10 (0.01, 0.20)</td>
<td>0.11 (-0.03, 0.20)</td>
<td>0.15</td>
<td>-0.13</td>
<td>0.000</td>
<td>0.86</td>
</tr>
<tr>
<td>(m/sec)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stair Climb Power (w)</td>
<td>-25.52 (-52.38, 1.35) -35.81 (-60.18, -11.44) -24.43 (-48.39,-0.48) -30.01 (-55.52,-4.51)</td>
<td>0.47 (0.07, 0.87)</td>
<td>0.000</td>
<td>0.79</td>
<td>0.000</td>
<td>0.79</td>
<td>0.000</td>
</tr>
<tr>
<td>Chair Stand (sec)</td>
<td>-2.32 (-4.27, -0.37) -1.54 (-3.08,-0.01)</td>
<td>-0.79 (-1.66, 0.09)</td>
<td>-0.63 (-1.50, 0.25)</td>
<td>-0.04</td>
<td>0.000</td>
<td>0.000</td>
<td>0.73</td>
</tr>
<tr>
<td>Six Minute Walk</td>
<td>6.94 (-25.62, -11.75) -9.56 (-25.22, 6.10)</td>
<td>-13.57 (-13.74, 8.60)</td>
<td>0.58 (-17.86, 19.03)</td>
<td>-0.05</td>
<td>0.01</td>
<td>0.01</td>
<td>0.28</td>
</tr>
<tr>
<td>Distance (m)</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Normally distributed data presented as mean ± SD. Non-normally distributed data were log-transformed before use with parametric statistics. Calculations of effect size were adjusted via Hedges’ bias-corrected effect size for small sample sizes. Ninety-five percent confidence intervals (CIs) for the relative ES were calculated. Effect Size = (Δ Treatment – Δ Control) / Pooled (Treatment + Control) Baseline.

\(^a\) P<0.05; significant differences between baseline and 6 months in the POWER group, \(^b\) p<0.05; significant differences between baseline and 12 months in the POWER group, \(^c\) P<0.05; significant differences between 6 months and 12 months in the POWER group, \(^d\) P<0.05; significant differences between baseline and 6 months in the SHAM group, \(^e\) p<0.05; significant differences between baseline and 12 months in the SHAM group, \(^f\) P<0.05; significant differences between 6 months and 12 months in the SHAM group, \(^g\) P<0.05; significant differences between the POWER and SHAM groups at 6 months, \(^h\) p<0.05; significant differences between the POWER and SHAM groups at 12 months.

ES: Effect Size

POWER: power training group

SHAM: Control group

CI: Confidence interval

T: Time

G×T: Group and time interaction

m: meter
Sec: second
### TABLE 6.5 COMPARISON OF BODY COMPOSITION BETWEEN POWER AND SHAM GROUPS

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mean Difference (95% CI) between baseline and 6 months</th>
<th>Mean Difference (95% CI) between baseline and 12 months</th>
<th>Relative ES (95% CIs)</th>
<th>T</th>
<th>T×G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POWER (n=47)</td>
<td>SHAM (n=53)</td>
<td>POWER (n=47)</td>
<td>SHAM (n=53)</td>
<td></td>
</tr>
<tr>
<td>Overall Body Composition</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body Mass Index (kg/m²)</td>
<td>-0.37 (-1.66, 0.92)</td>
<td>-0.05 (-1.06, 1.16)</td>
<td>-1.26 (-3.03, 0.51)</td>
<td>-0.76 (-2.26, 0.75)</td>
<td>-0.06 (-0.42, 0.36)</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Waist Circumference (cm) (ISAK)</td>
<td>-1.68 (08.16, 5.25)</td>
<td>-1.94 (-5.96, 5.57)</td>
<td>-7.06 (-15.25, 1.13)</td>
<td>-4.41 (-11.25, 2.63)</td>
<td>-0.15 (-0.54, 0.25)</td>
</tr>
<tr>
<td>Body Weight (kg)</td>
<td>-0.90 (-1.98, 0.18)</td>
<td>0.10 (-3.00, 3.20)</td>
<td>-1.062 (-2.63, 0.51)</td>
<td>-2.12 (6.40, 2.20)</td>
<td>-0.08 (-0.48, 0.31)</td>
</tr>
<tr>
<td>Skeletal Muscle Mass (kg)</td>
<td>0.10 (-4.02, 0.59)</td>
<td>0.17 (-3.36, 0.667)</td>
<td>0.23 (-0.28, 0.73)</td>
<td>0.18 (-0.35, 0.72)</td>
<td>0.00 (-0.39, 0.39)</td>
</tr>
<tr>
<td>Free Fat Mass (kg)</td>
<td>0.14 (-0.68, 0.96)</td>
<td>0.27 (-0.58, 1.13)</td>
<td>0.42 (-0.52, 1.35)</td>
<td>0.27 (-0.68, 1.1)</td>
<td>0.02 (-0.38, 0.41)</td>
</tr>
<tr>
<td>Total Fat Mass (kg)</td>
<td>-1.03 (-2.23, 0.16)</td>
<td>-0.00 (-0.89, 0.88)</td>
<td>1.33 (2.78, 0.12)</td>
<td>-0.00 (-0.00, 0.01)</td>
<td>-0.07 (-0.46, 0.32)</td>
</tr>
<tr>
<td>% Muscle</td>
<td>0.14 (-0.01, 0.029)</td>
<td>-0.00 (-0.006, 0.006)</td>
<td>0.01 (-0.01, 0.03)</td>
<td>-0.01 (-0.01, 0.03)</td>
<td>0.21 (-0.18, 0.61)</td>
</tr>
</tbody>
</table>

a: p < 0.01, *p* < 0.05, b: 0.01 < p < 0.05
TABLE 6.5 COMPARISON OF BODY COMPOSITION BETWEEN POWER AND SHAM GROUPS-CONTINUED

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mean Difference (95% CI) between baseline and 6 months</th>
<th>Mean Difference (95% CI) between baseline and 12 months</th>
<th>Relative ES(95% CIs)</th>
<th>T</th>
<th>T×G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POWER (n=47) SHAM (n=53)</td>
<td>POWER (n=47) SHAM (n=53)</td>
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<tr>
<td></td>
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</tr>
<tr>
<td>Regional Body Composition</td>
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<td></td>
</tr>
<tr>
<td>Total Abdominal</td>
<td>-30.86 (-46.95, -14.77)</td>
<td>-5.48 (-24.25, 13.38)</td>
<td>-24.66 (-46.43, -2.89)</td>
<td>-7.60 (-24.60, 9.40)</td>
<td>-0.15 (-0.55, 0.25)</td>
</tr>
<tr>
<td>Visceral Adipose Tissue (cm²)</td>
<td>-17.26 (-29.33, -5.19)</td>
<td>-1.31 (-13.98, 11.36)</td>
<td>-13.18 (-29.05, 2.68)</td>
<td>-1.50 (-13.41, 10.41)</td>
<td>-0.02 (-0.41, 0.37)</td>
</tr>
<tr>
<td>Subcutaneous Abdominal Tissue</td>
<td>-13.53 (-24.84, -2.12)</td>
<td>-2.97 (-12.78, 6.34)</td>
<td>-11.24 (25.02, 2.55)</td>
<td>-4.39 (-14.42, 5.64)</td>
<td>-0.08 (-0.47, 0.31)</td>
</tr>
<tr>
<td>Sagittal Abdominal Tissue (cm²)</td>
<td>-0.05 (-0.82, 0.72)</td>
<td>-0.71 (-1.28, -0.14)</td>
<td>-0.12 (-0.84, 0.60)</td>
<td>-0.53 (-1.17, 0.11)</td>
<td>-0.11 (-0.50, 0.28)</td>
</tr>
<tr>
<td>Diameter (cm)</td>
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</tr>
<tr>
<td>Thigh Muscle Area</td>
<td>5.33 (1.22, 9.44)</td>
<td>1.57 (-3.00, 6.14)</td>
<td>5.32 (1.57, 9.28)</td>
<td>-3.37 (-3.70, 2.96)</td>
<td>0.41 (0.02, 0.80)</td>
</tr>
</tbody>
</table>

<sup>a</sup> p < 0.05, <sup>b</sup> p ≤ 0.01, <sup>c</sup> p < 0.001
TABLE 6.5 COMPARISON OF BODY COMPOSITION BETWEEN POWER AND SHAM GROUPS-CONTINUED

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mean Difference (95% CI) between baseline and 6 months</th>
<th>Mean Difference (95% CI) between baseline and 12 months</th>
<th>Relative ES (95% CIs)</th>
<th>T</th>
<th>T×G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POWER (n=47) SHAM (n=53)</td>
<td>POWER (n=47) SHAM (n=53)</td>
<td></td>
<td>p value</td>
<td>p value</td>
</tr>
<tr>
<td>Subcutaneous Thigh</td>
<td>-1.84 (-5.00, 1.31) 1.56 (-3.66, 6.77)</td>
<td>0.82 (-5.27, 3.63) -3.18 (-8.10, 1.73)</td>
<td>0.05 (-0.34, 0.44)</td>
<td>0.23</td>
<td>0.10</td>
</tr>
<tr>
<td>Adipose Tissue (cm²)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Intermuscular Thigh</td>
<td>-0.12 (-1.34, 1.10) 1.07 (-2.64, 4.77)</td>
<td>0.09 (-1.62, 1.80) 2.52 (-1.80, 6.84)</td>
<td>-0.60 (-1.54, 0.33)</td>
<td>0.64</td>
<td>0.36</td>
</tr>
<tr>
<td>Adipose Tissue (cm²)</td>
<td>-0.86 (-1.41, -0.30) -0.99 (-1.49, -0.48)</td>
<td>-1.34 (-2.05, -0.63) -1.10 (-1.76, -0.44)</td>
<td>0.08 (-0.31, 0.48)</td>
<td>0.00&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.51</td>
</tr>
<tr>
<td>Thigh Muscle Density</td>
<td>-0.86 (-1.41, -0.30) -0.99 (-1.49, -0.48)</td>
<td>-1.34 (-2.05, -0.63) -1.10 (-1.76, -0.44)</td>
<td>0.08 (-0.31, 0.48)</td>
<td>0.00&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.51</td>
</tr>
</tbody>
</table>

Normally distributed data presented as mean ± SD. Non-normally distributed data were log-transformed before use with parametric statistics. Calculations of effect size were adjusted via Hedges’ bias-corrected effect size for small sample sizes. Ninety-five percent confidence intervals (CIs) for the relative ES were calculated. Effect Size = (Δ Treatment – Δ Control) / Pooled (Treatment + Control) Baseline.

<sup>a</sup>P<0.05; significant differences between baseline and 6 months in the POWER group, <sup>b</sup>P<0.05; significant differences between baseline and 12 months in the POWER group, <sup>c</sup>P<0.05; significant differences between 6 months and 12 months in the POWER group, <sup>d</sup>P<0.05;
significant differences between baseline and 6 months in the SHAM group, $^c$ P<0.05; significant differences between baseline and 12 months in the SHAM group, $^f$ P<0.05; significant differences between 6 months and 12 months in the SHAM group, $^g$ P<0.05; significant differences between the POWER and SHAM groups at 6 months, $^h$ P<0.05; significant differences between the POWER and SHAM groups at 12 months.

ES: Effect Size

POWR: power training

SHAM: Control group

SD: Standard deviation

CIs: Confidence interval

T: Time

G×T: Group and time interaction
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mean Difference (95% CI) between baseline and 6 months</th>
<th>Mean Difference (95% CI) between baseline and 12 months</th>
<th>Relative ES (95% CIs)</th>
<th>T</th>
<th>T×G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POWER (n=47) SHAM (n=53)</td>
<td>POWER (n=47) SHAM (n=53)</td>
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<tr>
<td>Quality of Life</td>
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<tr>
<td>SF-36 Physical</td>
<td>-1.21 (-3.78, 1.36)</td>
<td>2.44 (-0.68, 5.57)</td>
<td>-2.37 (-5.29, 3.87)</td>
<td>1.18</td>
<td>-0.44 (-0.83, -0.04)</td>
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<td>0.39</td>
<td>0.06</td>
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<tr>
<td>Component Summary (score)</td>
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<tr>
<td>SF-36 Mental</td>
<td>2.98 (-0.07, 6.03)</td>
<td>0.92 (-2.80, 4.62)</td>
<td>3.45 (-0.15, 7.05)</td>
<td>0.72</td>
<td>0.30 (-0.10, 0.69)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.10</td>
<td>0.41</td>
</tr>
<tr>
<td>Psychosocial Status</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Geriatric Depression</td>
<td>-1.45 (-2.85, 0.006)</td>
<td>-1.60 (-2.78, -0.42)</td>
<td>-1.28 (-2.76, 0.19)</td>
<td>-1.11</td>
<td>-0.06 (-0.45, 0.34)</td>
</tr>
<tr>
<td>Scale (0/30)</td>
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<td></td>
<td></td>
<td>0.00a, d, e</td>
<td>0.88</td>
</tr>
<tr>
<td>Physical Activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Activity Scale</td>
<td>5.50 (-13.46, 24.46)</td>
<td>-4.48 (-28.93, 19.24)</td>
<td>9.95 (-33.91, 14.02)</td>
<td>1.06</td>
<td>-0.06 (-0.46, 0.33)</td>
</tr>
<tr>
<td>For the Elderly (score)</td>
<td></td>
<td></td>
<td></td>
<td>0.72</td>
<td>0.30</td>
</tr>
</tbody>
</table>
Normally distributed data presented as mean ± SD. Non-normally distributed data were log-transformed before use with parametric statistics. Calculations of effect size were adjusted via Hedges’ bias-corrected effect size for small sample sizes.\(^6\) Ninety-five percent confidence intervals (CIs) for the relative ES were calculated. Effect Size = (Δ Treatment – Δ Control) / Pooled (Treatment + Control) Baseline.

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ES: Effect Size

POWR: power training

SHAM: Control group

SF-36: Short Form-36

SD: Standard deviation,

CI: Confidence interval

T: Time
GxT: Group and time interaction
Table 6.7 Comparison of Adipokines and Systematic Marker Between Power and Sham Groups

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Mean Difference (95% CI) between baseline and 6 months</th>
<th>Mean Difference (95% CI) between baseline and 12 months</th>
<th>Relative ES (95% CIs)</th>
<th>T</th>
<th>T x G</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>POWER (n=47)</td>
<td>SHAM (n=53)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C – Reactive Protein (mg/L)</td>
<td>0.22 (-0.78, 1.22)</td>
<td>-0.64 (-1.66, 0.38)</td>
<td>-0.01 (-1.18, 0.98)</td>
<td>-1.08 (-1.89, -0.26)</td>
<td>0.28 (-0.11, 0.68)</td>
</tr>
<tr>
<td>Serum HMW (ng/ml)</td>
<td>-1104.541</td>
<td>9.77</td>
<td>-370.72</td>
<td>-239.14</td>
<td>-0.01 (-0.41, 0.38)</td>
</tr>
<tr>
<td>Adiponectin (mg/ml)</td>
<td>-3575.63, 1366.55</td>
<td>(-1955.57, 1995.12)</td>
<td>(-3713.09, -2971.65)</td>
<td>(-2709.40, 2231.11)</td>
<td></td>
</tr>
<tr>
<td>Serum Total Adiponectin (ng/ml)</td>
<td>551.96</td>
<td>273.85</td>
<td>241.64</td>
<td>-382.70</td>
<td>0.07 (-0.32, 0.47)</td>
</tr>
<tr>
<td></td>
<td>(-2032.59, 3136.50)</td>
<td>(-796.37, 1344.06)</td>
<td>(-3095.48, 3578.76)</td>
<td>(-1690.29, 1924.88)</td>
<td></td>
</tr>
<tr>
<td>Serum HMW/Total Adiponectin</td>
<td>0.00 (-0.11, 0.11)</td>
<td>-0.01 (-0.07, 0.05)</td>
<td>-0.02 (-0.08, 0.12)</td>
<td>-0.05 (-0.13, 0.03)</td>
<td>0.02 (-0.37, 0.42)</td>
</tr>
</tbody>
</table>

Normally distributed data presented as mean ± SD. Non-normally distributed data were log-transformed before use with parametric statistics. Calculations of effect size were adjusted via Hedges’ bias-corrected effect size for small sample sizes. Ninety-five percent confidence intervals (CIs) for the relative ES were calculated.
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ES: Effect Size

POWR: power training

SHAM: Control group

CRP: C-reactive protein

HMW: High-Molecular-Weight

SD: Standard deviation,

CIs: Confidence interval

T: Time

G×T: Group and time interaction
<table>
<thead>
<tr>
<th>Changes in Body Composition Variable</th>
<th>Changes in Body Composition Variable</th>
<th>n</th>
<th>Standard Coefficient $\beta$</th>
<th>p</th>
<th>n</th>
<th>Standard Coefficient $\beta$</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Abdominal Adipose</td>
<td>Visceral Adipose Tissue</td>
<td>37</td>
<td>0.78</td>
<td>&lt;0.0001</td>
<td>43</td>
<td>0.79</td>
<td>&lt;0.0001</td>
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<tr>
<td>Tissue</td>
<td>Subcutaneous Abdominal Adipose</td>
<td>37</td>
<td>0.67</td>
<td>&lt;0.0001</td>
<td>43</td>
<td>0.74</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>Sagittal Abdominal Diameter</td>
<td>37</td>
<td>0.49</td>
<td>0.002</td>
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<td>0.71</td>
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</tr>
<tr>
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<td>Thigh Muscle Area</td>
<td>37</td>
<td>0.26</td>
<td>0.13</td>
<td>42</td>
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<td>0.04</td>
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<tr>
<td></td>
<td>Body Mass Index</td>
<td>36</td>
<td>0.77</td>
<td>&lt;0.0001</td>
<td>43</td>
<td>0.67</td>
<td>&lt;0.0001</td>
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<tr>
<td></td>
<td>Body Weight</td>
<td>36</td>
<td>0.78</td>
<td>&lt;0.0001</td>
<td>43</td>
<td>0.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Skeletal Muscular Mass</td>
<td>36</td>
<td>0.11</td>
<td>0.54</td>
<td>42</td>
<td>0.36</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Total Fat Mass</td>
<td>36</td>
<td>0.74</td>
<td>&lt;0.0001</td>
<td>42</td>
<td>0.44</td>
<td>0.004</td>
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<tr>
<td>Visceral Adipose Tissue</td>
<td>Subcutaneous Abdominal</td>
<td>37</td>
<td>0.06</td>
<td>0.73</td>
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<td>0.17</td>
<td>0.27</td>
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<tr>
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<td>43</td>
<td>0.59</td>
<td>&lt;0.0001</td>
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<tr>
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<tr>
<td>Changes in Body Composition Variable</td>
<td>Changes in Body Composition Variable</td>
<td>POWER Group</td>
<td>SHAM Group</td>
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<tr>
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<tr>
<td>Visceral Adipose Tissue</td>
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<td>36</td>
<td>0.71</td>
<td>&lt;0.0001</td>
<td>45</td>
<td>0.50</td>
<td>0.0005</td>
</tr>
<tr>
<td></td>
<td>Body Weight</td>
<td>36</td>
<td>0.78</td>
<td>&lt;0.0001</td>
<td>45</td>
<td>0.67</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td></td>
<td>Skeletal Muscular Mass</td>
<td>36</td>
<td>0.11</td>
<td>0.54</td>
<td>44</td>
<td>0.36</td>
<td>0.02</td>
</tr>
<tr>
<td></td>
<td>Total Fat Mass</td>
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## TABLE 6.8 RELATIONSHIPS BETWEEN CHANGES IN BODY COMPOSITION VARIABLE - CONTINUED

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β coefficient represents the correlation.
### TABLE 6.9 RELATIONSHIPS BETWEEN CHANGE IN METABOLISM AND CHANGE IN COGNITION

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<th>Changes in Cognitive Scores</th>
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<th>SHAM Group</th>
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<td>3MS</td>
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<td>HbA1c (%)</td>
<td>Word List Memory</td>
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<td>Word List Recall</td>
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### TABLE 6.9 RELATIONSHIPS BETWEEN CHANGE IN METABOLISM AND CHANGE IN COGNITION – CONTINUED

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<td>Word List Recall</td>
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<tr>
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β coefficient represents the correlation.

For Word List memory, Word List Recall, 3MS, a negative change value represents a worsening score (worse function).

For the Trail Making Test A, Trail Making Test B, and DIFFBA, a positive change value represents a worsening score (worse function).
Difference scores calculated (DIFFBA) as Trail Making Test B minus Trail Making Test A, a positive change value represents a worsening score (worse function).

Models are adjusted for age, gender, years of education, duration of diabetes, SF-36 Mental Component Summary, HbA1c, and cognitive score.

3MS: Modified Mini-mental State Examination
### TABLE 6.10 RELATIONSHIPS BETWEEN CHANGE IN PHYSICAL PERFORMANCE AND CHANGE IN COGNITION

<table>
<thead>
<tr>
<th>Changes in Physical Function Exercise Capacity</th>
<th>Changes in Cognitive Scores</th>
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<th>SHAM Group</th>
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### Table 6.10 Relationships between Change in Physical Performance and Change in Cognition - Continued

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### Table 6.10 Relationships between Change in Physical Performance and Change in Cognition - Continued

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</table>

β coefficient represents the correlation.

Models are adjusted for age, gender, years of education, duration of diabetes, SF-36 Mental Component Summary, HbA1c, and cognitive score.

For Word List memory, Word List Recall, 3MS, a negative change value represents a worsening score (worse function).

For the Trail Making Test A, Trail Making Test B, and DIFFBA, a positive change value represents a worsening score (worse function).

Difference scores calculated (DIFFBA) as Trail Making Test B minus Trail Making Test A, a positive change value represents a worsening score (worse function).

3MS: Modified Mini-mental State Examination
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TABLE 6.11 RELATIONSHIPS BETWEEN CHANGE IN BODY COMPOSITION AND CHANGE IN COGNITION – CONTINUED

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<tr>
<td>DIFFBA</td>
<td>36</td>
<td>-0.05</td>
<td>0.71</td>
<td>42</td>
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<td>3MS</td>
<td>36</td>
<td>-0.05</td>
<td>0.71</td>
<td>42</td>
<td>0.17</td>
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</tbody>
</table>

β coefficient represents the correlation.

For Word List memory, Word List Recall, 3MS, a negative change value represents a worsening score (worse function).

For the Trail Making Test A, Trail Making Test B, and DIFFBA, a positive change value represents a worsening score (worse function).

Difference scores calculated (DIFFBA) as Trail Making Test B minus Trail Making Test A, a positive change value represents a worsening score (worse function).

Models are adjusted for age, gender, years of education, duration of diabetes, SF-36 Mental Component Summary, HbA1c, and cognitive score.

3MS: Modified Mini-mental State Examination
### TABLE 6.12 RELATIONSHIPS BETWEEN CHANGE IN PSYCHOSOCIAL STATUS, QUALITY OF LIFE, AND PHYSICAL ACTIVITY CHANG IN COGNITION

<table>
<thead>
<tr>
<th>Changes in Psychosocial Status, Quality of Life and Habitudinal Physical Activity</th>
<th>Changes in Cognitive Scores</th>
<th>POWER Group</th>
<th>SHAM Group</th>
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<tbody>
<tr>
<td></td>
<td>n</td>
<td>Standard Coefficient β</td>
<td>p</td>
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<td>Word List Memory</td>
<td>377</td>
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</tr>
<tr>
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<td>Scales SF-36® (score)</td>
<td>Word List Recall</td>
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<tr>
<td></td>
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<td>for The Elderly (score)</td>
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<td>DIFFBA</td>
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</tr>
<tr>
<td></td>
<td>3MS</td>
<td>28</td>
<td>0.36</td>
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<tr>
<td>Geriatric Depression Scale (/30)</td>
<td>Word List Memory</td>
<td>36</td>
<td>-0.33</td>
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<td></td>
<td>Word List Recall</td>
<td>36</td>
<td>&lt;0.01</td>
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<tr>
<td></td>
<td>Word List Recognition</td>
<td>36</td>
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**TABLE 6.12 RELATIONSHIPS BETWEEN CHANGE IN PSYCHOSOCIAL STATUS, QUALITY OF LIFE, AND PHYSICAL ACTIVITY CHANGE IN COGNITION**

<table>
<thead>
<tr>
<th>Changes in Psychosocial Status, Quality of Life and Habitudinal Physical Activity</th>
<th>Changes in Cognitive Scores</th>
<th></th>
<th>POWER Group</th>
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<tr>
<td></td>
<td></td>
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<td>p</td>
<td>n</td>
<td>Standard Coefficient β</td>
<td>p</td>
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<td>0.59</td>
<td>45</td>
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<td>Scale (/30)</td>
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<td>0.43</td>
<td>46</td>
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β coefficient represents the correlation.

For Word List memory, Word List Recall, 3MS, a negative change value represents a worsening score (worse function).

For the Trail Making Test A, Trail Making Test B, and DIFFBA, a positive change value represents a worsening score (worse function).

Difference scores calculated (DIFFBA) as Trail Making Test B minus Trail Making Test A, a positive change value represents a worsening score (worse function).

Models are adjusted for age, gender, years of education, duration of diabetes, SF-36 Mental Component Summary, HbA1c, and cognitive score.

3MS: Modified Mini-mental State Examination
<table>
<thead>
<tr>
<th>Changes in Inflammation and Adiponectin</th>
<th>Changes in Cognitive Scores</th>
<th>POWER Group</th>
<th>SHAM Group</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Standard Coefficient β</td>
<td>p</td>
</tr>
<tr>
<td>C-reactive Protein (mg/L)</td>
<td>Word List Memory</td>
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<td>0.23</td>
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<td>Worse Word List Recognition</td>
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<td>DIFFBA</td>
<td>29</td>
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<td>3MS</td>
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<td>-0.16</td>
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<tr>
<td>Serum High Molecule</td>
<td>Word List Memory</td>
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<td>-0.31</td>
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<tr>
<td>Weight Adiponectin (ng/ml)</td>
<td>Word List Recall</td>
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<td>Better Trail Making Test B</td>
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TABLE 6.13 RELATIONSHIPS BETWEEN CHANGE IN INFLAMMATION AND ADIPOKINES AND CHANGE IN COGNITION – CONTINUED

<table>
<thead>
<tr>
<th>Changes in Inflammation and Adiponectin</th>
<th>Changes in Cognitive Scores</th>
<th>POWER Group</th>
<th>SHAM Group</th>
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<tr>
<td></td>
<td></td>
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<td>-0.14</td>
</tr>
<tr>
<td>Weight Adiponectin (ng/ml)</td>
<td>3MS</td>
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<td>-0.24</td>
</tr>
<tr>
<td>Serum Total Adiponectin (ng/ml)</td>
<td>Word List Memory</td>
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<td>Word List Recall</td>
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<td>Word List Recognition</td>
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<td></td>
<td>Trail Making Test A</td>
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<td>-0.49</td>
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<td>Trail Making Test B</td>
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<td>DIFFBA</td>
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<td>0.37</td>
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<td>Better 3MS</td>
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<td>Serum High-Molecular Weight/Total Adiponectin Ratio</td>
<td>Word List Memory</td>
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<td>Word List Recall</td>
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<td>0.20</td>
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<tr>
<td></td>
<td>Word List Recognition</td>
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<td>-0.24</td>
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<tr>
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<td>Trail Making Test A</td>
<td>17</td>
<td>0.05</td>
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</table>
### TABLE 6.13 RELATIONSHIPS BETWEEN CHANGE IN INFLAMMATION AND ADIPOKINES AND CHANGE IN COGNITION – CONTINUED

<table>
<thead>
<tr>
<th>Changes in Inflammation and Adiponectin</th>
<th>Changes in Cognitive Scores</th>
<th>POWER Group</th>
<th>SHAM Group</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Standard Coefficient β</td>
<td>p</td>
</tr>
<tr>
<td>Serum High-Molecular Weight/Total Adiponectin Ratio</td>
<td>17</td>
<td>-0.20</td>
<td>0.53</td>
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<td>DIFFBA</td>
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<tr>
<td>3MS</td>
<td>17</td>
<td>-0.24</td>
<td>0.28</td>
</tr>
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</table>

β coefficient represents the correlation.

For Word List memory, Word List Recall, 3MS, a negative change value represents a worsening score (worse function).

For the Trail Making Test A, Trail Making Test B, and DIFFBA, a positive change value represents a worsening score (worse function).

*Difference scores calculated (DIFFBA) as Trail Making Test B minus Trail Making Test A, a positive change value represents a worsening score (worse function).

Models are adjusted for age, gender, years of education, duration of diabetes, SF-36 Mental Component Summary, HbA1c, and cognitive score.

3MS: Modified Mini-mental State Examination
FIGURE LEGENDS

Figure 6.1: Consort Flow Diagram

n=sample size

Figure 6.2-6.8: Changes in the Word List Memory, Word List Recall, Word List Recognition, Trail Making Test A, Trail Making Test B, DIFFBA (Difference score between Trail Making Test B minus Trail Making Test A), and Modified Mini-mental State Examination (3MS) score

Figures showed change in the Word List Memory, Word List Recall, Word List Recognition, Trail Making Test A, Trail Making Test B, DIFFBA (Difference score between Trail Making Test B minus Trail Making Test A), and 3MS scores at baseline, 6 month, and 12 month intervention. Blue and red lines indicate the PRT and SHAM groups, respectively. Group mean and standard difference are shown in older adults with T2DM. Models are adjusted for age, gender, years of education, duration of diabetes, SF-36 Mental Component Summary, HbA1c, and cognitive score

Figure 6.9 Changes in HOMA 2-IR vs Change in 3MS (score)

Figure 6.9.1 Change in HOMA 2-IR vs Change in 3MS (score) in the POWER group
Figure 6.9.2 Change in HOMA 2-IR vs Change in 3MS (score) in the SHAM group

Figure 6.10 Change in Total Static Balance (sec) vs Change in 3MS (score)

Figure 6.10.1 Change in Total Static Balance (sec) vs Change in 3MS (score) in the POWER group

Figure 6.10.2 Change in Total Static Balance (sec) vs Change in 3MS (score) in the SHAM group

Figure 6.11 Change in Chair Stand (sec) vs Change in Word List Recognition (score)

Figure 6.11.1 Change in Chair Stand (sec) vs Change in Word List Recognition (score) in the POWER group

Figure 6.11.2 Change in Chair Stand (sec) vs Change in Word List Recognition (score) in the SHAM group

Figure 6.12 Change in Skeletal Muscle Mass (kg) vs Change in Word List Memory (score)

Figure 6.12.1 Change in Skeletal Muscle Mass (kg) vs Change in Word List Memory (score) in the POWER group

Figure 6.12.2 Change in Skeletal Muscle Mass (kg) vs Change in Word List Memory (score) in the SHAM group

Figure 6.13 Change in Thigh Muscle Area (cm²) vs Change in Trail Making Test A (score)

Figure 6.13.1 Change in Thigh Muscle Area (cm²) vs Change in Trail Making Test A (score) in the POWER group
Figure 6.13.2 Change in Thigh Muscle Area (cm²) vs Change in Trail Making Test A (score) in the SHAM group

Figure 6.14 Change in Skeletal Muscle Mass (kg) vs Change in 3MS (score)

Figure 6.14.1 Change in Skeletal Muscle Mass (kg) vs Change in 3MS (score) in the POWER group

Figure 6.14.2 Change in Skeletal Muscle Mass (kg) vs Change in 3MS (score) in the SHAM group

Figure 6.15 Change in Total Abdominal Adipose tissue (cm²) vs Change in Trail Making Test B (score)

Figure 6.15.1 Change in Total Abdominal Adipose Tissue (cm²) vs Change in Trail Making Test B (score) in the POWER group

Figure 6.15.2 Change in Total Abdominal Adipose Tissue (cm²) vs Change in Trail Making Test B (score) in the SHAM group

Figure 6.16 Change in Subcutaneous Adipose Tissue (cm²) vs Change in Word List Recall (score)

Figure 6.16.1 Change in Subcutaneous Adipose Tissue (cm²) vs Change in Word List Recall (score) in the POWER group

Figure 6.16.2 Change in Subcutaneous Adipose Tissue (cm²) vs Change in Word List Recall (score) in the SHAM group

Figure 6.17 Change in Body Mass Index and Change in Word List Recall (score)

Figure 6.17.1 Change in Body Mass Index and Change in Word List Recall (score) in the POWER group
Figure 6.17.2 Change in Body Mass Index and Change in Word List Recall (score) in the SHAM group

Figure 6.18 Change in Body Weight (kg) vs change in Word List Recall (score)

Figure 6.18.1 Change in Body Weight (kg) vs change in Word List Recall (score) in the POWER group

Figure 6.18.2 Change in Body Weight (kg) vs change in Word List Recall (score) in the SHAM group

Figure 6.19 Change in Total Abdominal Adipose Tissue (cm²) vs Change in Word List Memory (score)

6.19.1 Change in Total Abdominal Adipose Tissue (cm²) vs Change in Word List Memory (score) in the POWER group

Figure 6.19.2 Change in Total Abdominal Adipose Tissue (cm²) vs Change in Word List Memory (score) in the SHAM group

Figure 6.20 Change in Visceral Adipose Tissue (cm²) vs Change in Word List Memory (score)

Figure 6.20.1 Change in Visceral Adipose Tissue (cm²) vs Change in Word List Memory (score) in the POWER group

Figure 6.20.2 Change in Visceral Adipose Tissue (cm²) vs Change in Word List Memory (score) in the SHAM group

Figure 6.21 Change in Body Mass Index vs Change in Word List Memory (score)

Figure 6.21.1 Change in Body Mass Index vs Change in Word List Memory (score) in the POWER group
Figure 6.21.2 Change in Body Mass Index vs Change in Word List Memory (score) in the SHAM group

Figure 6.22 Change in Body Weight (kg) vs Change in Word List Memory (score)

Figure 6.22.1 Change in Body Weight (kg) vs Change in Word List Memory (score) in the POWER group

Figure 6.22.2 Change in Body Weight (kg) vs Change in Word List Memory (score) in the SHAM group

Figure 6.23 Change in Total Adiponectin (ng/ml) vs Change in 3MS (score)

Figure 6.23.1 Change in Total Adiponectin (ng/ml) vs Change in 3MS (score) in the POWER group

Figure 6.23.2 Change in Total Adiponectin (ng/ml) vs Change in 3MS (score) in the SHAM group

Figure 6.24 Change in HMW Adiponectin (ng/ml) vs Change in Trail Making Test B (score)

Figure 6.24.1 Change in HMW Adiponectin (ng/ml) vs Change in Trail Making Test B (score) in the POWER group

Figure 6.24.2 Change in HMW Adiponectin (ng/ml) vs Change in Trail Making Test B (score) in the SHAM group

Figure 6.25 Change in HMW Adiponectin (ng/ml) vs Change in Pure Executive Function (difference score between Trail Making Test B minus Trail Making Test A)
Figure 6.25.1 Change in HMW Adiponectin (ng/ml) vs Change in Pure Executive Function (difference score between Trail Making Test B minus Trail Making Test A) in the POWER group

Figure 6.25.2 Change in HMW Adiponectin (ng/ml) vs Change in Pure Executive Function (difference score between Trail Making Test B minus Trail Making Test A) in the SHAM group

Figure 6.26 Change in C-reactive protein (mg/L) vs Change in Word List Recognition (score)

Figure 6.26.1 Change in C-reactive protein (mg/L) vs Change in Word List Recognition (score) in the POWER group

Figure 6.26.2 Change in C-reactive protein (mg/L) vs Change in Word List Recognition (score) in the SHAM group

Figure 6.27 Change in Change in Total Muscle Strength (N) vs Change in Word List Recognition (score)

Figure 6.27.1 Change in Total Muscle Strength (N) vs Change in Trail Making Test A (score) in the POWER group

Figure 6.27.2 Change in Total Muscle Strength (N) vs Change in Trail Making Test A (score) in the SHAM group
FIGURE 6.1 CONSORT FLOW DIAGRAM

Enrolment

Assessed for eligibility

Excluded (n=324)
- Not meeting inclusion criteria (n=285)
- Declined to participate (n=15)
- Other reasons (n=24)

Randomized (n=103)

POWER Group
Allocated to intervention (n=49)
- Withdrew prior to commencing intervention (n=2)
- Received allocated intervention (n=47)

Lost to follow-up (n=10)
Medical (n=2),
Commitment issue (n=1),
Too hard (n=5),
Disinterest (n=1),
Adverse event (n=1)

47 Included in primary analysis

SHAM Group
Allocated to intervention (n=54)
- Withdrew prior to commencing intervention (n=1)
- Received allocated intervention (n=53)

Lost to follow-up (n=4)
Medical, (n=2),
Commitment issue (n=2)
Too hard (n=5),
Disinterest (n=1),
Adverse event (n=1)

Discontinued intervention (n=4)

53 Included in primary analysis

Allocation

Analysis
FIGURE 6.2 CHANGES IN THE WORD LIST MEMORY SCORES OVER 12 MONTHS

Panels showed change in Word List Memory scores at baseline, 6 month, and 12 month intervention. Blue and red lines indicate the POWER and SHAM groups, respectively. Group mean and standard deviation are shown in older adults with T2DM. The linear mixed models revealed significant time effect (p<0.001) only, but not group × time interactions in Word List Memory (p=0.54). I bar note the standard
FIGURE 6.3 CHANGES IN THE WORD LIST RECALL SCORES OVER 12 MONTHS

Panels show change in Word List recall scores at baseline, 6-month, and 12-month intervention. Blue and red lines indicate the POWER and SHAM groups, respectively. Group mean and standard deviation are shown in older adults with T2DM. The linear mixed models revealed significant time effect (p<0.001) only, but not group × time interactions in Word List Recall (p=0.19). I bar note the standard deviation.
FIGURE 6.4 CHANGES IN THE WORD LIST RECOGNITION SCORES OVER 12 MONTHS

Panels showed change in Word List recognition scores at baseline, 6 month, and 12 month intervention. Blue and red lines indicate the POWER and SHAM groups, respectively. Group mean and standard deviation are shown in older adults with T2DM. The linear mixed models revealed insignificant time effect (p=0.75) and group × time interactions in Word List Recognition (p=0.33). I bar note the standard deviation.
FIGURE 6.5 CHANGES IN THE TRIAL MAKING TEST A SCORES OVER 12 MONTHS

Panels showed change in Trial Making Test A scores at baseline, 6 month, and 12 month intervention. Blue and red lines indicate the POWER and SHAM groups, respectively. Group mean and standard deviation are shown in older adults with T2DM. The linear mixed models revealed significant time effect (p<0.001) only, but not group × time interactions in Trail Making Test A (P=0.73). I bar note the standard deviation.
Panels showed change in Trail Making Test B scores at baseline, 6 month, and 12 month intervention. Blue and red lines indicate the POWER and SHAM groups, respectively. Group mean and standard deviation are shown in older adults with T2DM. The linear mixed models revealed significant time effect ($p=0.02$) and group × time interactions in Trail Making Test B ($P=0.03$). I bar note the standard deviation.
DIFFBA; difference scores between Trail Making Test B minus Trail Making Test A.

Panels showed change in DIFFBA scores at baseline, 6 month, and 12 month intervention. Blue and red lines indicate the POWER and SHAM groups, respectively. Group mean and standard deviation are shown in older adults with T2DM. The linear mixed models did not revealed significant group × time interactions in DIFFBA (P=0.83) and significant time effect (p=0.43). I bar note the standard deviation.
FIGURE 6.8 CHANGES IN THE MODIFIED MINI-MENTAL STATE

EXAMINATION SCORES OVER 12 MONTHS

Panels showed change in 3MS scores at baseline, 6 month, and 12 month intervention.

Blue and red lines indicate the POWER and SHAM groups, respectively. Group mean and standard deviation are shown in older adults with T2DM. The linear mixed models revealed significant time effect (p<0.001) and group × time interactions in 3MS (P=0.04). I bar note the standard deviation.
FIGURE 6.9 CHANGE IN HOMA 2 IR VS CHANGE IN MODIFIED MINI-MENTAL STATE EXAMINATION (SCORE)

Figure 6.9.1 Change in HOMA 2 IR vs Change in 3MS (score) in the POWER group

n=32, r =0.08, p=0.64

Figure 6.9.2 Change in HOMA 2 IR vs Change in 3MS (score) in the SHAM group

n=37, r =-0.40, p<0.03
FIGURE 6.10 CHANGE IN TOTAL STATIC BALANCE VS CHANGE IN MODIFIED MINI-MENTAL STATE EXAMINATION (SCORE)

6.10.1 Change in Total Static Balance vs Change in 3MS (score) in the POWER group

n=35, r =0.27, p=0.03

6.10.2 Change in Total Static Balance vs Change in 3MS (score) in the SHAM group

n=46, r =0.02, p=0.89
FIGURE 6.11 CHANGE IN CHAIR STAND (SEC) VS CHANGE IN WORD LIST RECOGNITION (SCORE)

Figure 6.11.1 Change in Chair Stand (sec) vs Change in Word List Recognition (score) in the POWER group

n=30, r =0.16, p=0.53

Figure 6.11.2 Change in Chair Stand (sec) vs Change in Word List Recognition (score) in the SHAM group

n=38, r=0.39, p=0.02
FIGURE 6.12 CHANGE IN SKELETAL MUSCLE MASS VS CHANGE IN WORD LIST MEMORY (SCORE)

Figure 6.12.1 Change in Skeletal Muscle Mass vs Change in Word List Memory (score) in the POWER group

![Graph showing the relationship between change in skeletal muscle mass and change in word list memory (score) in the POWER group.](image)

Figure 6.12.2 Change in Skeletal Muscle Mass vs Change in Word List Memory (score) in the SHAM group

![Graph showing the relationship between change in skeletal muscle mass and change in word list memory (score) in the SHAM group.](image)
FIGURE 6.13 CHANGE IN THIGH MUSCLE AREA VS CHANGE IN TRAIL MAKING TEST A (SCORE)

Figure 6.13.1 Change in Thigh Muscle Area vs Change in Trail Making Test A (score) in the POWER group

![Graph showing the correlation between change in thigh muscle area and change in Trail Making Test A score in the POWER group.]

n=36, r=-0.36, p<0.05

Figure 6.13.2 Change in Thigh Muscle Area vs Change in Trail Making Test A (score) in the SHAM group

![Graph showing the correlation between change in thigh muscle area and change in Trail Making Test A score in the SHAM group.]

n=44, r=-0.07, p=0.72
FIGURE 6.14 CHANGE IN SKELETAL MUSCLE MASS (KG) VS CHANGE IN MODIFIED MINI-MENTAL STATE EXAMINATION (SCORE)

Figure 6.14.1 Change in Skeletal Muscle Mass (kg) vs Change in 3MS (score) in the POWER group

Figure 6.14.2 Change in Skeletal Muscle Mass (kg) vs Change in 3MS score in the SHAM group

n=36, r=-0.06, p=0.65

n=44, r=0.20, p<0.05
FIGURE 6.15 CHANGE IN TOTAL ABDOMINAL ADIPOSE TISSUE (CM²) VS CHANGE IN TRAIL MAKING TEST B (SCORE)

Figure 6.15.1 Change in Total Abdominal Adipose Tissue (cm²) vs Change in Trail Making Test B (score) in the POWER group

Figure 6.15.2 Change in Total Abdominal Adipose Tissue (cm²) vs Change in Trail Making Test B (score) in the SHAM group

n=36, r=-0.40, p=0.04

n=44, r=0.05, p=0.75
FIGURE 6.16 CHANGE IN SUBCUTANEOUS ADIPOSE TISSUE (CM²) VS CHANGE IN WORD LIST RECALL (SCORE)

Figure 6.16.1 Change in Subcutaneous Adipose Tissue (cm²) vs Change in Word List Recall (score) in the POWER group

$$n=37, r=0.39, p=0.03$$

Figure 6.16.2 Change in Subcutaneous Adipose Tissue (cm²) vs Change in Word List Recall (score) in the POWER group

$$n=44, r=0.04, p=0.76$$
FIGURE 6.17 CHANGE IN BODY MASS INDEX VS CHANGE IN WORD LIST RECALL (SCORE)

Figure 6.17.1 Change in Body Mass Index vs Change in Word List Recall (score) in the POWER group

Figure 6.17.2 Change in Body Mass Index vs Change in Word List Recall (score) in the SHAM group
FIGURE 6.18 CHANGE IN BODY WEIGHT (KG) VS CHANGE IN WORD LIST
RECALL (SCORE)

Figure 6.18.1 Change in Body Weight (kg) vs Change in Word List Recall (score) in
POWER group

n=36, r=0.44, p=0.01

Figure 6.18.2 Change in Body Weight (kg) vs Change in Word List Recall (score) in
SHAM group

n=47, r=0.19, p=0.16
FIGURE 6.19 CHANGE IN TOTAL ABDOMINAL ADIPOSE TISSUE (CM$^2$) VS CHANGE IN WORD LIST MEMORY (SCORE)

Figure 6.19.1 Change in Total Abdominal Adipose Tissue (cm$^2$) vs Change in Word List Memory (score) in the POWER group

Figure 6.19.2 Change in Total Abdominal Adipose Tissue (cm$^2$) vs Change in Word List Memory (score) in the SHAM

n=37, r =0.12, p=0.51

n=42, r =0.35, p=0.01
FIGURE 6.20 CHANGE IN VISCERAL ADIPOSE TISSUE (CM²) VS CHANGE IN WORD LIST MEMORY (SCORE)

Figure 6.20.1 Change in Visceral Adipose Tissue (cm²) vs Change in Word List Memory (score) in the POWER group

n=37, r =-0.14, p=0.44

Figure 6.20.2 Change in Visceral Adipose Tissue (cm²) vs Change in Word List Memory (score) in the SHAM group

n=44, r =0.38, p=0.03
FIGURE 6.21 CHANGE IN BODY MASS INDEX (CM$^2$) VS CHANGE IN WORD LIST MEMORY (SCORE)

Figure 6.21.1 Change in Body Mass Index vs Change in Word List Memory (score) in the POWER group

n=36, r =0.11, p=0.56

n=46, r =0.31, p=0.01

Figure 6.21.2 Change in Body Mass Index vs Change in Word List Memory (score) in the SHAM group
FIGURE 6.22 CHANGE IN BODY WEIGHT VS CHANGE IN WORD LIST MEMORY (SCORE)

Figure 6.22.1 Change in Body Weight vs Change in Word List Memory (score) in the POWER

![Graph showing the relationship between change in body weight and change in word list memory (score) in the POWER group.](image)

$n=36$, $r=0.07$, $p=0.72$

Figure 6.22.2 Change in Body Weight vs Change in Word List Memory (score) in the SHAM

![Graph showing the relationship between change in body weight and change in word list memory (score) in the SHAM group.](image)

$n=47$, $r=0.41$, $p=0.01$
FIGURE 6.23 CHANGE IN SERUM TOTAL ADIPONECTIN (NG/ML) VS CHANGE IN MODIFIED MINI-MENTAL STATE EXAMINATION (SCORE)

Figure 6.23.1 Change in Serum Total Adiponectin (ng/ml) vs Change in 3MS (score) in the POWER group

Figure 6.23.2 Change in Serum Total Adiponectin (ng/ml) vs Change in 3MS (score) in the SHAM group

n=17, r=0.57, p=0.03

n=16, r=-0.10, p=0.59
FIGURE 6.24 CHANGE IN SERUM HMW ADIPONECTIN (NG/ML) VS CHANGE IN TRAIL MAKING TEST B (SCORE)

Figure 6.24.1 Change in Serum HMW Adiponectin (ng/ml) vs Change in Trail Making Test B (score) in the POWER group

Figure 6.24.2 Change in Serum HMW Adiponectin (ng/ml) vs Change in Trail Making Test B (score) in the SHAM group
**FIGURE 6.25 CHANGE IN SERUM HMW ADIPONECTIN (NG/ML) VS CHANGE IN PURE EXECUTIVE FUNCTION (DIFFERENCE SCORE BETWEEN TRAIL MAKING TEST B MINUS TRAIL MAKING TEST A)**

Figure 6.25.1 Change in Serum HMW adiponectin (ng/ml) vs Change in Pure Executive Function in the POWER group (Difference score between Trail Making Test B minus Trail Making Test A)

Figure 6.25.2 Change in Serum HMW Adiponectin (ng/ml) vs Change in Pure Executive Function in the SHAM group (Difference score between Trail Making Test B minus Trail Making Test A)
FIGURE 6.26 CHANGE IN SERUM HMW ADIPONECTIN/TOTAL ADIPONECTIN RATIO VS CHANGE IN WORD LIST MEMORY (SCORE)

Figure 6.26.1 Change in Serum HMW Adiponectin / Total Adiponectin Ratio vs Change in Word List Memory (score) in the POWER group

Figure 6.26.2 Change in Serum HMW Adiponectin / Total Adiponectin Ratio vs Change in Word List Memory (score) in the SHAM group

n=16, r=-0.66, p=0.41

n=16, r=-0.96, p=0.01
FIGURE 6.27 CHANGE IN C-REACTIVE PROTEIN (MG/L) VS CHANGE IN WORD LIST RECOGNITION (SCORE)

Figure 6.27.1 Change in C-reactive protein (mg/L) vs Change in Word List Recognition (score) in the POWER group

n=29, r=0.17, p=0.51

Figure 6.27.2 Change in C-reactive protein (mg/L) vs Change in Word List Recognition (score)

n=36, r=-0.35, p=0.02
FIGURE 6.28 CHANGE IN TOTAL MUSCLE STRENGTH (N) VS CHANGE IN TRAIL MAKING TEST A (SCORE)

Figure 6.28.1 Change in Total Muscle Strength (N) vs Change in Trail Making Test A (score) in the POWER group

Figure 6.28.2 Change in Total Muscle Strength (N) vs Change in Trail Making Test A (score) in the SHAM group
CHAPTER 7

DISCUSSION AND CONCLUSIONS
7.1 DISCUSSION

The aims of this thesis were firstly to outline the current level of evidence for the morphological, biochemical, and functional adaptations in the brain to exercise training from animal models and human clinical trials with diabetes or insulin resistance or impaired glucose tolerance, secondly to investigate the correlates of cognitive function and the cognitive benefits of power training in older adults with T2DM; and finally to identify possible underlying mechanisms of benefit, in particular modulation of insulin sensitivity and glucose homeostasis, body composition, psychosocial status, physical activity level, systemic inflammatory cytokines, and adipokines.

CHAPTER 2 provided a review of morphology, biochemistry, and function in the brain after any form of exercise intervention within animal models with diabetes or insulin resistance or hyperglycaemia. The purpose of this review was to examine changes at the level of neurogenesis, metabolism, and function which may explain the overall benefits of exercise on brain plasticity in animal models. The most consistent adaptations were in the areas of improved cell proliferation, synaptic plasticity, dendritic spine density, brain-derived neurotrophic factor (BDNF), neurotransmitter (glutamate), glucocorticoid receptor in the hippocampus, as well as memory testing, with inconsistent evidence for beneficial adaptations in insulin levels. Some of those studies\textsuperscript{1-3} reported concomitant correlations between improved memory and adaptations to exercise in the areas of cell proliferation, synaptic plasticity, and nerve growth factor. However, only one randomised controlled trial (RCT) reporting the concomitant relationship between new neuron cell and memory existed, with a small number of animals involved, so preliminary results reviewed here still need to be confirmed in additional larger controlled trials in animal models. Future studies will need to refine the design of animal studies investigating the cognitive effects
of exercise to increase their relevance and translatability to humans. In particular, the use of animal models representative of T2DM rather than T1DM, and exercise paradigms which are voluntary rather than forced, and anabolic in addition to aerobic, and would advance knowledge in this field.

**CHAPTER 3** examined the existing literature on the cognitive adaptations to any form of exercise intervention or physical activity exposure within individuals with T2DM or impaired glucose tolerance, and investigated the relationships between glucose metabolism and cognition for an at-risk group of older adults. This review only identified 5 studies that assessed the effects of exercise or physical activity on cognitive function and explored the relationship between changes in indices of either insulin resistance or glucose homeostasis and change in cognition following an exercise intervention. The data from these limited studies indicate that improvements in cognitive function, when they occur, can be partly explained by improvements in insulin resistance and glucose homeostasis, but the effect of exercise was inconsistent and modest across these cohorts. Notably, only two of the studies were RCTs, with a small number of participants involved, and few potentially mechanistic factors measured. No studies of anabolic exercise exposure and cognition were identified in this cohort. Thus, given the limited data available, additional robust research is required to fully understand the effects of exercise/physical activity exposure on cognitive function in individuals with T2DM, and to determine whether exercise may assist in reduction of incident dementia in this vulnerable cohort.

**CHAPTER 4** described the methodology of this GREAT2DO trial. This included an overview of the design, rationale, and methods of the GREAT2DO trial. The general aim of this
GREAT2DO sub-study was to determine whether the resistance training treatment of diabetes, a major risk factor for Alzheimer disease and vascular dementia, can reduce the early decline in cognitive function that could later evolve into more cognitively disabling conditions. This study conformed to all design and reporting requirements for randomised controlled trials recommended by the CONSORT group.

CHAPTER 5 was described using baseline cognitive function measures collected in the Graded Resistance Exercise And Type 2 Diabetes in Older adults (GREAT2DO) sub-study. This chapter also investigated important relationships between these baseline characteristics. Specifically, the cross-sectional relationships between cognitive function and insulin resistance, glucose homeostasis, inflammatory and anti-inflammatory factors, health status, body composition, muscle function, quality of life and physical performance were investigated in this cohort.

The cohort we enrolled was at least as burdened with chronic illnesses and metabolic abnormalities as older with diabetes in Australia and previous clinical trials of exercise in T2DM, suggesting the potential generalisability of our clinical trial outcomes to this cohort. At baseline, metabolic dysfunction was linked to both body composition and functional capacity. We have shown for the first time that poorer physical performance and exercise capacity were related to some aspects of poorer cognitive function, a systematic inflammatory marker and insulin resistance in older people with T2DM. Thus targeting insulin resistance and inflammation may be important for improving physical performance and ultimately cognition in this cohort. Insulin resistance and inflammatory markers have been associated with cognitive impairment and Alzheimer’s disease (AD) in other studies. Thus, it is possible that an exercise intervention which could improve
metabolic profile may also have benefits for cognitive health as well as functional capacity.

In addition to the above factors, body composition appears to be important in relation to cognitive function in this cohort. Although many previous investigations have explored the relationship between body composition and cognition in healthy people, this thesis presents data that advances the existing literature due to the use of gold standard methods of regional adiposity assessment, and investigating multiple domains of cognitive performance in an at-risk group. Most notably, our results have confirmed that central obesity best predicts the cognitive status of older adults with T2DM, particularly in men, reducing central adiposity may thus both be critical for improving insulin resistance, glucose control, physical performance and exercise capacity, pro- and anti-inflammatory balance, and ultimately improved cognitive function. Our data suggest that lifestyle interventions robustly targeting body composition are therefore warranted to investigate their benefit for the cognitive health of this vulnerable cohort. Moreover, this was the first evidence that inflammatory profile (both C-reactive protein and adiponectin) is related to some aspects of cognition in older people with T2DM. These data expand evidence from animal models and healthy individuals, showing for the first time in the same study in older adults with T2DM that central adiposity, C-reactive protein and adiponectin are related to body composition, glucose metabolism and cognitive health in this cohort.

CHAPTER 6 described the cognitive outcomes of the first RCT of power training on in older adults with T2DM enrolled in the GREAT2DO study. We hypothesised that high intensity power training would result in beneficial cognitive performance, and that lean tissue and peripheral adipose tissue adaptations, insulin sensitivity, glucose homeostasis, and systemic inflammation
would be associated with improved cognitive function compared to low intensity SHAM exercise. Contrary to our hypotheses, there were no significant benefits of power training on the cognitive domains tested in this study following the intervention, although both group improved significantly over time in most cognitive outcomes. Unexpectedly, the SHAM group improved significantly more than the power training group on measures of attention/executive function and global cognitive function in fact. Similarly, contrary to our hypothesis, insulin sensitivity, systemic inflammation, and whole body composition did not change over time or between groups. Glycosylated haemoglobin did improve significantly and similarly in both groups over time, although it was well controlled at baseline, a fact which may have attenuated any possible benefits of the intervention on metabolic profile.

However, as we hypothesised, increased (higher) thigh muscle area and whole body skeletal muscle mass were related to improved cognition over 12 months, but only in the power training group, suggesting that improvements in muscle mass and cognition may share common mechanisms such as growth factors and inflammatory profile, both of which may be targeted by robust anabolic exercise. In addition, increased adiponectin level after 12 months was associated with improved cognitive function, as we expected.

There are some limitations within this thesis.

- Chapters 2 and 3 were limited to published data and English-language literature and did not include studies in press or published within the 6 months prior to submission of this thesis
Chapters 5 presented cross-sectional data from 103 older adults with T2DM who were enrolled in the GREAT2DO randomized controlled trial (RCT). While these were the first such comprehensive data in this specific clinical cohort, similar investigations should be carried out in larger cohorts, both with T2DM and other chronic diseases, and within young and middle aged adults to further validate, and understand these relationships. As these data were taken from the baseline characteristics of a volunteer sample of older adults enrolled in a clinical trial of exercise, selection bias relevant to all such volunteer samples may have limited generalisability to clinical cohorts. Notably, the health status of our subjects was worse in most aspects than older adults with T2DM in Australia however, suggesting that this bias was minimal and did not invalidate our findings.

Chapters 6 provided primary cognitive analysis of patients with a 6-month or 12 month memory, information processing speed, executive function, and global cognitive scores: 49 assigned to receive power training and 54 assigned to receive SHAM exercise. In order to maximize the robustness of our hypothesis testing, and eliminate Hawthorne and other non-specific effects of enrolling in an exercise trial, higher training intensity and velocity were the only differences between the POWER training and SHAM-exercise control group, and the subjects were blinded to our hypotheses as to which was the effective exercise modality.

Another factor might have attenuated treatment differences in cognitive scores. Higher training intensity and velocity were the only differences between the POWER training and SHAM-exercise control group, and not all participants in POWER training group reached the intended high intensity training range. Thus, the differences in training modality between the
two groups were not quite as distinct as planned, and adherence was high and equivalent in both groups. This could have minimised the group differences observed. Our SHAM-exercise control design, although more robust and ethically justified than if a waitlist control group or advice-only control group had been used instead, may have led to an actual underestimation of POWER training efficacy. Future trials may need to include a non-exercise control group as well, although this raises ethical concerns of clinical equipoise in a year-long trial of T2DM, as exercise is considered part of the standard care of this cohort.

Due to participant burden constraints, our measure of insulin resistance was restricted to the use of the HOMA2-IR, which is an estimate of fasting hepatic insulin sensitivity. While this has been validated against the hyperinsulinaemic/euglycaemic clamp,\textsuperscript{4,5} the use of the latter method may provide more specific data related to skeletal muscle insulin sensitivity and glucose disposal, and future studies should confirm our findings using this methodology. Furthermore, it has been shown that estimates of hepatic and skeletal muscle insulin resistance can also be derived from oral glucose tolerance tests.\textsuperscript{6} Moreover, the use of an oral glucose tolerance test may provide additional information that is not provided by HbA1c alone regarding glucose homeostasis.

It should be noted that only C-reactive protein (CRP) was used as a marker for systemic inflammation. Many other pro-inflammatory cytokines exist, and the relationships presented here with CRP may not reflect those of other pro-inflammatory cytokines. While resistance training has been shown to reduce levels of other inflammatory cytokines in some studies,\textsuperscript{7} future research should be directed towards their relationship with modifications to cognition,
body composition, and in particular skeletal muscle mass, as well as insulin resistance and glucose homeostasis, adiponectin, and brain-derived neurotrophic factor (BDNF). In addition, CRP and adiponectin measurements were only available in a subset of the study participants due to funding constraints, and sample size limitations could have contributed to Type II errors for some relationships and outcomes.

Tight control of glucose and lipids via medications may have limited the range of values in metabolic variables and blunted relationship with cognitive measures due to ceiling effects. Future studies including those with less well-controlled metabolic profiles at baseline are warranted.

The GREAT2DO study enrolled both men and women. While randomisation stratified by sex ensured that men and women were equally distributed amongst the intervention and SHAM groups, it is possible that sex effects may explain heterogeneity in responsiveness amongst those participants in the intervention (POWER) group. Our investigation however was not sufficiently powered to explore any such effects. Thus future studies should be appropriately designed to explore for any potential sex effects between body composition, metabolic health, and cognitive function in older adults with T2DM, and the subsequent effect of a high intensity POWER training or other intervention on this characteristic.

Our cohort had relatively normal cognitive function at baseline. Thus, their ability to improve on the cognitive outcomes chosen may have been blunted, limiting apparent effectiveness of our intervention at 12 months. Thus, starting with more impaired individuals with mild cognitive impairment for example, may have produced more robust changes in cognition, as we have
published in a recent trial of resistance training in older adults with MCI. The Study of Mental and Resistance Training (SMART) Study—Resistance Training and/or Cognitive Training in Mild Cognitive Impairment: A Randomized, Double-Blind, Double-SHAM Controlled Trial.\textsuperscript{8} In this study, high intensity resistance training has been shown to improve in cognitive function relative to sham exercise or cognitive training.\textsuperscript{8} In addition, the cognitive improvements observed over time in the overall cohort were predominantly in the more difficult tests such as delayed memory and attention/executive function, suggesting that use of neuropsychological assessments with an ability to identify a very early stage of cognitive dysfunction and which have a very high sensitivity to change over time are required to advance knowledge in this field. Furthermore, longer term follow-up (which is ongoing in GREAT2DO out to 6 years post-baseline assessment) may be needed to discern significant cognitive decline or incident dementia, and determine whether exercise or any intervention can attenuate the rate of such decline.

**Future directions**

Our initial systematic review highlighted that only 8 RCTs examined the morphological, biochemical, and functional adaptation to aerobic exercise in the brain, and supported the cerebral neuroplasticity to learning and memory in animal models with diabetes or insulin resistance or hyperglycaemia. Additional research is needed to facilitate translation to clinical trials such as use of animal models more analogous to T2DM, behavioural tests with relevance to humans, precise definition of the effects of dose and modality of exercise on cognitive function or cerebral morphology/biochemistry benefits, and identifying mechanisms of any exercise intervention effects observed.

Our second systematic review found that only 2 RCTs have been published to date to our
knowledge which have assessed the efficacy of aerobic exercise on cognitive function, and examined the potential associations between cognitive function and insulin sensitivity in adults with diabetes mellitus or impaired glucose tolerance. Our own data suggest that there is a potential link between anabolic adaptations to POWER training and cognitive benefits, and many more investigations are needed to expand these findings in this very small literature and to understand the mechanisms behind these relationships.

In order to assess the full effects of our exercise program compared to a sedentary population, comparing our protocol (anabolic exercise) to a usual care advice-only exercise group as well as to an aerobic training group may be needed. This would also provide an insight into the potential neuropsychological benefits gained by various modalities of exercise compared to usual care.

Development of dissemination models allowing robust anabolic exercise (both standard PRT and POWER training) to be conducted in the community with minimal or remote supervision only is also needed if such RCT results are to be translated cost-effectively to clinical practice while maintaining efficacy and fidelity. This is much more difficult for PRT or POWER training than it is with aerobic exercise interventions such as walking for example, due to the need for adequate equipment allowing for progression and high intensity, and in some individuals supervision, for safety. Collaboration with exercise equipment manufacturers to produce versions of such anabolic exercise equipment suitable for home or community centre use would be extremely important in this translational work. In addition, development of tools to monitor and provide feedback on anabolic exercise via Health tools such as smartphone applications, videoconferencing, and web-based trainers, etc. are vital to advancements in this field.
Dissemination should only follow demonstration of efficacy in RCTs obviously, so these efforts are appropriate once the primary data are sufficient to warrant their widespread recommendation and implementation for cognitive improvements in this cohort.

Muscle mass (thigh muscle) is the primary site for glucose disposal, and thus it is possible that increases in muscle quality and quantity simply increase the available storage depot for glucose and improve insulin sensitivity, and thereby contribute to cognitive function. However, more complex interactions are likely and may also contribute to these outcomes, as suggested below, which require elucidation in future studies.

Part of the hypertrophic stimulus resulting from PRT is attributable to increases in IGF-1. Mechanical stimulation of skeletal muscle results in the local production of two isoforms of IGF-1: IGF-1E, these are the principal growth factors thought to mediate the effects of exercise on brain plasticity, function, and health. Administration of intra-hippocampal injection of anti-IGF-1 prevents enhancement of spatial recall. Resistance training increases peripheral IGF-1, leading to improved insulin sensitivity, restored insulin–IGF-1 signaling and improved brain health and cognitive function. Furthermore, pro-inflammatory cytokines impair IGF-1 signal transduction in neurons. Exercise might counteract the negative effects of this inflammation by acting to restore IGF-1 signaling, because it reduces circulating pro-inflammatory cytokines and Aβ. Thus, it is therefore possible that a potential link between augmentation of skeletal muscle mass and cognition exists due to the reduction in central and peripheral inflammation and increase in IGF-1 signaling. These pathways require many more investigations in both animal and human models of T2DM.
Previous literature suggests that sarcopenia, representing loss of muscle mass and strength, is associated with systemic inflammation and functional impairment.\textsuperscript{15} CRP has been shown to have catabolic effects on skeletal muscle, and thus may have potentially inhibitive effects on intended adaptations to an anabolic stimulus such as high intensity POWER training. Our data extend these findings, as we have shown that lower muscle mass was associated with higher CRP levels at baseline, and that increased CRP expression over 12 months was correlated with cognitive decline in our cohort. Therefore, given the ‘progressive’ nature of the training intervention within our study, increases in skeletal muscle mass may have resulted in greater IGF-1 levels from skeletal muscle during subsequent training bouts, resulting in greater anti-inflammatory effects (lower CRP and other unmeasured cytokines) over the course of the intervention. This may explain why increases in muscle area and skeletal muscle mass in POWER training were associated with improved memory in GREAT2DO. This line of inquiry should be confirmed and extended in future trials with a more expansive set of cytokines, with intramuscular measurements of growth factors and markers of inflammation and insulin signaling pathway components, and more precise whole body measures of skeletal muscle mass such as dual energy absorptiometry.

Another potential mediating factor associated with exercise may be alterations in adiponectin expression and function. We observed a positive relationship between changes in adiponectin and cognitive function after POWER training as well as after SHAM exercise (Chapter 6). Previously, only one study to our knowledge has investigated this relationship, and it was within individuals with cognitive impairment.\textsuperscript{16} Thus, our study is the second to investigate this relationship and the first to show a relationship between increases in adiponecctin in response to either high or low intensity exercise and cognition in T2DM. The increase of adiponectin by
exercise may serve as a common mechanism to reduce the risk for both diabetes and cognitive decline, and although levels did not change significantly over 12 months in either group, in those who did increase adiponectin, this increase was related to positive cognitive outcomes. It was unexpected that this would occur after low intensity exercise exposure, and further study is required to confirm and extend these findings, and define dose-response characteristics of this relationship, as well as longterm clinical implications of alterations of adiponectin in relation to body composition, metabolic health, and cognition. In particular, investigations should be directed toward the nature of the observed relationship between increases in adiponectin and improvements in cognition, as this could have significant impacts on future therapeutic interventions. Identification of the characteristics of individuals who were able to express more adiponectin after exposure to exercise and thereby improve cognition is required to more robustly provoke this adaptation. For example, if this relationship is driven by the catabolic effects of adipokines, then complementary interventions aimed at further increasing adiponectin (such as reducing adiposity through diet, use of anti-inflammatory agents, etc.) may improve efficacy of exercise in reducing insulin resistance and HbA1c, as well as associated cognitive improvements. Alternatively, if this relationship between cognition and adiponectin is driven by the reduced visceral adipose tissue and increased lean tissue itself, then interventions maximising these body composition changes are warranted to increase adiponectin.

7.2 CONCLUSIONS

This thesis investigated the effect of exercise or physical activity exposure on cognitive function and explored the relationship between body composition, adipokines, and the cognitive health of older adults with T2DM. Furthermore, the effect of a one-year power training intervention on
body composition, physical performance, and adipokines, and subsequently improving the cognitive health within this cohort was determined. In addition, our data addressed gaps in the literature by including older adults with multiple comorbidities, including a high prevalence of cardiovascular disease, compared to most previous studies. Previously, trials from animal models and human clinical trials have not examined the effects of any form of exercise intervention the relationship between changes in skeletal muscle mass, adiponection, and improvements in either cognition or metabolic dysfunction within individuals with T2DM. This makes our trial the first to investigate these relationships within older adults, and the first to show any relationship between increases in skeletal muscle mass, physical performance, and adiponectin levels and improvements in cognitive function.

We have confirmed that abdominal adipose tissue, systemic inflammation, and serum adiponectin level play a significant role in cognitive impairment in this cohort, and that such impairment is related to physical performance, and exercise capacity. Power training was shown to improve the cognitive health of older adults with T2DM, but only provided they increased muscle mass, decreased systemic inflammation and insulin resistance and/or increased adiponectin level, and these cognitive benefits were related to improved lower extremity exercise capacity and physical performance related to strength, power and balance. However, even SHAM exercise demonstrated some relationships between improved insulin resistance and adiponectin with cognitive benefits, and SHAM exercise outperformed power training in terms of cognitive improvements in some domains, which may have been due in part to their slightly more impaired cognitive status at baseline. Additional study is required to refine the elements of the exercise prescription in this cohort, identify the most important pathways mediating cognitive improvement,
optimise apparently important mediators such as muscle hypertrophy and inflammatory/anti-inflammatory profile, and confirm that longterm clinical benefits accrue, in particular attenuation of the rate of cognitive decline and incident dementia in this high-risk cohort.
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doi:10.1371/journal.pone.0024263.


APPENDIX (MANUAL OF PROCEDURES)
The GREAT2DO study is a randomised, double-blind, SHAM-exercise controlled trial. Subjects (n=103) were randomised to the experimental (high intensity progressive resistance training-PRT) or control condition (SHAM resistance training with the subjects blinded to investigators’ hypotheses as to which is the experimental group) for 12 months, in addition to usual care from their GP. Blinded outcome assessments will be conducted at 0, 6, and 12 months in all subjects regardless of adherence to the intervention. (Figure 1) The exercises target the majority of the large muscle groups of the arms, legs, and trunk: seated row, chest press, leg press, knee extension, hip flexion, hip extension and hip abduction. In addition, these are symmetrical muscle groups and functionally relevant to the activities of daily living, gait, and balance of older adults. For each exercise, subjects will perform 3 sets of 8 repetitions (2 sets of 8 on each leg for the three hip exercises) with a fast concentric and slow eccentric phase on pneumatic resistance training machines (approximately 6 seconds per repetition with 2 minutes of rest between sets). The intensity will be set at 80% of the most recently determined peak strength (1 repetition maximum or 1RM). Resistances used will be increased as tolerated using Borg scale rating of perceived exertion on a continuous basis throughout the 12 months, and 1RM testing will be repeated at 2-week intervals to ascertain progress and regulate intensity. Where 1RM testing was not feasible, resistances were increased by targeting a Borg scale rating of perceived exertion between 15 and 18.

SHAAM exercise subjects will be supervised by the same trainers in the same facility, but at different hours to avoid contamination and unblinding. These subjects will perform 3 sets of 8 repetitions on the same machines, but with no loading beyond the bar of the machine, using slow concentric and eccentric contraction speed. No interim 1RM testing
and no progression will take place.

Subjects recruited for the study will undergo three separate days of assessments at baseline, 6 and 12 month re-assessment, spread over two weeks.

Figure 1 – Study Design and Participant flow
Recruitment
- Local media
- GP referral

Screening
- Telephone screening (n=500)
- Informed consent
- Physician screening (n=150)

Baseline Assessment

Randomisation
- 103 participants

Intervention
- Experimental Group
  - PRT at 80% 1RM
  - 8 upper and lower-body exercise
  - 3 sets x 8 reps, 3 days/week
  - 12 months
- Shan Exercise Control
  - No added resistance
  - 8 upper and lower-body exercise
  - 3 sets x 8 reps, 3 days/week
  - 12 months

Primary Outcomes
- Insulin Resistance
- Glucose Homeostasis
- Cognitive Function

Secondary Outcomes
- Cardiovascular Health
- Lipid Metabolism
- Physical performance
- Exercise capacity
- Adipokines/Inflammation
- Body composition
- Quality of Life
- Neuropsychological Profile

Covariates
- Age, Gender, and Years of education, nutrition, energy Expenditure

Participant Criteria
- Community-dwelling men and women sedentary
- Age $\geq 60$ with
- Type 2 diabetes mellitus and
- Metabolism Syndrome
- No recent change in diabetes medications
- Fasting glucose $> 11.1$ mmol/L
- No cognitive impairment
APPENDIX A. ASSESSMENT PROTOCOLS (ASSESSMENT A)

ASSESSMENT A PROTOCOLS
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**Software used to Initialize, Download and Analyse Data**

**Actigraph Initialization (Set Up) Procedures**

**Placement of Actigraphs on Subject**

**Instructions to Subject**

**Actigraph Download Procedures**

**Procedure for Viewing Uploaded Sleep Data**

**Physical and Sedentary Activity Data**

**Procedure for Viewing and Cleaning Physical and Sedentary Activity Data**
Variables created by the C2R Macro
PARTICIPANT INFORMATION SHEET

Purpose
It is important for the participant to understand what is involved in the study if they wish to participate. The Participant Information Sheet describes, in detail, the testing and training protocols of the GREAT2DO study. By explaining each of the procedures, the participant is given a greater opportunity to ask questions and put to rest any concerns they may have.

Protocol
Go through each testing protocol, explaining the details thoroughly and be open to questions. Provide a copy of the information sheet in the Participant Information Pack taken home by the participant later that day.
PARTICIPANT CONSENT FORM

Purpose
To gain the consent of the participant whilst informing them of all procedures to ensure understanding and provide an opportunity to have questions answered.

Protocol
Ensure that the participant has the chance to read through the statements on the sheet and to have any questions that arise answered clearly. Most people feel pressured to ‘sign on the dotted line’ so it may help to lean back and sit away from the subject so that they feel comfortable to read the consent form fully.

If the participant consents to the terms of the study, they must:

- Write their name at the top of the sheet
- Sign the bottom of the sheet
- Date the bottom of the sheet

Ensure that you:

- Witness their signature
- Sign the bottom of the sheet
- Date the bottom of the sheet
- Make a photocopy of the signed consent form and place it in the Participant’s Information Pack that will be taken home later that day
PROCEDURE FOR THE ADMINISTRATION OF THE CERAD NEUROPSYCHOLOGICAL ASSESSMENT BATTERY

To ensure the results are reliable, it is essential that the cognitive function tests are administered precisely according to the instructions provided.

- Each CERAD task should be administered in the order in which it is presented.

- Moreover, the entire CERAD battery should always be administered before any other neuropsychological items.

- RA’s should encourage the completion of the task without adding to the stress of the situation, and should offer neutral phrases as support when subjects cannot complete the tasks.

- Feedback to the patients should be positive but should not offer information to the correctness of the response. Appropriate phrases include “That’s fine” and “You’re doing alright”.

- The score sheets should not be placed within the patients view.

J4 WORD LIST MEMORY TASK

To assess the patients’ ability to remember newly learned information, this task asks the patient to recall 10 common nouns. To ensure the patient is familiar with the word, they are asked to read the words printed on separate cards in the CERAD flip book. The 10 words are presented at a constant rate (1 word every 2 seconds) and then the subject is immediately asked to recall as many of the words shown as possible.
The instructions for the first trial are:

- “I am going to show you ten printed words. Read each word out loud as I show it to you. Later I will ask you to recall all ten words”

If the subject cannot read the word, say it for him/her and tick the ‘can’t read’ column on the score sheet. After the last word has been read, ask the patient to recall as many words as they can. Allow a maximum of 90secs. Continue with the second and third sets in the same way, changing you instructions slightly to encourage the patient.

The subject’s score for each trial is the number of words correctly recalled. Be sure to record on each trial the number of words that the patient ‘recalls’ that are not on the list (intrusions).

Refer to the scoring protocol for the CERAD neuropsychological Assessment Battery for more information.

**J6 WORD LIST RECALL**

This task is to determine how well subjects can remember the words presented in the J4 form. Allow ‘distraction’ time by completing another task, such as the medications review.

The instructions for this recall task are:

- “A few minutes ago I asked you to learn a list of 10 words which you read one at a time from cards. Now I want you to try to recall as many of those 10 words as you can. OK, now tell me as many of those 10 words as you can remember.”

Allow the patient a maximum of 90seconds. Number each word in its corresponding block
on the score sheet in the order it is recalled. Score the number of words correctly recalled. Also record and score the number of words not on the list (intrusions), that the subject reports.

Refer to the scoring protocol for the CERAD neuropsychological Assessment Battery for more information.

**J7 Word List Recognition**

The instructions for this recognition test are:

- "Now I am going to show you a set of words printed on cards. Some of the words are from the list you saw earlier and some are words I haven’t shown you before. I want you to tell me which words are from the list you saw earlier (show the first word). Is this one of the words you saw earlier?"

Repeat the question, or say, ‘how about this one?’ for each word. Record the subject’s response. The scores for this test include the number of correctly recognised words previously seen (correct ‘yes’ responses) and the number of correctly rejected new words (correct ‘no’ responses).

Urge the patient to give ‘yes’ or ‘no’ responses, since ‘don’t know’ responses are unscorable.

Refer to the scoring protocol for the CERAD neuropsychological Assessment Battery for more information.
SCORING FOR WORD LIST MEMORY /RECALL TASKS

Word List Memory

- Task Scoring
  - Score each administration separately (i.e., 3 scores out of 10).
  - You can then decide which administration to use (some investigators use only the score on the third administration) or you can sum the three scores to get a score out of 30.
  - Score separately for number of correct responses, and for number of intrusions.

- Scoring for Intrusions
  - An intrusion is any word that is not on the list of words presented. If, for example, a word that is given in response to the word list memory task that the patient has not been shown as part of the task.
  - Intrusions are scored separately, and do not affect the score obtained when the subject gives a correct response.
  - Repeating a word that is on the list is not considered an intrusion. The repetition is not counted. An intrusion is a word that is not on the list.
Word List Recall

- Use the same rules as the word list memory task.

Word List Recognition

- Task Scoring

  - The total score is out of 20. Score the correctly identified original words and the correctly identified new words.
MEDICATION REVIEW

Complete the Medication Review after the J4 Word List Memory Task but before the J6 Word List Recall task. This allows ‘distraction time’ between the two memory tests.

Complete the name, dose and regularity (compliance) information in the spaces provided on the form.
Construction of the SF-36®

The SF-36® was constructed to satisfy minimum psychometric standards necessary for group comparisons involving generic health concepts — that is, concepts that are not specific to any age, disease, or treatment group. The eight health concepts were selected from 40 included in the Medical Outcomes Study (MOS) (Stewart and Ware, 1992) to represent those hypothesized to be most frequently measured in widely-used health surveys and those most affected by disease and treatment (Ware et al., 1993; Ware, 1995). They also represent multiple operational definitions of health, including: function and dysfunction, distress and well-being, objective reports and subjective ratings, and both favorable and unfavorable self-evaluations of general health status (Ware et al., 1993). Most items have their roots in instruments that have been in use for more than 20 years (Stewart and Ware, 1992), including: the General Psychological Well-Being Inventory (Dupuy, 1984), various physical and role functioning measures (Patrick, Bush, and Chen, 1973; Hulka and Cassel, 1973; Reynolds et al., 1974; Stewart, Ware and Brook, 1981), the Health Perceptions Questionnaire (Ware, 1976), and other measures that proved to be useful during the Health Insurance Experiment (HIE) (Brook, Ware et al., 1979). MOS researchers selected and adapted questionnaire items from these and other sources and developed new measures for a 149-item Functioning and Well-Being Profile (Stewart and Ware, 1992), which was the source for SF-36® items.

SF-36® Measurement Model

Figure 1 illustrates the measurement model underlying the construction of the SF-36®
scales and summary measures. This model has three levels: (1) items, (2) eight scales that aggregate 2-10 items each, and (3) two summary measures that aggregate scales. All but one of the 36 items (self-reported health transition) are used to score the eight SF-36® scales. Each item is used in scoring only one scale.

The eight scales are hypothesized to form two distinct higher-ordered clusters due to the physical and mental health variance that they have in common. Factor analytic studies have confirmed physical and mental health factors that account for 80-85% of the reliable variance in the eight scales in the US general population (Ware et al., 1994), among MOS patients (McHorney et al., 1993; Ware et al., 1994), and in general populations in Sweden (Sullivan et al., 1994) and the UK (Ware et al., 1994). Three scales (Physical Functioning, Role-Physical, Bodily Pain) correlate most highly with the physical component and contribute most to the scoring of the Physical Component Summary (PCS) measure (Ware et al., 1994). The mental component correlates most highly with the Mental Health, Role-Emotional, and Social Functioning scales, which also contribute most to the scoring of the Mental Component Summary (MCS) measure. Three of the scales (Vitality, General Health, and Social Functioning) have noteworthy correlations with both components.

Administration Methods and Data Quality

The SF-36® is suitable for self-administration, computerized administration, or administration by a trained interviewer in person or by telephone, to persons age 14 and older. The SF-36® has been administered successfully in general population surveys in the US and other countries (Ware, Keller, Gandek, et al., 1995) as well as to young and old
adult patients with specific diseases (Ware, Snow, Kosinski, et al., 1993; McHorney, Ware, Lu, et al., 1994). It can be administered in 5-10 minutes with a high degree of acceptability and data quality (Ware, Know, Kosinski, et al., 1993). Indicators of data quality that have yielded satisfactory results in studies to date include very high item completion rates and favorable results for a response consistency index based on 15 pairs of SF-36® items, which is scored at the individual level (Ware et al., 1993). Computer administered and telephone voice recognition interactive systems of administration are currently being evaluated.

Scaling and Scoring Assumptions
A major objective in constructing the SF-36® was achievement of high psychometric standards. Guidelines for testing were derived from those recommended for use in validating psychological and educational measures by the American Psychological Association, the American Education Research Association, and the National Council on Measurement in Education (APA, 1984). Extensive psychometric testing has been conducted on the SF-36® in the United States (McHorney et al., 1994; Garratt et al., 1993; Jenkinson et al., 1993; Wagner et al., in press), and in numerous other countries (Sullivan, 1994; Rampall et al., 1994; Sullivan et al., in press; Bullinger, in press; McCallum et al., in press).

On the strength of favorable results from tests to date, nearly all studies have used the method of summated ratings and standardized SF-36® scoring algorithms documented elsewhere (MOT, 1991; Ware et al., 1993). This method assumes that items shown in the
same scale in Figure 1 can be aggregated without score standardization or item weighing. Standardization of items within a scale was avoided by selecting or constructing items with roughly equivalent means and standard deviations. Weighing was avoided by using equally representative items (that is, items with roughly equivalent relationships to the underlying scale dimension). All items have been shown to correlate substantially (greater than 0.40, corrected for overlap) with their hypothesized scales with rare exceptions (McHorney et al., 1994; Ware et al., 1993). These results support analysis as interval-level measurement scales.

Reliability and Confidence Intervals

The reliability of the eight scales and two summary measures has been estimated using both internal consistency and test-retest methods. With rare exceptions, published reliability statistics have exceeded the minimum standard of 0.70 recommended for measures used in group comparisons; most have exceeded 0.80 (McHorney et al., 1994; Ware et al., 1993). Reliability estimates for physical and mental summary scores usually exceed 0.90 (Ware et al., 1994). One review of 15 published studies revealed that the median reliability coefficients for each of the eight scales was equal or greater than 0.80 except Social Functioning, which had a median reliability across studies of 0.76 (Ware, Snow, Kosinski, et al., 1993). In addition, a reliability of 0.93 has been reported for the Mental Health scale using the alternate forms method, suggesting that the internal-consistency method underestimated the reliability of that scale by about 3% (McHorney and Ware, 1995).
The trends in reliability coefficients for the SF-36® scales and summary measures summarized above have also been replicated across 24 patient groups differing in socio-demographic characteristics and diagnoses (Ware et al., 1993; Ware et al., 1994; McHorney et al., 1994). While studies of subgroups indicate slight declines in reliability for more disadvantaged respondents, reliability coefficients consistently exceeded recommended standards for group level analysis.

Standard errors of measurement, 95% confidence intervals for individual scores, and distributions of change scores from test-retest and one-year stability studies have been published (Brazier et al., 1992; Ware et al., 1993; Ware et al., 1994). Confidence intervals around individual scores are much smaller for the two summary measures than for the eight scales +/- 6-7 points versus +/- 13-32 points, respectively) (Ware, Kosinski, and Keller, 1994). Estimates of sample sizes required to detect differences in average scores of various magnitudes have been documented for five different study designs for each of the eight scales and for the two summary measures (Ware et al., 1993; Ware et al., 1994).

Norms for General and Specific Populations

The SF-36® has been normed in the general US population and for representative samples from Denmark, Germany, Sweden, and the UK using common translation and norming protocols developed by the International Quality of Life Assessment (IQOLA) Project (Ware, Gandek et al., 1994; Sullivan et al., in press; Bullinger, in press). Other norming studies, which are underway in Australia, Denmark, France, Italy, and The Netherlands will be completed in 1995. From the general US population, norms for age and sex groups
and for 14 chronic diseases have been published along with estimates of the effect of telephone-relative to self-administered versions (McHorney et al., 1994; Ware et al., 1993; Ware et al., 1994).

For patients with chronic conditions participating in the MOS, cross-sectional norms and average changes over a one-year follow-up period have been published for congestive heart failure, diabetes (Type II), hypertension, myocardial infarction (recent survivors), and for depressive disorder (Ware et al., 1993; Ware et al., 1994). In addition, norms have been published for uncomplicated hypertensive patients with the following comorbid conditions: angina (recent), chronic obstructive pulmonary disease, back pain/sciatica, osteoarthritis, musculoskeletal complaints, benign prostatic hypertrophy, varicosities, and dermatitis.

Validity

Studies of validity are about the meaning of scores and whether or not they have their intended interpretations. Because of the widespread use of the SF-36® across a variety of applications, evidence of all types of validity is relevant. Studies to date have addressed content, concurrent, criterion, construct, and predictive validity.

The content validity of the SF-36® has been compared to that of other widely used generic health surveys (Ware et al., 1993; Ware et al., 1995). Systematic comparisons indicate that the SF-36® includes eight of the most frequently represented health concepts. Among the content areas included in widely-used surveys, but not included in the SF-36®, are: sleep adequacy, cognitive functioning, sexual functioning, health distress, family functioning,
self-esteem, eating, recreation/hobbies, communication, and symptoms/problems that are specific to one condition. Symptoms and problems that are specific to a particular condition are not included in the SF-36® because the SF-36® is a generic measure. To facilitate the consideration of concepts not included, the SF-36® Users’ Manuals include tables of correlations between the eight scales and the two summary measures and 32 measures of other general concepts (Ware et al., 1993; Ware et al., 1994) and 19 specific symptoms. SF-36® scales correlate substantially (r=0.40 or greater) with most of the omitted general health concepts and with the frequency and severity of many specific symptoms and problems. A noteworthy exception is sexual functioning, which correlates relatively weakly with SF-36® scales and is a good candidate for inclusion in questionnaires that supplement the SF-36®.

Because most SF-36® scales were constructed to reproduce longer scales, much attention has been given to how well the short-form versions perform in empirical tests relative to the full-length versions. Relative to the longer MOS measures they were constructed to reproduce, SF-36® scales have been shown to perform with about 80-90% empirical validity in studies involving physical and mental health "criteria" (McHorney et al., 1993).

The validity of each of the eight scales and the two summary measures has been shown to differ markedly as would be expected from factor analytic studies of construct validity (McHorney et al., 1993; Ware et al., 1994; Ware et al., 1995). Specifically, the Mental Health, Role-Emotional, and Social Functioning scales and the MCS summary measure have been shown to be the most valid mental health measures in both cross-cultural and
longitudinal tests using the method of known-groups validity. The Physical Functioning, Role-Physical, and Bodily Pain scales and the PCS have been shown to be the most valid physical health measures. Criteria used in the known-groups validation of the SF-36®, which include accepted clinical indicators of diagnosis and severity of depression, heart disease, and other conditions, are well documented in peer-reviewed publications and in the two users’ manuals (Kravitz et al., 1992; McHorney et al., 1993; Ware et al., 1993; Ware et al., 1994; Ware et al., 1995).

The Mental Health scale has been shown to be useful in screening for psychiatric disorders (Berwick et al., 1991; Ware et al., 1994), as has the MCS summary measure (Ware et al., 1994). For example, using a cutoff score of 42, the MCS had a sensitivity of 74% and a specificity of 81% in detecting patients diagnosed with depressive disorder (Ware et al., 1994).

Relative to other published measures, SF-36® scales have performed well in most tests published to date (Weinberger et al., 1991; Brazier et al., 1992; Kantz et al., 1992; Krousel-Wood, 1994 a & b). Predictive validity studies have linked SF-36® scales and summary measures to utilization of health care services (Ware et al., 1994), the clinical course of depression (Wells et al., 1992), loss of job within one year (Ware et al., 1994), and 5-year survival (Ware et al., 1994).

Results from clinical studies comparing scores for patients before and after treatment have largely supported hypotheses about the validity of SF-36® scales based on factor analytic
studies. For example, clinical studies have shown that the three most valid physical scales (Physical Functioning, Role-Physical, and Bodily Pain) tend to be most responsive to the benefits of knee replacement (Kantz et al., 1992), hip replacement (Kantz et al., 1992; Lanky et al., 1992), and heart valve surgery (Phillips and Lanky, 1992). Likewise, the three most valid mental health scales (Mental Health, Role-Emotional, and Social Functioning) in factor analytic studies have been shown to be most responsive in comparisons of patients before and after recovery from depression (Ware et al., 1995).

The discovery that 80-85% of the reliable variance in the eight SF-36® scales led to the construction of psychometrically-based physical and mental health summary measures. It was hoped that they would make it possible to reduce the number of statistical comparisons involved in analyzing the SF-36® (from eight to two) without substantial loss of information. In both cross-sectional and longitudinal studies reported to date, this appears to be the case (Ware et al., 1994; Ware et al., 1995). The advantages and disadvantages of analyzing the eight-scale SF-36® profile versus the two summary measures are illustrated and discussed elsewhere (Ware et al., 1994; Ware et al., 1995).

Finally, the SF-36® self-evaluated health transition item (five levels from "much better" to "much worse"), which is not used in scoring the scales or summary measures, has been shown to be useful in estimating average changes in health status during the year prior to its administration. In the MOS, measured changes in health status during a 1-year follow-up period corresponded substantially, on average, to self-evaluated transitions at the end of the year. Using the 0-100 GHRI scale (Davies and Ware, 1981) as a "criterion," those who
evaluated their health as "much better" improved an average of 13.2 points. The average change was 5.8 points for those who reported that they were "somewhat better." An average decline of -10.8 was observed for those who reported that their health was "somewhat worse" and 34.4 for those reporting "much worse." (It should be noted that the latter category had only 29 patients.) Change scores for those choosing the "about the same" category averaged 1.6 points. These results are encouraging with regard to the use and interpretation of self-evaluated transitions at the group level. Pending results from ongoing studies of the reliability of responses to the SF-36® self-evaluated transition item, it should be interpreted with caution at the individual level. Additional results and their implications are discussed elsewhere (Ware et al., 1993; Ware et al., 1994).

*Summary of Information About SF-36® Scales & Summary Measures*

Table 1 summarizes information about the eight SF-36® scales and two summary measures that is important in their use and interpretation. The eight scales are ordered in terms of their factor content (i.e., construct validity) as they are in the SF-36® profile to facilitate interpretation. The first scale is Physical Functioning (PF), which has been shown to be the best all around measure of physical health; the last scale, Mental Health (MH) is the most valid measure of mental health in studies to date (McHorney et al., 1993; Ware et al., 1993; Ware et al., 1994). Interestingly, MH and PF are the poorest measures of the physical and mental components, respectively. Scales in between are ordered according to their validity in measuring physical and mental health. The Vitality and General Health scales have substantial or moderate validity for both components of health status and should be interpreted accordingly.
The number of items and levels and the range of states defined by each scale are also shown in Table 1. These attributes have been linked to their empirical validity (McHorney et al., 1992). The most precise (least coarse) scales are those with 20 or more levels (PF, GH, VT, and MH). They also define the widest range of health states and, therefore, usually produce the least skewed score distributions. The relatively coarse role disability scales (RP and RE) each measure only four or five levels across a restricted range and, therefore, usually have the most problems with ceiling and floor effects.

Means and standard deviations for each of the eight scales in the general US adult population are also presented. These can be used to determine whether a group or individual in question scores above or below the US average. Detailed normative data including frequency distributions of scores and percentile ranks are documented in the two users’ manuals (Ware et al., 1993; Ware et al., 1994). Reliability estimates and 95% confidence intervals for individual scores are also presented. These estimates are based on internal-consistency reliability coefficients and standard deviations from the general US population, as documented elsewhere (Ware et al., 1993; Ware et al., 1994).

Table 1 illustrates the practical implications of a number of theoretical advantages of the PCS and MCS summary measures as compared to the eight SF-36® scales. These advantages include a very large increase in the number of levels defined, much smaller confidence intervals for individual scores relative to each of the eight scales, as well as the elimination of both floor and ceiling effects. The implications for the use of the PCS and MCS in clinical practice and research are currently being evaluated; preliminary results are
encouraging (Ware, Kosinski, and Keller, 1994).

**Documentation and Availability**

The scoring of the eight SF-36® scales and two summary measures and detailed interpretation guidelines (content-based, norm-based, and criterion-based) are documented in two users' manuals (Ware et al., 1993; Ware et al., 1994). A third manual documents English-language adaptations and scoring algorithms for use in Australia, Canada, and the UK (MOT, 1992), and a fourth manual documents the Swedish translation and related norms and validations (Sultan et al., 1994). Others are forthcoming from the IQOLA Project. Order the manuals.

**Permission to Use**

Permission to reproduce the SF-36® items and scoring algorithms has also been granted to computer software vendors and dozens of commercial survey and data processing firms offering a wide range of services based on standard SF-36® scoring algorithms and interpretation guidelines. If you would like permission to use, click here.

**Discussion**

The widespread adoption of the SF-36® in general population surveys, clinical trials, and clinical practice is evidence that more practical measurement tools are more likely to be used. The standardization of measurement across studies is producing considerable information about norms and benchmarks useful in comparing "well" and "sick" populations and for estimating the burden of specific conditions. At the time of writing this
chapter, 85 publications reporting results for the SF-36® had been identified. (Studies reporting results for one or more of the SF-36® scales are starred in the reference list.)

The brevity of the SF-36® was achieved by focusing on only eight of 40 health concepts studied in the MOS and by measuring each concept with a short-form scale. The scales chosen (other than General Health) have been shown to explain about two-thirds of the reliable variance in individual evaluations of their current health status in the UK, US, and Sweden (Ware, Keller, Gandek et al., 1995, in press). In the US, addition of 14 multi-item measures (e.g., sleep problems, family and sexual functioning) added only about five percent to the variance explained.

Although many studies appear to be relying on the SF-36® as the principal measure of health outcome, it may be best to rely upon it as a "generic core," pending further research. A generic core battery of measures serves the purpose of comparing results across studies and populations and greatly expands the interpretation guidelines that are essential to determining the clinical, economic, and human relevance of results. Because it is short, the SF-36® can be reproduced in a questionnaire with ample room for other more precise general and specific measures. Numerous studies in progress and some that have been published (Wagner et al., in press; Kantz et al., 1992; Nerenz et al., 1992) adopted this strategy and have illustrated the advantages of supplementing it.

How useful is the SF-36® for purposes of comparing general and specific population groups, relative to longer surveys? Some SF-36® scales have been shown to have 10-20%
less precision than the long-form MOS measures they were constructed to reproduce (McHorney et al., 1992). This disadvantage of the SF-36® should be weighed against the fact that some of these long-form measures require 5-10 times greater respondent burden. Empirical studies of this tradeoff suggest that the SF-36® provides a practical alternative to longer measures and that the eight scales and two summary scales rarely miss a noteworthy difference in physical or mental health status in group level comparisons (Ware et al., 1993; Ware et al., 1994; Katz et al., 1992). Regardless, the fact that the SF-36® represents a documented compromise in measurement precision (relative to longer MOS measures leading to a reduction in the statistical power of hypothesis testing should be taken into account in planning clinical trials and other studies. To facilitate such planning, five tables of sample size estimates for differences in scores of various amounts for conventional statistical tests are published in the two SF-36® Users' Manuals (Ware et al., 1993; Ware et al., 1994). In relation to longer non-MOS measures, such as the Sickness Impact Profile, the SF-36® has performed equally well or better in detecting average group differences or changes over time (Katz et al., 1992; Beaton et al., 1994).

The value of general and specific population norms, which was demonstrated well for the Sickness Impact Profile (Bergner et al., 1981) and later for the MOS SF-20 (Stewart et al., 1988; 1989) and other measures, has also been demonstrated for the SF-36®. In addition to the 20 medical conditions described in the MOS and 14 conditions described in the US population norming survey (Ware et al., 1994), other publications have reported descriptive data for patients with cardiac disease (Krousel-Wood et al., 1994; Jette et al., 1994), epilepsy (Vickrey et al., 1992; Wagner et al., in press), diabetes mellitus (Nerenz et al.,
1992; Jacobsen et al., 1994), migraine headache (Osterhaus et al., 1994), heart transplant patients (Rector et al., 1993), ischemic heart disease (Phillips and Lansky, 1992), ischemic stroke (Kappelle et al., 1994), low back pain (Garratt et al., 1993; Lansky et al., 1992), lung disease (Viramontes et al., 1994), menorrhagia (Garratt et al., 1992), orthopedic conditions leading to knee replacement (Kantz et al., 1992), knee surgery (Katz et al, 1992), and hip replacement (Katz et al., 1992; Lansky et al., 1992), and for renal disease (Kurtin et al., 1992; Meyer et al., 1994; Benedetti et al., 1994). Whereas some of the initial descriptive studies using the SF-36® were performed primarily to validate scale scores (McHorney et al., 1992), on the strength of validation studies to date, SF-36® scales appear to be increasingly accepted as valid health measures for purposes of documenting disease burden. Relatively little is known about population health in comprehensive terms, the relative burden of disease, or the relative benefits of alternative treatments. One reason has been the lack of practical measurement tools appropriate for widespread use across diverse populations. The SF-36® was constructed to provide a basis for such comparisons of results.

As predicted when it was first published (Ware and Sherbourne, 1992), the SF-36® has been widely adopted because of its brevity and its comprehensiveness. Although these two measurement goals are competing, the SF-36® appears to have achieved a psychometrically-sound compromise between them. Population and large-group descriptive studies and clinical trials to date suggest that the SF-36® will prove very useful for descriptive purposes such as documenting differences between sick and well patients and for estimating the relative burden of different medical conditions. Experience to date,
however limited, suggests that the SF-36® may also have potential in evaluating the benefits of alternative treatments. Additional research is necessary before that potential and the features of study designs essential to success can be well understood.

Acknowledgments

Development and validation of the SF-36® Health Survey was supported by a grant from the Henry J. Kaiser Family Foundation to The Health Institute, New England Medical Center (J. E. Ware, Jr., Principal Investigator). Development of the SF-36® PCS and MCS summary measures was supported by unrestricted research grants for the International Quality of Life Assessment (IQOLA) Project for the Glaxo Research Institute, Research Triangle Park, North Carolina and Schering-Plough Corporation, Kenilworth, New Jersey (J. E. Ware, Jr., Principal Investigator).
Standard Interview Script for SF-36 HEALTH SURVEY (4-WEEK RECALL)

SCRIPT FOR INTERVIEW ADMINISTRATION

These first questions are about your health now and your current daily activities.

Please try to answer every question as accurately as you can.

1) In general, would you say your health is: [READ RESPONSE CHOICES] (Circle one number)
   1. Excellent
   2. Very good
   3. Good
   4. Fair
   5. Poor

2) Compared to one year ago, how would you rate your health in general now? Would you say it is: [READ RESPONSE CHOICES] (Circle one number)
   1. Much better now than one year ago
   2. Somewhat better now than one year ago
   3. About the same as one year ago
   4. Somewhat worse now than one year ago
   5. Much worse now than one year ago

3) Now I'm going to read a list of activities that you might do during a typical day. As I read each item, please tell me if your health now limits you a lot, limits you a little, or does not limit you at all in these activities. [READ RESPONSE CHOICES] [IF RESPONDENT SAYS S/HE DOES NOT DO ACTIVITY; PROBE: Is that because of your health?] (Circle one number for each question)
| 3a) vigorous activities, such as running, lifting heavy objects, participating in strenuous sports | 1 | 2 | 3 |
| 3b) moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | 1 | 2 | 3 |
| 3c) lifting or carrying groceries | 1 | 2 | 3 |
| 3d) climbing several flights of stairs | 1 | 2 | 3 |
| 3e) climbing one flight of stairs | 1 | 2 | 3 |
| 3f) bending, kneeling, or stooping | 1 | 2 | 3 |
| 3g) walking more than a mile (or more than 1.6 kilometres) | 1 | 2 | 3 |
| 3h) walking several hundred yards (or several hundred metres) | 1 | 2 | 3 |
| 3i) walking one hundred yards (or 100 metres) | 1 | 2 | 3 |
| 3j) bathing or dressing yourself | 1 | 2 | 3 |

4) The following four questions ask you about your physical health and your daily activities as a result of your physical health during the past four weeks. [READ RESPONSE CHOICES] (Circle one number for each question)
<table>
<thead>
<tr>
<th></th>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of The time</th>
<th>None of The time</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a) how much of the time have you had to cut down on the amount of time you spent on work or other daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4b) how much of the time have you accomplished less than you would like?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4c) how much of the time were you limited in the kind of work or other regular daily activities you do?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>4d) how much of the time have you had difficulty performing work or other regular daily activities (for example, it took extra effort)?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>
5) The following three questions ask about your emotions and your daily activities as a result of any emotional problems, such as feeling depressed or anxious during the past four weeks. [READ RESPONSE CHOICES] (Circle one number for each question)

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>5a</strong></td>
<td>how much of the time have you had to cut down the amount of time you spent on work or regular daily activities?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>5b</strong></td>
<td>how much of the time have you accomplished less than you would like?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>5c</strong></td>
<td>how much of the time did you do work or other regular daily activities less carefully than usual?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
6) During the past four weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups? Has it interfered: [READ RESPONSE CHOICES] (Circle one number)

1. Not at all
2. Slightly
3. Moderately
4. Quite a bit
5. Extremely

7) How much bodily pain have you had during the past four weeks? Have you had: [READ RESPONSE CHOICES] (Circle one number)

1. None
2. Very mild
3. Mild
4. Moderate
5. Severe
6. Very severe

8) During the past four weeks, how much did pain interfere with your normal work, including both work outside the home and housework? Did it interfere: [READ RESPONSE CHOICES] (Circle one number)

1. Not at all
2. A little bit
3. Moderately
4. Quite a bit
5. Extremely
9) The next questions are about how you feel and how things have been with you during the past four weeks. As I read each statement, please give me the one answer that comes closest to the way you have been feeling; is it all of the time, most of the time, some of the time, a little of the time, or none of the time? [READ RESPONSE CHOICES] (Circle one number for each question)

<table>
<thead>
<tr>
<th>Question</th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of The time</th>
<th>None of The time</th>
</tr>
</thead>
<tbody>
<tr>
<td>9a) did you feel full of life?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9b) have you been very nervous?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9c) have you felt so down in the dumps that nothing could cheer you up?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9d) have you felt calm and peaceful?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9e) did you have a lot of energy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9f) have you felt downhearted and depressed?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9g) did you feel worn out?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9h) have you been happy?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9i) did you feel tired?</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>
10) During the past four weeks, how much of the time has your physical health or emotional problems interfered with your social activities like visiting with friends or relatives? Has it interfered: [READ RESPONSE CHOICES] (Circle one number)

1. All of the time
2. Most of the time
3. Some of the time
4. A little of the time
5. None of the time

11) These next questions are about your health and health-related matters. Now, I'm going to read a list of statements. After each one, please tell me if it is definitely true, mostly true, mostly false, or definitely false. If you don't know, just tell me. [READ RESPONSE CHOICES] (Circle one number for each question)

<table>
<thead>
<tr>
<th></th>
<th>All of the time</th>
<th>Most of the time</th>
<th>Some of the time</th>
<th>A little of the time</th>
<th>None of the time</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>11a</strong></td>
<td>I seem to get sick a little easier than other people</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>11b</strong></td>
<td>I am as healthy as anybody I know</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>11c</strong></td>
<td>I expect my health to get worse</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td><strong>11d</strong></td>
<td>My health is excellent</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>
Gender:

1. Male
2. Female

Age:

1. Less than 64 years
2. 65-74 years
3. 75-84 years
4. 85 and older

Comments:
________________________________________________________________________
________________________________________________________________________
________________________________________________________________________

*Code each test using the format below in the comments column:*

1= protocol completed
2= not completed due to death
3= not completed due to refusal, drop-out or loss to follow up
4= not completed due to medical illness or incapacity
5= not completed due to equipment failure or examiner error
6= not completed due to other cause (specify)
ANTHROPOMETRY

MEASUREMENT OF BODY MASS (WEIGHT)

Equipment:

- Weighing Scale (AND HW-100k & SECA Wedderburn (>100 kgs)
- Free weights of known mass (range x kgs, x kgs)

Calibration of Scale

- The site staff must ensure that calibration of the weighing scale is performed following the instructions outlined by the manufacturer's user manual. The frequency of calibration must be as recommended by the manufacturer of the scale.
- Three objects of known weight (eg, dumbbells which have been accurately weighed on a force platform) are EACH placed on the weighing scale on three separate occasions, and the weight to the nearest 0.1kg as displayed by the weighing scale recorded.

The calibration factor to be used for correcting the subject weight is then obtained by following the steps below:

- The average of the three attempts for EACH of the three known weights is calculated
- The ratio of the scale average to each of the known weights is calculated
e.g. Scale weight averages = 5.1 kg, 10.5, 20.7 kg
Known weights= 4.9 kg, 10.1 kg, 20.3 kg
Ratios=5.1/4.9; 10.5/10.1; 20.7/20.3

The average of these 3 ratios is the **calibration factor**.

- Each measured weight of the subject is divided by the average calibration factor to obtain the TRUE WEIGHT, which is entered into the source document.

- The calibration factor may change during the course of the study and it is important that site staff maintain a log of the date/time that each calibration is undertaken. It is strongly recommended that the calibration factors are part of the calibration log and kept with the weighing scale.

**Body Weight**

- Body weight is recorded three times while the subject is wearing only a robe (with a measured weight) and no shoes.

- Any unusual conditions should be noted (e.g. presence of a cast or other non-removable appliance such as a brace, amputation).

- Pockets and heavy jewelry, hats, etc., should be removed prior to having the subject step on the weighing scale.

- The subject should step on and off the scale for EACH of the three attempts, whenever possible.
• All three weights are recorded, corrected with the calibration factor as described above, and entered into the source document.

Note:

• For RMR, body mass in robe minus the weight of the robe is the entered measurement.

• For max test on the treadmill, body mass is entered including the weight of the clothes and shoes that the subject is wearing.
MEASUREMENT OF STRETCH STATURE (STANDING HEIGHT)

Equipment:

- Wall mounted Holtain stadiometer (Holtain Limited, Crymmych Pembs., UK),
calibrated with steel calibration measuring stick of known length

- Height must be measured in all subjects at baseline assessment. It is not measured
  at follow-up assessments, unless it was not recorded at baseline. In this case, a
  follow-up height is taken and used as a “baseline height”.

Protocol

- Subject is barefoot with the feet together and heels, buttocks, and shoulder blades
  against the wall, or as close to this position as possible (if the vertical position of
  the body is distorted it may be just the buttocks against the wall mount.

- Head must be in Frankfort plane:
  - Orbitale (lower edge of eye socket) is in the same horizontal plane as the
    tragion (the notch superior to the tragus of the ear).
  - Vertex of skull will be at the highest point.
  - The examiner should assist the subject in the attainment of the Frankfort plane
    by gentle positioning of the head and neck to attain as fully erect a
    posture as possible, telling them to direct his/her gaze straight ahead.

- A walking frame may be placed in front of the volunteer for security and
stabilisation as long as the heels and the shoulder blades remain touching the wall and there is no forward flexion of the spine to hold onto the walker.

- Instruct the subject to take a deep breath in and hold it at full inspiration during each measurement.

- At the end of inspiration, with the head still in the Frankfort plane, an assistant should lower the headboard down gently and completely on vertex of the skull, crushing hair as much as possible, but not so hard as to compress neck or spine. If there is no assistant, place the headboard down before the stretch and then read the measurement where the height is attained while the board travels in contact with the vertex.

- Height is taken at full inspiration to the nearest mm in triplicate.

- The 3 readings (which should be within 5mm of each other) are recorded on the data sheet. If readings are further apart than this, take additional readings until 3 close measures are obtained. All three measurements are entered into the data base to allow calculation of CV's.

**BODY MASS INDEX**

The body mass index (BMI) is calculated by dividing the subject's body weight in kilograms by the square of their height in meters.
GAIT SPEEDS

Habitual and Maximal gait speeds need to be reviewed during the physician screen prior to the maximal stress test. After timing gait as per the protocols below, use the gait speed calculator on the “Q-stress” system to calculate gait speeds. Change printer to “C-Block” printer and print. Leave on the desk in C111 with subject’s medical records and screening file for Professor Maria Fiatarone Singh to review.

HABITUAL GAIT VELOCITY

Equipment

- Ultra-timer with working battery

Purpose

This test is meant to record the normal walking speed of the volunteer, as if he or she were not being observed. Gait velocity is a very good overall indicator of functional status, and it is typically slowed by both aging and disease. In the elderly, muscle weakness and poor balance contribute substantially to abnormal gaits.

Preparing the volunteer

- Volunteer should be wearing normal, low-heeled walking shoes, comfortable clothing, eye glasses and hearing aides, if any.
- They should have been offered to use the restroom prior to starting the test. If an assistive device is normally used for walking, the person should use this during the
test, and the device used should be recorded on the worksheet.

- The same assistive device should be used at all timepoints if possible, unless the person has advanced to a higher level device (e.g. walker instead of a cane) due to changing medical condition.

- If the volunteer rarely uses a cane, do not use it during the testing.

Environmental Considerations
The gait speed test should be conducted in an indoor room or hallway which is entirely free of traffic or clutter. An open path of at least 10 meters in length is needed. Preferably, there should be no wall directly in front of the volunteer as they are walking forward. The path should be well lighted by natural or artificial lighting. A non-slip, non-carpeted surface such as tile or linoleum is best, but if carpeted floor must be used it should be low pile wall-to-wall carpeting, and the same surface must be used at all timepoints.

Protocol
- Place the Ultra-timer receiver on the belt so that it is positioned in the middle of the subject’s back and is in a direct line with the examiner’s transmitter.

- Fasten belt snugly around waist, and make sure no clothing or belt loops are covering the “eye” of the box.

- Stand directly behind the subject and tell them to walk at a normal pace, as though you were not there observing them.
• Tell the subject this is “Not a test of their fastest walking speed”, which will come later on.

• The subject is to start walking when you say “Begin” and not stop until instructed.

• Turn on the transmitter. If no numbers appear on the dial, the battery needs to be replaced before continuing.

• When the subject has moved approximately 2 meters away from you, press the “Start” button on the transmitter you are holding, making sure that it is pointed directly at the receiver and that you do not change your hand or foot position at all during the test.

• As soon as the subject has moved an additional 2 meters away from you, the box will automatically stop timing and you can then tell the subject to stop walking.

• Record the numbers you see on the dial. This is the number of seconds it took the subject to walk 2 meters. If this number is divided by 2, this is the number of seconds it takes to walk 1 meter. Inverting this will give you gait velocity in meters/second (m/sec) which are the required units.

  e.g.:  4.00 = Ultra-timer readout
         2.00 = seconds to walk 1 meter
         1/2.00 = 0.50 = gait velocity in m/sec

• After recording the numbers, press the reset button on the transmitter.
• Repeat the entire test procedure above and record the numbers you see on the dial.

The average of the two readings of gait velocity will be the final score which is used.

At the screening visit, it will be necessary to:

1) average the two reading of gait velocity from the Ultra-timer, and

2) convert this average score to m/sec, the required units.

Once the score is in m/sec, you can determine if the subject meets the inclusion criteria for habitual gait speed. Habitual gait speed should be between:

• 0.6 - 1.3 m/sec (inclusive) for males; and,

• 0.6 to 1.2 m/sec (inclusive) for females.

• If a subject’s score in m/sec is .55 to .59, this can be rounded up to 6.0 and thus the subject would be eligible for the study.

• Any score in m/sec above 1.3 for males and 1.2 for females makes a subject ineligible for the study.

For all follow-up testing, you will only be required to enter the two readings from the Ultra-timer onto the CRF and the computer will calculate the average and then convert the score to m/sec.

**Common problems/questions**

Make sure to let the person walk 2 meters before pressing the start button, so that
acceleration is not factored into the speed. Similarly, you do not want deceleration to be part of the measurement, so do not mark a finish line or give the subject any indication as to when the walk will end. The receiver and transmitter cannot be more than 7 meters apart to work. Therefore, do not let the person “warm-up” for more than 2-3 meters, or you will run out of distance before the measured 2 meter walk is over. The two readings should be almost identical, unless the person has not understood your directions or other errors have been made. If they are not in close agreement, do the test a third time and discard the outlying reading.

Be sure to turn off the transmitter after each test or the battery will wear down quickly. Always have a spare battery with you in the Ultra-timer case to avoid delays in testing

**Maximal Gait Velocity**

**Equipment**

- Ultra-timer with working battery

**Purpose**

This test is meant to record the maximal walking speed of the volunteer, as if he or she were exerting and covering as much ground as possible without breaking into a jog or run. Maximal gait velocity in healthy young people may be twice as fast as habitual gait velocity. The difference between habitual and maximal velocity narrows considerably with age. Very frail older people are able to make little or no adjustments to their customary walking speed, due to low endurance, muscle weakness, imbalance, arthritic pain or orthopaedic limitations.
Preparing the volunteer

Volunteer should be wearing normal, low-heeled walking shoes, comfortable clothing, eye glasses and hearing aides, if any. They should have been offered to use the restroom prior to starting the test. If an assistive device is normally used for walking, the person should use this during the test, and the device used should be recorded on the worksheet. The same assistive device should be used at all timepoints if possible, unless the person has advanced to a higher level device (e.g. walker instead of a cane) due to changing medical condition. If the volunteer rarely uses a cane, do not use it during the testing.

Environmental considerations

The maximal gait speed test should be conducted in an indoor room or hallway which is entirely free of traffic or clutter. An open path of at least 10 meters in length is needed. Preferably, there should be no wall directly in front of the volunteer as they are walking forward. The path should be well lighted by natural or artificial lighting. A non-slip, non-carpeted surface such as tile or linoleum is best, but if carpeted floor must be used it should be low pile wall-to-wall carpeting, and the same surface must be used at all timepoints.

Protocol

- Place the Ultra-timer receiver on the belt so that it is positioned in the middle of the subject’s back and is in a direct line with the examiner’s transmitter.

- Fasten belt snugly around waist, and make sure no clothing or belt loops are covering the “eye” of the box.
• Stand directly behind the subject and tell them to walk as fast as they can, and they will be timed to measure their speed.

• Tell the subject this is a test of their fastest walking speed, unlike the normal gait speed test they just completed.

• The subject is to start walking when you say “1, 2, 3, GO!!!” and not stop until instructed. It is important to give this command to elicit maximal acceleration.

• Turn on the transmitter. If no numbers appear on the dial, the battery needs to be replaced before continuing.

• When the subject has moved approximately 2 meters away from you, press the “Start” button on the transmitter you are holding, making sure that it is pointed directly at the receiver and that you do not change your hand or foot position at all during the test.

• As soon as the subject has moved an additional 2 meters away from you, the box will automatically stop timing and you can then tell the subject to stop walking.

• Record the numbers you see on the dial. This is the number of seconds it took the subject to walk 2 meters. If this number is divided by 2, this is the number of seconds it takes to walk 1 meter. Inverting this will give you gait velocity in m/sec, which are the required units.

  e.g.: 4.00 = Ultra-timer readout
  2.00 = seconds to walk 1 meter
1/2.00 = 0.50 = gait velocity in m/sec

- After recording the number, press the reset button on the transmitter.

- Repeat the entire test procedure above. Record the numbers from the Ultratimer.

- Both of these numbers will be entered onto the CRF. The computer will then convert these scores to m/sec, the required units.

- The best (highest) of the two readings of maximal gait velocity in m/sec will be picked by the computer as the final score which is used. It is not necessary for you to do any calculations to determine maximal gait velocity!

**Common problems/questions**

Make sure to let the person walk 2 meters before pressing the start button, so that acceleration is not factored into the speed. Similarly, you do not want deceleration to be part of the measurement, so do not mark a finish line or give the subject any indication as to when the walk will end. The receiver and transmitter cannot be more than 7 meters apart to work. Therefore, do not let the person “warm-up” for more than 2-3 meters, or you will run out of distance before the measured 2 meter walk is over.

The two readings should be almost identical, unless the person has not understood your directions or other errors have been made. If they are not in close agreement, do the test a third time and discard the outlying reading.

It is good to tell the person the first result and encourage them to beat it on the second try.

If you are concerned about balance problems, position the subject near the wall or railing so that they can immediately grab it if they start to fall. Subjects will normally not walk faster than they feel they safely can, but you may test someone whose judgment is not good.
in this regard, so be aware during the initial gait test of any potential problems during this more stressful test and be prepared to spot them. If necessary, two examiners can be used for the very frail, one timer and one spotter.

Be sure to turn off the transmitter after each test or the battery will wear down quickly. Always have a spare battery with you in the Ultra-timer case to avoid delays in testing.
STATIC BALANCE

Equipment

- Measuring Tape
- Stopwatch that can measure time in seconds to 0.01 seconds
- Chair

Purpose

These tests are progressively more difficult tests of both static and dynamic balance, both of which are related to the quality of gait and risk of falling in older adults. Balance is a complex phenomenon with many inputs, including vision, proprioception, coordination, muscle strength, reaction time, and others. In static balance testing, by narrowing the base of support over which a person’s centre of gravity rests, the task of standing still without moving or falling becomes progressively more difficult. Removing visual cues makes this even more difficult. This is the purpose of the timed stands. Dynamic stresses include moving through space with a narrow base of support (tandem walking), or more difficult versions of this kind of test.

Preparing the subject

Subject should be wearing normal, low-heeled walking shoes, comfortable clothing, eye glasses and hearing aides, if any. The subject should have been offered to use the restroom prior to starting the test. If an assistive device is normally used for walking, the person cannot use this during the test, as it reduces the difficulty of the tasks greatly. If the
subject is unable to stand without the use of an assistive device, this should be recorded in the source documents, as the person being unable to do the test.

**Environmental considerations**

A quiet area with vinyl flooring or very low pile carpeting, good lighting, and with at least a 30 foot straight, unobstructed path is needed. The same flooring should be used at all time points.

**Protocol for static balance**

Be sure to demonstrate all positions to the subject one at a time as you explain that you will be testing balance, and “the task is to keep the feet in the desired position for 15 seconds while being timed”. Arms and trunk may be moved slightly during the test if needed to maintain balance, but the timing ends when the full 15 seconds is reached or when either foot moves, or if you or any object in the environment is touched by the subject, whichever comes first.

The subject must wear comfortable, low-heal shoes for these tests; tests may not be conducted with the subject in bare feet as these tests are devised to ascertain balance in activities of daily living. Position the subject so that his/her back is about 1 ft in front of a chair, in case the subject begins to fall. You should be positioned just to either side, close enough to spot the subject and prevent a fall but not touching the subject. For each position, demonstrate and then allow the subject to try to assume the correct position unassisted. If this is not possible, assist the subject in doing so, and then let go of him/her. For the most
difficult tests, you may position the subject and hold onto one of his/her hands, letting go just when you begin to time the subject, otherwise the subject may lose his/her balance before the test actually begins. The person must feel secure when doing these tests. It is acceptable to position a subject’s walker just in front of the subject during the static balance tests as long as the subject doesn’t touch it during the test, as the subject may feel more confident to try in that case.

Do not repeat tests unless it is clear directions were misunderstood, as practice makes the subject learn how to do the task very rapidly, and it is unfair to compare single and multiple attempts among different subjects. Subject must stand up as straight as possible as bending the knees during the balance test reduces the difficulty of the task greatly. The series of static balance stands are done in the following order:

**Static Balance Tests**

1) Wide Stance

2) Narrow Stance

3) Semi-tandem Stance

4) Tandem Stance

5) One Leg, Eyes Open

6) One Leg, Eyes Closed
1) Wide stance, no hand support

- Subject's feet are positioned so that the feet are lined up approximately hip width apart and in parallel.
- Record the number of seconds to the nearest 0.01 seconds from the stopwatch, up to a maximum of 15 seconds.
- Tell the person to relax (eg, widen their stand by moving the feet to be shoulder width apart; subject should not be allowed to sit down) at the end of the 15 seconds as they watch you demonstrate the next position.

2) Narrow stance, no hand support

- Subject's feet are positioned so that the feet are lined up next to each other pointing straight ahead and are touching all along the length of the foot.
- If bunions or other conditions prevent this, position the feet so that the heels are touching each other.
- Record the number of seconds to the nearest 0.01 seconds from the stopwatch, up to a maximum of 15 seconds.
- Tell the person to relax (eg, widen their stand by moving the feet to be shoulder width apart; subject should not be allowed to sit down) at the end of the 15 seconds as they watch you demonstrate the next position.
3) Semi-tandem stand, no hand support

- Subject's feet are positioned so that the toes of one foot are at the level of the instep of the other foot, and feet are touching.

- Either foot may be placed ahead of the other according to preference/comfort as the position is tried out.

- Record the number of seconds to the nearest 0.01 seconds from the stopwatch, up to a maximum of 15 seconds.

- Tell the person to relax (e.g., widen their stand by moving the feet to be shoulder width apart; subject should not be allowed to sit down) at the end of the 15 seconds as they watch you demonstrate the next position.

4) Tandem stand, no hand support

- Subject's feet are positioned so that the toes of one foot are touching the heel of the other foot, and feet are both pointing directly forward.

- Either foot may be placed ahead of the other according to preference/comfort as the position is tried out.

- Record the number of seconds to the nearest 0.01 seconds from the stopwatch, up to a maximum of 15 seconds.

- If necessary, hold onto the subject's hand, and start the stopwatch as soon as you let go.
• Tell the person to relax (eg, widen their stand by moving the feet to be shoulder width apart; subject should not be allowed to sit down) at the end of the 15 seconds as they watch you demonstrate the next position.

5) One leg, eyes open, no hand support

• The subject needs to lift one foot so that it is clear of the floor. They may choose whichever foot they feel most comfortable with.

• Start timing after the foot position is attained correctly.

• If necessary, hold onto the subject’s hand, and start the stopwatch as soon as you let go.

• Record the number of seconds to the nearest 0.01 seconds from the stopwatch, up to a maximum of 15 seconds.

• Tell the person to relax (eg, widen their stand by moving the feet to be shoulder width apart; subject should not be allowed to sit down) at the end of the 15 seconds.

6) One leg, eyes closed, no hand support

• As above for the one leg stand, except that the eyes are closed after the foot position is attained correctly.

• If necessary, hold onto the subject’s hand, and start the stopwatch as soon as
you let go.

- Subjects’ eyes must be closed before the stopwatch is started.

- Record the number of seconds to the nearest 0.01 seconds from the stopwatch, up to a maximum of 15 seconds.

- Tell the person to relax (e.g., widen their stand by moving the feet to be shoulder width apart; subject should not be allowed to sit down) at the end of the 15 seconds.

Note that all positions must be tried in the order listed, regardless of the level of performance on the preceding test. If a subject attempts but is unable to achieve a position and start the timing, even with you helping them get in position, record unable to do in the source documents. The time recorded in the source documents will consist of all the digits offered by the stopwatch; when transcribing the time to the case report forms (CRFs), the time should be rounded to the nearest 0.01 sec. If the subject is able to achieve the desired position, with or without your assistance, and the stopwatch is started, record whatever time is achieved, even if it is only a fraction of a second.
Physician Screen

BLOOD PRESSURE MEASUREMENT

Time since last exercise, medications, hydration status, time since last meal, test room temperature, cuff size, sphygmomanometer angle and positioning, and arm angle upon standing may all affect the results of this measurement and therefore should be standardized, or recorded on the data sheet.

Equipment

- Mercury Sphygmomanometer (Enter Make, Model)
- Stethoscope

  a. A cuff size appropriate to the size of the arm should be selected.
  b. The cuff is placed snugly over the upper arm with the bladder centred over the brachial artery, as indicated by the arrow on the cuff, and the lower edge of the cuff about 1 cm above the crease of the elbow.
  c. The patient should be seated for at least 5 minutes before the measurement is taken, with feet flat on floor, and no environmental distractions present.
  d. The patient’s arm, from which the measurement is made, is supported by the assessor taking the measurement at the heart level, or preferably is supported on a table or arm of a chair.
  e. The right arm should be used unless it is not possible (lymph node dissection, amputation, other).
  f. The position of the sphygmomanometer is at eye level.
  g. Blood pressures are recorded in even numbers and read to the closest 2
mmHg mark.

h. The bladder should inflated quickly to 200 mmHg, and then be deflated slowly.

i. The first Korotkoff sound (first of a repetitive series of sounds that are heard) should be recorded as systolic pressure.

j. The pressure at the point the last sound fades out completely should be recorded as diastolic pressure.

k. If the measurement needs to be repeated, one minute or longer must elapse between reading...
MAXIMAL TREADMILL TEST PROTOCOL

Equipment

- BreezeSuite software, version 6.2a
- Quinton 4500 Stress Test Monitor (Bothell, WA, U.S.A)
- Quinton Automatic BP monitor model 412 (Bothell, WA, U.S.A)
- 3M Electrodes
- Pneumotach
- Medgraphics mask (Pat. #6718982, Taiwan)

Medgraphics Equipment and Software Preparation

1. Turn Ultima PFX “on” via the wall switch (white cord) at least 40 min before use.
   Wait until the red light on the Ultima PFX turns from red to green. This indicates that it is ready for use.

2. Select the program “Breeze” from the desktop of the computer.

3. The window which appears in front of you when you first open the program is the ‘Patient’ screen. Select the ‘New’ option at the bottom of the window. Enter in patient’s last, middle and first names, gender race and Date of Birth in the boxes provided. Press ‘Add visit’. This information is only entered at the first visit, and is
retrieveable subsequent visits. To retrieve, when the ‘Patient’ screen is open, select the patients file from the list present, press ‘add visit’.

4. The next screen that will appear is another patient information screen.

5. DO NOT enter this information because you will still be waiting on some details (height and weight). This can be filled out after the anthropometry is assessed, prior to testing. This screen can be in the background as you prepare the software for testing.

6. Select

7. Wait until the red coloured numbers next to “GX Vac” turn into a green “READY”. This takes 10 minutes.

8. Select

This calibrates the pneumotach. You will need to enter the temperature, humidity and barometric pressure at bottom of window/screen PRIOR to calibrating. Room temperature (°C) and humidity (%) are obtained from the temperature and humidity gauge on the shelves located on your left. The barometric pressure (hPa) is obtained from the Bankstown airport Website:
9. Attach pneumotach to the blue end of the 3L calibration syringe. Remove the gas analyser from the front of the Ultima system and attach it to the pneumotach/syringe configuration. (NOTE: the gas analyser is attached to the pneumotach correctly; the notch on the gas analyser is at opposite sides to the notch on the pneumotach)

10. Select “Zero flow” (whilst holding your palm over the end of the pneumotach). If there a caution message that the ‘flow is out of range’, check correct configuration of the syringe/pneumotach/gas analyser configuration and retry. If there was no caution message, this mean the ‘zero flow’ was successful.

11. When ready, you will be asked to calibrate different flow rates using the known volume of air in the syringe. Press ‘start’ and then pull syringe pistol in and out - at a speed to match the lines on the graph displayed on the screen. Do this at five different speeds. (NOTE: To re-do or reset, select “Stop”, then “Start” – and try calibrating again)

12. If calibration is successful, ‘calibration successful’ will appear on the screen. If the calibration was unsuccessful, ‘calibration unsuccessful’ will appear. You will need to retry until ‘calibration successful’ appears.

13. Select “OK” when done. This will close the calibration window.

14. To perform the ‘Calibration of gases’, turn the handles on both gas cylinders in a counter-clockwise direction to open cylinders (the gas cylinders are located at the
back of the cart). You do not need to open the knobs all the way. They only need to be turned 90 degrees from the starting position. (Do not touch the knobs where indicated by signs ‘DO NOT TOUCH!’).

15. Return the gas analyser into the Ultima PFX (with the 2 pins on top).

16. Select

A caution message ‘Calibrating Gas Analysers’ will appear while auto calibrating the gas cylinders. A summary window will appear once the calibration is complete, indicating that the calibration was successful.

17. Select “OK”.

18. Turn gases off completely (twist knobs clockwise) when calibration is complete. If left open, the gases will be depleted.

19. Now that the anthropometry has been measured, enter the details into the patient page.

20. Select

The “Gas Exchange” tab is located at the bottom of the screen.

21. The ‘settings’ page will be the page appearing on the screen.

22. Enter the details of the test you will be conducting. In this case it will be a ‘treadmill test’. Enter physician and technician details in the appropriate places. Select the ‘HR monitor’ in the ‘External Device’ column. This will allow the Medgraphics system to register heart rate reading from the Quinton ECG machine. Heart rate
reading will be displayed with the other variables on the computer screen.

23. Select the ‘Test’ tab. At this point the page displays a blank data section (located in the top portion of the screen with variables such as V02, VCO2 RER and HR) and two blank graphs.
WITH THE PATIENT PRESENT

- Remind the patient whether they need to visit the bathroom prior to the test

- Explain purpose of test. Illustrate how to straddle the treadmill and then begin walking on the moving belt.

- Explain the electrode placement, and the purpose of having the electrodes.

- Explain the placement of the mask and its purpose

- Explain the placement of the BP cuff and its purpose

- Explain that the research assistant and MD will encourage patient throughout the test. Explain/show ‘thumbs up’ for doing well/keep going, for the test to continue.

- Explain/show ‘thumbs down’ if they can not go on anymore for the test to cease immediately followed by a 1-2 minute cool down.
CONNECTING THE PATIENT TO THE TESTING APARATUS

The patient will be attached to three pieces of testing equipment:

- ECG
- BP
- MEDGRAPHICS

The patient preparation will take place in three positions:

- Supine
- Seated
- Standing

Patient supine

- Enclose the testing area by drawing the curtains to ensure the patients privacy during electrode placement.
- Ask subjects to remove, open or lift their shirt (females are instructed to wear a crop-top/bikini top/singlet top). Electrodes are placed while the patient is in a supine position. Any body hair is shaved off with a disposable razor when necessary.
- Electrodes are placed on subjects using the 12-lead placement and positioned as follows: (refer to picture of correct 12-lead placement)
- RA and LA: just below the right/left clavicle medial to the deltoid.
- RL and LL: just above the right/left iliac crest along the midaxillary line.
- V1-V6: as described in Rautaharju et al

- Attach the leads to the electrodes, check correct placement of electrodes by selecting “Check Electrodes” on the Quinton Computer. If the signal does not look good, make sure the electrodes are in the right place and are properly attached. If the signal appears normal, select the “Exercise Test” option.

**Patient seated**

- Place the BP cuff snugly around the subject’s left arm, after palpating the brachial artery pulse.

- Use the Blood Pressure cuff which is peripherally attached to the Quinton 4500. Take supine BP manually by placing the BP monitor in ‘manual’ mode. Press the ‘Start’ button on the BP monitor until ‘systolic pressure’ is inflated to approximately 200.

- Ask the patient to be seated in a chair, and may re-button/readjust their shirt.

- Resting ECG readings are viewed by Doctor, while final stages of Medgraphics preparation are taking place.

- Another manual BP measurement is taken while the patient is in the seated position. While still in ‘manual’ mode press the ‘Start’ button on the BP monitor until
‘systolic pressure’ is inflated to approximately 200.

- Provide a couple of sizes of mask for the patient to try on. The mask should be snug, but not too tight so that the flesh surrounding the mask is protruding. Ask the patient to take a few breaths so that you could feel any air escaping from around the nose or around the chin.

- Ascertain the correct size mask for the patient, then remove the mask and ask the patient to stand on the treadmill.

NOTE: Wearing the mask is uncomfortable, and this time should not be prolonged unnecessarily.

**Patient standing**

- Patient to assume the ‘straddle’ position on the treadmill.

- Standing blood pressure measurement is taken in the standing position.

- While still in ‘manual’ mode press the ‘Start’ button on the BP monitor until ‘systolic pressure’ is inflated to approximately 200.

- Replace the mask on the patient's face and feed the gas analyser and tube through the cord which is suspended from the roof.

- Placing the mask onto the patient, and attach the gas analyser is the last step of the preparation phase.
• Press the button located on the top left hand corner of the screen. This will start the collection of the data from the mask into the Medgraphics system. The empty data screen and graphs will now have information appearing.

• Obtain standing resting measurements for approximately one minute to ensure that all equipment is in working order.

• The patient is now ready to begin the testing procedure. Simultaneously press ‘Start exercise’ on all machines (BP, ECG, and Metabolic cart) and begin treadmill protocol.

TESTING PROTOCOL

• Measure habitual gait speed (refer to the Ultratimer protocol). Convert this value from time taken to travel 2 minutes to km/hour

• Set treadmill as close as possible to that speed. Adjust up or down to achieve a mechanically efficient walking motion on the treadmill.

• For older or frailer patients, start with 80% of habitual gait speed; adjust up or down as needed.

• For younger patients, start at 100% habitual gait speed; adjust up or down as needed.

• Ask subject to very lightly grasp the handrails for balance. Record if 1 or 2 hands
were used during the test.

- Start the exercise test a 0% incline walking at/around habitual gait speed. Incline is increased by 2% per minute.

- Blood Pressure is taken automatically at 2 minute intervals throughout the test and at the end of the test.

- Encourage the subject every minute from the start of the test, until they start displaying signs of fatigue, then encouragement is provided more often.

- The intention is for the test to continue for a minimum of 6 minutes but no longer than 10 minutes. The test will be terminated when the subject requests to discontinue (volitional fatigue).

- Other reasons for terminating a test include abnormalities of pulse or ECG noted by physician/research assistant, failure of technical equipment, drop in SBP ≥10mmHg despite an increase in workload, and signs of poor perfusion (light-headedness, confusion, pallor, nausea, cold and clammy skin) The same protocol (including starting speed and grade) is used for each subject at baseline and follow-up.

- When the test is terminated because of any of the above reasons:
  
  - Reduce the incline to 0% and the speed to 1.1km/hr.
  
  - The stop button is pressed on all machines. At this point the Quinton 4500 will automatically take the patient’s BP.
- Remove the mask from the patient at the earliest convenience.

- Patient is to continue walking at the above mentioned speed, with the ECG and BP measurements continuing to take place.

- At the Physician’s cue, the patient may cease walking, at this point they are provided with a chair and a glass of water if they like. The physician continues to monitor ECG, BP and HR readings. Once the Physician is satisfied with the measures returning almost to rest levels, the procedure is stopped at the physician’s cue.

- At the earliest convenience, proceed to cleaning the mask, pneumotach and coupler (as described in the maintenance section)
PERFORMANCE BASED TESTS OF FUNCTION

GENERAL GUIDELINES

Performance-based testing is a means to quantitatively define or estimate the maximal physiologic capacity in a variety of domains which are thought to be relevant to functional status and mobility in the elderly. These tests are valid and reproducible only if the directions are followed meticulously, so as to avoid inter-tester differences which can otherwise be quite large. **Although each test is simple to perform, small errors in timing, instructions to the volunteer, or changes in environmental conditions have large effects on the outcome.**

For each test, its purpose, necessary equipment, volunteer preparation, environmental considerations, and exact protocol and data collected are indicated in the sections which follow/

Because the attempt is to elicit maximal performance in each of these areas, it is essential that the volunteers be aware of the requirements of the test, mentally and physically capable of giving a maximal effort, as well as being as unfatigued as possible. **The tests are meant to be performed in the order listed** in order to reduce the possibility of fatigue interfering with the subsequent test.  In general a five minute rest period is given between tests during which time water may be offered and additional explanations given. However, if a volunteer appears to need a longer break, than it should always be given. As this will not adversely affect test scores in any way.
Before beginning testing, an assessment should be made that the volunteer is competent to undergo testing, has signed the informed consent papers, and is medically stable. If there is any doubt that the person is at their baseline medical condition, or if an acute, previously undiagnosed serious symptom is discovered on questioning, seek advice from medical personnel of coordinators before continuing with the protocols. Always err on the side of safety in this regard. If a volunteer refuses all or part of the testing in the middle of a session, for any reason, adhere to their wishes and stop at that point.

**Demonstrate all tests** for the volunteer as well as giving the verbal instructions indicated, as this is usually far easier for most people to grasp. Encouragement to elicit maximal performance is an essential part of these testing procedures and should always be used. Record all data from each test immediately on data sheets or computers so that no information is lost.
**SIT-TO-STAND**

**Equipment**
- Standard chair
- Stopwatch

**Purpose**
This test is used as a proxy for lower extremity power, or the ability to generate high forces rapidly. The hip extensor and knee extensor muscle groups are primarily used in this task, which may be quite difficult for frailer individuals. As frailty increases, the time taken to complete the task extends, and muscle endurance begins to play a role in addition to muscle power.

**Preparing the volunteer**
The volunteer should be wearing normal, low-heeled walking shoes, comfortable clothing, eyeglasses and hearing aides, if any. They should have been offered to use the restroom prior to starting the test.

**Environmental considerations**
The standard chair should be placed with the back directly against a wall so that it is secure during testing. If a walker is normally used for ambulation it may be placed 2 feet in front of the volunteer if they think they may need to steady themselves at the end of the test, but they should not touch it unless absolutely necessary.
Protocol

Instruct the volunteer that the purpose of the test is to stand up and sit down as rapidly as possible 5 times in a row. Encouragement to achieve maximal performance is critical in this test, as they may otherwise forget the nature of the task in the middle.

Position the volunteer in the chair so that their back is against the back of the chair, feet are planted on the ground (It is okay if the subject’s feet do not reach the ground), knees bent at 90 degrees, and arms crossed in front of chest. When you say “1,2,3, GO!” start the stopwatch. The subject should rise fully and sit down fully a total of 5 times in a row. Stop the watch when they have achieved a fully erect standing position for a 5th time. DO NOT WAIT until they have resumed their initial position in the chair.

Tell them that they should try to do it without using their arms, but if they find at any point during the test that they need to use their arms to push off the chair or complete a stand, they should do so and continue with the test. Record the time taken to complete 5 stands to the nearest 0.01 second on the worksheet, as well as whether or not the volunteer used their arms for assistance.

This test is done one time only!

Common problems/questions

Make sure that the subject does not begin to move forward in the chair or reposition their feet until you actually begin the test. On each stand, they must come to a complete erect posture; evaluate their standing posture before you begin so that you will know what “erect”
means for them. Similarly, they must return all the way back to the starting position in the chair between each rise; it is not sufficient to barely touch the seat and then come back up. If someone tries over and over to rise without their arms unsuccessfully when you start the test, and is clearly going to be unable to do it, stop them and tell them to start with their arms crossed, but as soon as you say go, uncross their arms and use them to assist for all of the rises if necessary.

You will also need to stop the test if the person is not following the directions to rise or sit down fully. Since it is fatiguing to repeat this test, and will adversely affect test scores, it is much better to anticipate and demonstrate these common errors for the volunteer before they actually try it themselves.
**STAIR CLIMB**

Volunteer should be wearing normal, low-heeled walking shoes, comfortable clothing, eyeglasses and hearing aids, if any. Hand rails may be used if necessary.

Environmental conditions

Lighting and ventilation should be adequate. Close off the area to other traffic during testing.

Protocol

- Instruct the subject that the purpose of the test is to climb the stairs as rapidly as possible. The subject should start with hands by their sides at the foot of the stairs, close to one of the handrails in case they need to use it, but they should attempt the test without using their hands.
- Say “1, 2, 3, GO!” and start the stopwatch, following them up the stairs as they go. Stop the watch when both of their feet are on the landing at the top of the stairs.

Calculation

Power (Watts) is calculated from the formula:

\[ P = (M \times D) \times \frac{9.8}{t} \]

Where:

- \( P \) = Power (Watts)
- \( M \) = Body mass (kg)
D = Vertical distance (m)

t = Time (s)

D = vertical height of the staircase= height of 1 step in meters x number of steps (if they are all the same height)

NOTE: Units must be in kg and meters for correct calculation of power in Watts.
SIX MINUTE WALK TEST

Equipment

- Measure Meter
- Stopwatch

Purpose

The six minute walk is a proxy for overall cardiovascular endurance capacity (aerobic capacity). In addition to cardiovascular efficiency, however, in the elderly subject it may be determined by muscle strength and endurance, balance, orthopaedic or neurologic abnormalities, and other problems. It works best as an estimate of aerobic capacity in individuals who cannot run, so that variations in walking velocity describe most of the possible range of function. Therefore it is very appropriate in very frail or elderly volunteers as well as healthy elderly.

Preparing the volunteer

Volunteer should be wearing normal, low-heeled walking shoes, comfortable clothing, eye glasses and hearing aids, if any. They should have been offered to use the restroom prior to starting the test. If an assistive device is normally used for walking, the person should use this during the test, and the device used should be recorded on the data sheet. The same assistive device should be used at all timepoints if possible, unless the person has advanced to a higher level device (e.g. walker instead of a cane) due to changing medical condition. If the volunteer rarely uses a cane, do not use it during the testing.
Environmental considerations

This test requires a long open circuit around which the volunteer can walk continuously for six minutes. Long circular or square corridors around the perimeter of a building without many turns are ideal. All testing should be done indoors rather than outdoors, as there are too many uncontrolled variables in outdoor areas. The path should be free of clutter and all other traffic should be closed off if possible during the testing. No steps, inclines, doors, or other obstacles should be in the path of the volunteer, and lighting and ventilation should be adequate.

Protocol

The person should be instructed that they are to “cover as much ground as possible in six minutes” by “walking as fast as they can the entire time”. They must be encouraged and reminded of the task at least every 30 seconds during the test or they will tend to slow down. Line up the Measure Meter (with the dial reset to read 000) with the volunteer’s feet on the starting line. Prior to beginning the test, ascertain that the volunteer’s pulse rate, breathing rate, and blood pressure are in their normal range. Say “1,2,3, GO!” and begin the stopwatch. Follow closely behind the volunteer with the Measure Meter, attempting to follow their path as closely as possible without getting in their way or influencing their gait speed. The number of metres travelled at the end of 6 minutes is recorded to the nearest foot from the wheel. Use standardized statements such as:

• “Keep Going!”
• “You’re Doing Well!”
• “Keep up the Good Work”
If the volunteer needs to stop to rest during the test, the watch continues to run, and they should be instructed to start back up again as soon as they are able.

If they develop angina during the test, or any other symptoms which seem severe, the test should be terminated immediately and emergency medical help should be contacted. However, shortness of breath, fatigue, and slight muscle or joint pain are not unusual and are not an indication for stopping the test. If claudication occurs, the person may need to stop momentarily, but can go on as soon as they feel able.

Record if an assistive device used, the number of stops made during the test, any symptoms which developed during the test, reason for stopping prematurely, if any, and the total distance covered in 6 minutes to the nearest 0.1 metre. This test is only performed once.

Common problems/questions
The volunteer should be well rested prior to beginning this test, as it requires physical stamina and mental alertness. The exact wording above should be used to instruct the volunteer so that consistency is maintained. The volunteer is not allowed to break into a run; if this happens, stop the test and begin again. If a chair is anticipated to be needed for rest stops, a second examiner can follow closely behind the timer with a wheelchair which can be positioned behind the volunteer as needed. If a volunteer can only ambulate by pushing themselves in a wheelchair, the test can be conducted in this way, but no assistance in moving the wheelchair from anyone else is allowed.
MUSCLE STRENGTH TESTING (ASSESSMENTS)

Initial strength testing will be performed after the subject screening and before assignment to one of the two groups. Baseline, 6 and 12 month follow-up assessments will be conducted on the Keiser equipment in C-block. These assessments include both PRT and SHAM groups. The assessor is blind to the interim strength test results of the subject, as only the PRT group undergoes these tests during training.

Equipment

- Keiser pneumatic-resistance training equipment with K400 electronics (Keiser Sports Health Equipment, Inc., Fresno, CA) is used for muscle strength, power and endurance testing (in C-block).

- The compressor should be turned on at both the power point and the distribution box 2-3 hours prior to use.

- For assessments, 1RM testing is carried out on the following equipment:
  
  - seated leg press
  - seated chest press
  - seated knee extension
  - seated row
  - seated knee flexion

Instructions to Subjects for 1 RM testing

- Before initiating EACH session, you should ask the subject if he/she needs to use the toilet. As strength testing may provoke incontinence, this is particularly important in
older women.

- As applicable, distance vision corrective lenses and hearing aides must be in working order and in place.

- Ensure that proper footwear, such as jogging shoes with non-slip soles, are worn by the subject, in addition to loose pants. It is helpful to be able to visualise the knee if capris or stretch pants are worn by women and sweat pants by men.

- Prior to beginning the test, demonstrate to the subjects the correct technique for performing each of the exercises, which muscle group it isolates, and where this muscle group is located.

- You should explain to the subject why emphasis is placed upon proper breathing technique and avoidance of the Valsalva manoeuvre.

- Demonstrate proper breathing technique (i.e., breathe in before lifting/pushing the weight; breathe out during the “concentric” or lifting/pushing phase).

- Reinforce correct form and breathing during the rest period between repetitions.

- Inform subjects that this is a test of maximum muscle strength. Explain that the objective of the exercise is to find the greatest amount of weight he/she can lift with good form for the whole range of motion one time only. Instruct the subject to push/pull against the footplate or arm of the machine until it is in the fully extended position, as you demonstrate the action.

- Once the movement has been performed, the weight should be lowered carefully.
• Strong verbal encouragement should be given throughout the test.

• Probe for any symptoms such as pain or other discomfort during the rest periods between attempts and document these in the source document.

Procedure

Muscle strength is defined as the maximal weight that can be lifted in good form, one time only, known as the one repetition maximum or 1RM.

• The Keiser air compressor should be turned on at both the power point and the distribution box 2 hours prior to use.

• Record the settings for each piece of equipment positioning on data sheet.

• Allow subject to familiarise with the equipment with 2-3 unweighted repetitions.

NOTE: for the leg press, add only the amount of resistance required to hold the footplates up against the weight of the legs, if necessary. For most subjects, the lowest available resistance holds the footplates up against the weight of the legs. Make sure the bar connecting the two footplates is engaged so that both footplates move as one.

• Using the SETUP key from any mode will bring up the SETUP SCREEN.

• Measure the unweighted range of motion twice by noting the arrow head position on the left side of the display panel. Ensure that good form is used during these repetitions, or the range will be too high and unreachable in good form once the load is increased.
• PRESS position mode and use the arrows to adjust the load. Add a small amount of weight and ask subject the level of difficulty (use Borg RPE Scale)

• For each repetition, record the force in Newtons or Newton-metres from the BOTTOM of the display panel, the BORG rating and whether successful or not (i.e. the range of motion was full and good form was maintained).

• Attempt to reach a BORG rating of 15 in 3-4 lifts, resting 20-30 seconds between each lift.

• Ensure 1 minute rest between each repetition once the BORG rating is > 15.

• Failure is defined as a lift short of the full range of motion (determined in the unweighted position) on at least 2 attempts at least 60 seconds apart. Therefore, if a repetition is failed, either repeat again or lower weight slightly and repeat, depending on the degree of failure.

• On machines with 2 cylinders (i.e., leg press, chest press), note maximum weight for both limbs and write down both on the data sheet.

• To minimise risk of injury, carefully position the subject on each piece of equipment, taking extra care with mounting and dismounting as well as correct exercise position.
Seated Leg Press (bilateral)

Machine Setup

- Assist the subject onto the machine by backing up towards the seat and sitting down first; then assist or observe as the legs are lifted up onto the footplates.

- Move the seat to a position where the hips and knees are bent at approximately 90°. The seat may be moved while the subject is seated, as long as they are stabilised by you and warned that the seat is going to move slowly.

- If subjects cannot flex hips to 90° due to hip pain or abdominal girth, move the seat back to a tolerable position.

- Record the final seat position from the numbered plate in the source document.

Movement Performance

- Subjects’ feet should be placed at the bottom of each foot plate, with the heel resting on the rubber “lip” at the bottom of the foot plate; or if joint pain is encountered, a position allowing pain free movement.

- Extra caution should be used for those subjects who have chronic lower back discomfort, ensuring that they are not twisting the spine and are keeping their back, neck, and head against the padded seat.

- The subject may stabilise the upper body by using handgrips on each side of the seat, making sure that his/her thumb is not touching the force control knob accidentally. The subject’s shoulders and neck should be relaxed.
• The subject should then be instructed to push both legs forward simultaneously and to control the return of the weight back to a resting state.

• It is important that you communicate to the subject that the knees travel in line with the toes, and that they do not drift medially (which is common in subjects with arthritis or weak ligaments around the knee).

• The push should be generated through the whole foot, particularly the heel, not through the forefoot/toes, to ensure activation of the gluteus and hamstring muscles, not just the plantar flexors/quads. You may show the subject where the active muscle area.

• The subject should push until the knees are just short of being “locked” in full extension; that is there should be a very slight bend at the knee.

• Subjects who have osteoarthritis may have limited extension and may not achieve this full range of motion. A subject whose knees are correctly positioned (not locked) will have to use muscle force to keep the footplate out. When the knees are locked, no muscle force is being used, and the bones of the leg are keeping the footplate up. This should be explained and demonstrated explicitly so the subject knows what it feels like to perform the exercise correctly (versus incorrectly).

• Excessive movement of the buttocks completely rising up off the seat is not considered good form but slight movements are tolerated.

**Chest Press**

**Machine Setup**
• Adjust the height of the seat such so the subject’s forearms run parallel with the floor. Record this setting in the source document.

• Range of motion should be determined in the unweighted position.

• Adjust arm levers to the comfort level of the subject and note position. This may depend on the joint limitations and ROM of the rotator cuff. The range limiter will be set at 3 for most subjects.

Movement Performance

• Subject should sit upright facing forward with the back pressed against the back pad.

• The position while gripping the handles should avoid excessive extension of the wrist throughout the range.

• Subject should push to full range without locking the elbows and then slowly allow the arms to control the return of the weight back to resting position.

• The shoulders should not be elevated to compensate for the effort.
Knee Extension

Machine Setup

- Move backrest position so that back and upper legs of the subject are fully supported after the subject is assisted onto the machine.

- The pad should rest just behind the subject’s knee in the popliteal fossa; the subject’s back should be securely supported by the backrest.

- Record the final seat position number in the source document from the numbered plate or notches on the back rest.

- With the subject well positioned in the seat, move the weighted bar position so that it sits just above the malleoli (ankle) level and the foot can still dorsiflex below the weighted bar. Record the position number of the bar in the source document. This may be recorded to the nearest 0.5 (e.g. 3.5) if it is between 2 engraved numbers on the machine.

- Start position is always 90° of knee flexion, to avoid overstretching of the patellar tendon that may cause knee pain. Adjust by pulling out the knob on the range limiter until the correct number appears in the window. No limitation on extension range is imposed during strength testing or training however. Unscrew the range-limiting knob and leave it off the machine. Most subjects will have full extension short of this. Record the start and end positions of the range limiter in the source document.

Movement Performance
• The subject’s hands should be resting lightly on the grips, making sure that his/her thumb is not touching the force control accidentally.

• Similarly, the subject’s shoulders and neck should be as relaxed as possible.

• The subject should then be instructed to straighten his/her legs without any ballistic movement as far as possible, keeping the ankle in neutral position (90º of flexion), and then control the return of the weight back to a resting state.

• Failure is defined as not reaching full extension.

• Do not allow subjects to arch their backs more than very minimally or lift their thigh off the seat to qualify as “good form”.
Seated Row

Machine Setup

- Adjust the seat height so that xiphoid process is positioned in the middle of the chest pad then record this position.

- Adjust the chest pad so that arms are comfortable at full extension and record this position.

- Range of motion should be determined in the unweighted position and recorded.

- Wide grip will be used for 1RM testing, although in training wide grip is used for the PRT group and narrow grip for the SHAM group.

Movement Performance

- The subject’s hands should be resting lightly on the grips, making sure that his/her thumbs are not touching the force control accidentally.

- The chest should remain in contact with the pad, the back should remain straight and motionless and arching the back and neck should be avoided.

- The handles should move to the level or if possible behind the chest pad while contracting the shoulder blades together and then slowly allow their arms to control the return of the weight back to resting position.

- Failure is defined as not reaching within 50 of the recorded full extension (derived from the unweighted range).
**Knee Flexion**

**Machine Setup**

- Move backrest position so that back and upper legs of the subject are fully supported after the subject is assisted onto the machine.

- Note the lever position so that ankles just hang over the edge of the foot padding.

- Record the position number of the bar in the source document. This may be recorded to the nearest 0.5 (e.g. 3.5) if it is between 2 engraved numbers on the machine.

- Ensure that upper legs are held firmly in place by the padding and clicked into place.

- Start position is maintained at -10° of knee flexion. Adjust by pulling out the knob on the range limiter until the correct number appears in the window.

- Unscrew the range limiting knob and leave it off the machine. Record the start and end positions of the range limiter in the source document.

**Movement Performance**

- The subject’s hands should be resting lightly on the grips.

- The subject’s shoulders and neck should be relaxed.

- The subject should then be instructed to bend his/her legs without any ballistic movement as far as possible, keeping the ankle in neutral position, and then allow the legs to control the return of the weight back to an extended position.

- Failure is defined as not reaching full flexion.
• Do not allow the subject to arch the back more than very minimally to qualify as “good form”.

• The subject may need to be reminded to reposition on the seat to ensure the lower back is in contact with the back pad.
**ACTIGRAPH MONITORS**

Physical activity and sleep quality will be monitored using two Actigraph monitors worn over seven days at each timepoint (baseline, 6 and 12 months). The Actigraph used to measure physical activity data is worn around the waist. The Actigraph used to measure sleep quality is worn on the wrist.

Software used to Initialize, Download and Analyse Data

Two separate software programs are used to initialize (set the start times), download and analyse data from the Actigraphs, the ActiLifeGT1M (version 2.2.3) and the ActiWeb Client (version 4.2.2) programs.

ActiLifeGT1M = This program will be used to initialize and download data from the “waist” Actigraph for analysis of physical activity.

ActiWeb Client = This program will be used to initialize, download and upload data from the “wrist” Actigraph to the online ActiWeb Server for analysis of sleep quality.

Actigraph Initialization (Set Up) Procedures

Initialisation sets up the Actigraph for use and clears data from previous collection period.

NOTE: Make sure that Actigraph data from the last collection period has been downloaded (and in the case of the “wrist” Actigraph, uploaded) prior to re-initialization.
“Waist” (Physical Activity) Actigraph

1. Connect “Waist” Actigraph to USB on Computer
2. Go to ‘programs’ and select ‘ActilifeGT1M.exe’
3. A caution window will appear, Click ‘OK’
4. The Main window will appear. You will see a ‘start’ and ‘download’.
5. Click on ‘Start’

‘GT1M Driver Enumerated on COM6 (or similar)
Click OK to continue.
There is (1) device plugged into the System’

6. Click ‘OK’
7. The next screen that will appear is the ‘Initialize Data’
a. Enter Epoch period: 10 second (waist actigraph)
b. Select both ‘Activity Mode’ and ‘Step Count Mode’
c. Enter the desired times and days to begin and end the data collection. For the GREAT2DO study Data is collected for 7 consecutive days.
d. Enter Subject name, waist, timepoint in alphanumeric characters only (eg John Smith_waist_baseline).
8. Once you have entered the appropriate information, click ‘OK’.
9. A caution window saying:
’Sending Initialize Command and Data’

will appear. This step may take a while to complete.

10. A final window for the set-up phase will appear. It will say:

‘Initialize: GT1M will begin taking data at (desired date and time).
Please remove USB connector’

Remove the USB connector and click ‘OK’. The Actigraph is now ready to be worn and collect Data.

“Wrist” (Sleep Quality) Actigraph

1. Connect “Wrist” Actigraph to USB on Computer
2. Go to ‘programs’, then ‘ActiGraph’, then select ‘ActiWeb’
3. The ‘ActiWeb Client’ window will appear. You will see a ‘start’ and ‘download’.
4. Click on ‘Start’
   ‘GT1M Driver Enumerated on COM6 (or similar)
Click OK to continue.
There is (1) device plugged into the System’
5. Click ‘OK’
6. The next screen that will appear is the ‘Initialize Data’
a. Enter the Start Time (from drop down menu)

b. Enter the Start Date (from drop down menu)

c. Enter Subject Name (eg. Surname_wrist_timepoint).

For the GREAT2DO study Data is collected for 7 consecutive days. There is no option to select a Stop Time and Date. Default Epoch time is 60 sec and can not be modified.

7. Once you have entered the appropriate information, click ‘OK’.

8. A window saying:

‘Sending Initialize Command and Data’

will appear. This step may take a while to complete.

9. A final window for the set-up phase will appear. It will say:

‘Initialize: GT1M will begin taking data at (desired date and time).

Please remove USB connector’

Remove the USB connector and click ‘OK’. The Actigraph is now ready to be worn and collect Data.

Placement of Actigraphs on Subject

1. Actigraphs are normally placed on patient after Assessment A.

2. Place the waist actigraph (activity) on the non dominant ASIS, and place the wrist actigraph (sleep) on the non-dominant wrist.

Instructions to Subject

1. Actigraphs are to be worn over 7 consecutive days (from Assessment A to Assessment
2. Both “wrist” and “waist” Actigraphs are NOT to be wet and MUST be removed during showering/bathing or swimming.

3. “Waist” Actigraph is to be removed when getting into bed and put back on when getting out of bed. (MUST leave the “wrist” Actigraph ON while sleeping).

4. Ensure the subject understands how to complete the ‘Actigraph Log’, recording exact “ON” and “OFF” times during the week.

5. The subject should be asked to avoid sleeping with their monitored wrist across their chest or abdomen to minimise movement artefact due to the rise and fall of the chest/abdomen during breathing. (This instruction is on the log).

6. The subject should be asked whether they sleep with an active/restless partner (“Does your partner toss and turn or get in and out of bed frequently during the night” - Circle “yes/no” on the Actigraph log). Reverberations from an active bed partner may overestimate the subject’s movement and number of awakenings.

7. The subject should be asked if they sleep in a water, rocking or vibrating bed (for the reason stated above). Circle “yes/no” on the Actigraph log)

8. The subject should be asked if they have a movement disorder which causes them to move without waking, for example restless leg syndrome, periodic limb movement disorder or sleep walking. Circle “yes/no” on the Actigraph log.

9. The subject should be asked if they take any medications which disturb their sleep – The research assistant will have a list of relevant medications. If any of the listed medications are used, the subject should circle “yes/no” for use on each day monitored on the Actigraph log.
10. The subject should also be asked to circle “yes/no” for each day on the Actigraph log if they ingest caffeine, alcohol or nicotine within 2 hours of bed time.

11. For participants at 6 and 12 month time points, the “Waist” Actigraph is to be removed (by research assistant) and placed on a table during study exercise sessions (Wed, Fri, and Mon) and put back on at the end of each session.

For additional information on standards of practice and other issues on the role of Actigraphy for sleep study, refer to:


Actigraph Download Procedures

“Waist” (Physical Activity) Actigraph

1. Connect Actigraph to USB on Computer
2. Go to ‘programs’ and select ‘ActilifeGT1M.exe’
3. A caution window will appear, Click ‘OK’
4. The Main window will appear. You will see a ‘start’ and ‘download’.
5. Click on ‘Download’
’GT1M Driver Enumerated on COM6 (or similar)

Click OK to continue.

There is (1) device plugged into the System’


’The ActiLife Software is initiating the downloading
phase of the data from the Actigraph’

7. Click ‘Yes’ for the option ‘Would you like to save data to file?’. The Downloaded data
needs to be saved on the computer for analysis. The initial file name that you used in the
initializing/saving process will appear. This step completes the downloading phase of this
assessment.

“Wrist” (Sleep Quality) Actigraph

1. Connect “Wrist” Actigraph to USB on Computer
2. Go to ‘programs’, then ‘ActiGraph’, then select ‘ActiWeb’
3. The ‘ActiWeb Client’ window will appear. You will see a ‘start’ and ‘download’.
4. Click on ‘Download’

’GT1M Driver Enumerated on COM6 (or similar)

Click OK to continue.
There is (1) device plugged into the System’

5. Click ‘OK’.

6. Next Screen will read: ‘Information required for Actigraph download process’. The ‘Faculty and Physician Info’ should be present.

7. Enter ‘User Data’ (i.e. Patient details) including name, age, sex, height, weight, race, sleep analysis.

8. Click the position the Actigraph was worn on the diagram (i.e. left or right wrist). The wrist the Actigraph was worn should have been recorded on the participants Actigraph diary.

9. Click on ‘Continue’

10. Next Screen will read: ‘Please Enter your ActiWeb Login Info’

11. Type in the following: 343NAT (username); 343DEV (password)

12. Click on ‘Login’

13. Messages will pop-up reading “Downloading Data”, then “Processing”

14. Next Screen will be a web page reading “Actiweb Data Analysis File Upload”

a. Enter Username and Password (as above)

b. Copy and paste the text in the ‘Confirm file upload’ box into the blank text box below (This is the excel [.csv] file containing sleep data. It is saved by default to C:\Program Files\Actigraph\ActiWeb\files...csv)

15. Next Screen will read ‘File Upload’; ‘Please Wait’

16. Next Screen will be a web page (http://actiwebpro.com/uploadProcessDEBUG... ) You should see a long list of data with the following message superimposed: “Data upload
complete…Processing data for analysis. Based on number of days, this may take a moment…” This can take up to 30 mins.

*** IMPORTANT ***

Files can not be uploaded from the computer to the ActiWeb Server. Failure to complete the upload process at the time data is downloaded will prevent analysis of sleep data using the online program.

Procedure for Viewing Uploaded Sleep Data

Once data is uploaded to the server, ActiWeb will automatically calculate sleep quality variables including:

- Sleep Efficiency
- Sleep Latency (and time of sleep onset)
- Minutes Asleep
- Minutes Awake
- Number of Awakenings
- Average time (duration) of awakenings

To view sleep variables:

a. Open the ‘ActiWeb Client” program

b. At the top of screen, click “Patient Management”, then “View Downloaded Patient
c. In the “Patient Management” screen you should see the file you have just uploaded. Tick the “select” box for that file, then click the “Load Selected File(s)” button at the top of the window. (NOTE: You can also email patient files to others to view remotely)

d. You may be prompted to Login to ActiWeb (use previous username and password – click ok).

e. You will now be on the “ActiWeb Server” and should see the name of the file under “patients”. Clicking the file link will graphically display the complete 7 days data using ActiWeb’s online Sleep Analysis program.

f. Click the date on the calendar for the recorded data you want to view

g. Enter the “Time in Bed” (bed time) and “Time out of Bed” (wake up time) from the subject’s Actigraph Log for that particular day. Click the “Store times and refresh” button

h. You will now see the above variables calculated for the period spent in bed.

Special Section

For data that were not uploaded to the ActiWeb server prior to deletion from the actigraph

For data that does not display/analyse properly on the ActiWeb server (incorrect date convention, i.e. mm/dd/yyyy)

These data need to be analysed using specially created Excel Macros
Sadeh Macro – for data captured with the Actigraph “Step Counter” function turned ON

Zhao 1 minute Macro – for data captured with the Actigraph “Step Counter” function turned “OFF”

Zhao 3 minute Macro – for data captured with the Actigraph “Step Counter” function turned “OFF”

Follow the following steps:

Reintegrate the .dat file: Sleep data is captured in 30 second epochs but needs to be changed to 60 second epochs to be ran through the macros.

  * Open ActiLife program
  * Go to “Analyze Data” => “.dat file Re-Integrator”
  * Go to “File” => “Re-integrate .dat file”
  * Find the .dat (wrist) file you need to reintegrate

Save output file as the same name as the original file with “_reintegrated” added to the end of the file name.

Create an excel .csv file from the reintegrated .dat file

  * Go to “Analyze Data” => “Show Data Table”

Open the reintegrated .dat file and save the .csv file using the following naming convention:

  “Surname, first initial_wrist_Xmths”
Change the “Mode” in the excel csv file from 3 to 1

Go to row 9 of the .csv file and change Mode 3 to Mode 1 (just delete “3” and type “1”)

Check to see if the Step Counter function is ON or OFF

   Step Counter is OFF if:
       Any step count is >200 or
       Step counts are higher than activity counts

If the step count is deemed to be ON, run the .csv file using the Sadeh Macro

If the step count is deemed to be OFF, run the .csv file using the Zhao 1 and 3 Macros

Note: The same method of sleep analysis must be used at each time-point for an individual.

Physical and Sedentary Activity Data

Physical and sedentary activity during waking hours will be estimated using the Actigraph accelerometer and intialised using the ActiLifeGT1M (version 2.2.3) as described above.

Physical and sedentary activity will be analysed using the Crouter 2 regression (C2R) macro in Microsoft Excel. The data analysis options from the ActiLifeGT1M software will NOT be used.

The C2R macro was developed by Dr Scott Crouter and enables estimation of time spent
in sedentary activity and categories of light, moderate, and vigorous physical activity over 5 days.

For equation methodology and validation data refer to:

For data preparation/processing refer to:

Contact Details for Dr Scott Crouter:

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(fax) 617-287-7527
Email: Scott.Crouter@umb.edu

** All manuscripts will acknowledge Dr Crouter’s generous contribution in sharing these
analytic procedures with us.**

Procedure for Viewing and Cleaning Physical and Sedentary Activity Data

*** May need to change Mircosoft Excel security setting to “enable macros” ***

1. Open Excel
2. Click “Tools” from top taskbar
3. Click “Options” from menu
4. Click “Security” tab from options dialog box
5. Click “Macro Security” button
6. Click “Medium – choose whether to run potentially unsafe macros” setting

Overview:

- Waist” Actigraph data is downloaded as a .dat file. This .dat file must be saved as an excel.csv file using the ActiLifeGT1M software.

- The excel.csv file is then cleared of erroneous data and data captured during times when the Actigraph was removed (i.e., during bathing/swimming, study exercise training sessions, and time in bed at night). Refer to the participant’s Actigraph log and training diary for “ON/OFF” times. The “wearing time” and “number of wearing interruptions” must be calculated, as well as determining whether the day was a “valid” day, the “number of valid days” and the “number of weekdays”

- The “cleaned” excel.csv file is then imported to the Excel spreadsheet running the C2R macro for analysis of the first 5 days of data.
• The C2R macro must be run a second time, importing the data from the “cleaned” excel.csv file captured beyond day 5.

Saving .dat file as an excel.csv file

Procedure:

1. Go to ‘programs’ and select ‘ActilifeGT1M.exe’
2. Click “Analyse Data”, then “Show Activity Table” (click “OK” when prompted to create an activity file)
3. Select the Actigraph .dat file (Path: My Documents => GREAT2DO Study => Actigraph => Actigraph files.) you want to analyse. Files will be named by “Subject Name_waist_timepoint”. Click “Open”.
4. Next you will be prompted to “Save Actigraph Activity File”. This will save the .dat file as an excel .csv file. Type in a file name using the same naming convention above. Eg. “Toovey,B_waist_6mths”. Click “Save”
5. Click “Yes” to view file in Excel when prompted.

Cleaning the excel.csv file (identifying erroneous data, removal intervals, calculation of wearing time, and determination of valid days)

1. The Excel.csv file will show 3 columns of data: Date; Time; and Activity Count (note: may not be titled as such)
2. Visually screen the Activity Count column for erroneous data. Erroneous data will be
identified by an activity count \( \geq 1600 \) or if the activity count is held at the same number (>0) for 10 minutes (ref. Masse et al, 2005). This data will be deleted and treated as missing data.

3. Activity Count data will be deleted for periods when the “waist” Actigraph was removed (i.e. bathing/showering/swimming, study exercise training sessions, and night sleeping times).

4. Use the participants ‘Actigraph Log’ (data sheet) as a guide to the approximate “waist” actigraph removal intervals. The actual removal intervals will be denoted by a long succession of “0” activity counts within the .csv file beginning around the “OFF” time, and ending around the “ON” time, indicated on the participant’s Actigraph Log.

5. Write these times (first and last “0” of actual removal interval) on the participant’s Actigraph Log beside the approximate “OFF/ON” times.

6. Highlight and delete all “0” activity count cells within actual removal intervals. DO NOT DELETE THE “DATE” AND “TIME” DATA.

7. NOTE: ‘Actigraph Log’ indicates removal intervals during bathing / showering / swimming and sleeping only. During follow-up testing periods (6 & 12mths), participants also remove the ‘waist’ actigraph during scheduled study exercise training sessions (Wed/Fri/Mon). To identify removal intervals during these periods, the participants training time and attendance must be confirmed via review of the training diary and communication with the RA supervising training. Write training attendance (yes/no) and training time for each scheduled session on the participants Actigraph Log.

8. Calculate “Wearing Time” for each day. The Actigraphs are initialised to start at 6pm on the day of Assessment A. Day 1 of activity analysis will begin the following day.
Determine the number of waking hours between the time the actigraph was put “ON” (disruption of continuous “0”’s) upon getting up in the morning and the time the actigraph was taken “OFF” (beginning of continuous “0”’s) around the indicated bed time. Calculate the summed time of all removal intervals. Wearing time (hrs) = waking hours (hrs) – total removal interval time (hrs). Record this time on the data sheet, as well as indicating the number of removal intervals.

9. Determine if the day was a “Valid Day”: a day is considered valid if the ‘wearing time’ is at least 60% of ‘waking hours’ (ref. Masse et al, 2005) Calculate this for each day and record ‘yes/no’ on the data sheet as well as the number of valid days during the week.

10. Complete this “cleaning” procedure for all days of the week.

11. Click “Save”

**Importing “cleaned” data from .csv file into C2R Marco**

1. Click on column “C” (activity count data), highlighting the entire column.

2. Click “Edit” (top task bar), then “copy” (from drop down menu)

3. Open the “2Regression Macro-5day-3-9-07” excel file (Path: My Documents => GREAT2DO Study => Actigraph => Actigraph C2R Macro files)

4. Be sure to click “enable macros” when prompted.

5. Click on column “C”, highlighting the entire column

6. Click “Edit” (top task bar), then “paste” (from drop down menu). This will paste the ‘activity count’ data of the subject into the C2R macro which will calculate all the variables to be analysed.
7. Columns A (date) and B (time) from the subjects .csv file should also be copied and pasted into the respective columns of the C2R macro in the same way so data can be referenced against the participant’s “Actigraph Log” (However, dates and times do not effect the how data is calculated).

8. This Macro file now needs to be saved for this participant. Click “File” (top task bar), then “Save As” (from drop down menu).

9. Name the file using the same naming convention as above in addition to adding “macro” to denote it as such. Eg. “Toovey,B_waist_6mths_macro”.

10. Save the file in the “Actigraph C2R Macro files” folder (Path: My Documents => GREAT2DO Study => Actigraph => Actigraph C2R Macro files)

Variables Created By the C2R Macro

The C2R Macro will automatically calculate physical activity variables including
APPENDIX B. ASSESSMENT PROTOCOLS (CT SCAN)

CT SCAN PROTOCOLS
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CT Scans of Thigh and Abdomen for Soft Tissue Measurements by Digital Analysis

EQUIPMENT: GE HIGH SPEED CTI SCANNER

LOCATION: ROYAL PRINCE ALFRED HOSPITAL RADIOLOGY DEPARTMENT

CONTACT PERSON FOR ADMINISTRATIVE ISSUES: CHARBEL SAADE, CT SECTION CHIEF, 9515-7444

Contact Person for Appointment Scheduling: Leila, Radiology, 9515-8947

Note: Procedures in **Bold** are done by CT technicians, the rest is done by the research assistant.

**Initial Scanning Protocol:**

1. Subject is changed into hospital gown, removing all constricting underwear, stockings, belts, etc and actigraphs (record time off and on).

2. Subject lies on scanner bed with non-dominant leg flexed at the hip and flexed 90° at the knee. Dominant leg is used if there is a metal prosthesis in the non-dominant leg. NOTE the time “first supine” on the data sheet.

3. Measure the thigh length with an anthropometric tape from the inguinal crease to the proximal pole of the patella. Mark the mid-point of this distance with a black marker and then tape a metal ball bearing over the black mark.
4. Return the leg to resting position and separate the legs so that the skin is not touching between the thighs by abducting the leg that is not to be scanned. This may require a foam pad to be placed between the knees in some subjects. Keep the scanned leg straight (parallel to the scanner bed).

5. Measure the distance between the iliac crest and the lower costal margin on the left side and mark the mid-point with a marker and then tape a metal ball bearing over the spot.
Note that the mid-point between the hip and rib located when the patient is supine is not the same as the mid-point between the hip and rib located when the patient is standing. The “laser mark” is not representative of the IDF waist circumference. The addition is useful for comparing WC to other diabetes data.

6. A long scout film is taken of the trunk region down to the tibia with the ball bearings visualised.

7. The abdominal cross-sectional slice is marked with a horizontal line on the scanner. After the scout is checked, the ball bearing is removed from the abdomen.

8. A vertical line is drawn from the femoral notch to this horizontal line
9. This distance at a 0 degree vector is noted on data sheet

10. A horizontal line is drawn at thigh midpoint (in line with ball bearing)

11. A vertical line is drawn from the femoral notch to this horizontal line

12. This distance at a 0 degree vector is noted on data sheet

Scan Scout

13. The CT scanner measures the distance from the notch between the femoral condyle and the lines indicating the position of the abdominal slice and the position of the thigh slice. These numbers are recorded on the header of the electronic files and also by the researcher or research assistant (RA) on the data sheet. IT IS IMPORTANT THAT THESE DETAILS ARE RECORDED FOR FOLLOW-UP SCANS.
14. The scanner is set to take a 1mm thick slice at the abdominal marker. The DFOV should be 45 – 48 (up to 50 on the new scanner). The patient is instructed to hold his or her breath while the scan is being taken. Ensure that the entire abdomen is visible, including all skin. Note the time the CT was taken on the data sheet in the space provided.

15. The scanner will now take a 1mm cross sectional slice of the thigh at the measured midpoint of the thigh. Ensure the entire cross section of the thigh is visible, including all the skin. Note the time the CT was taken on the data sheet in the space provided. DFOV will usually be 25 – 30.

16. The DFOV may be different for every patient depending on his or her size. The larger the patient, the larger the DFOV. The DFOV does not have to be the same at all timepoints, although it usually is, as the subject size has not changed markedly. It must be correctly recorded for analysis of each scan.

17. KEEP THE CENTERING LASER LIGHTS ON. The scanner bed is moved out of the scanner with the subject still lying in the same position as when they were scanned. The circumference of the thigh and abdomen at the black marks is measured in triplicate by the research assistant after the scans have been taken, while the subject is still lying supine on the scanner bed. The abdominal circumference should be taken while the
subject is holding his/her breath just as during the scan. Note the time girth measurements were taken on the data sheet in the space provided.

18. Assist subject off scanner bed with consideration for back and shoulder discomfort as well as orthostatic hypotensive symptoms.

19. **Remind the CT technician to save data on a CD. This CD will be sent to the front desk but may not be ready** immediately. CDs can be stored for pick up at subsequent appointment.

20. RA checks the CD’s to see that all the correct images have been transferred. If anything is missing, it must be retrieved from RPA CT scanner as soon as possible, or it will be deleted from the archived files.

21. At the end of each scan, the radiographer must SELECT REMOTE HOST from the network express 100X and send to PACS as normal to RPAHANWG1.

**Instructions for repeat scans in a previously scanned subject:**

1. Bring the original data sheet and use the stored scout film taken at baseline to compare measurement lines and reproduce the position precisely.

2. There is no need to measure the anthropometric sites or tape on a ball bearing.
3. Position the patient as in the initial scan. **Use the details from the first CT scan data (distance from femoral notch) to find the same points where the CT was originally taken.** Compare body position (femur) with the original and adjust if needed and take another scout.

4. **Technician will draw lines on the scout which are the exact distance as at baseline, and take 2 cross-sectional slices at the 2 locations;** record the time each CT slice was taken. RA will ensure that the lines start from the same spot on the distal femur and that the subject positioning is as close to the baseline scout as possible. The RA and technician should check where the abdominal line intersects the vertebral body or space to make sure the scan location is the same as the previous scan/s.

5. Turn on laser light and mark spots on the skin where two cross-sections were taken. Then move the scanner bed out of the scanner, without changing the position of the subject.

6. Take anthropometric measurements at both points and record time measurements are taken.
7. **Remind the CT technician to save data on a CD. The CD will be sent to the front desk, but if it is not ready immediately, it may be stored for collection at the subsequent appointment.**

8. **RA checks the CD’s to see that all the correct images have been transferred. If anything is missing, it must be retrieved from RPA CT scanner as soon as possible, or it will be deleted from the archived files.**

9. **At the end of each scan, the radiographer must send SELECT REMOTE HOST from the network express 100X and send to PAX as normal to RPAHANWG1**
Step 1. Copying Scans onto the Computer

Open the program named ‘Osirix’ (by double-clicking on the HD icon, opening ‘Applications’, and then double-clicking the ‘Osirix’ icon OR by clicking on the icon in the “dock”). Osirix is a program that allows you to view CT films in their raw format.

Scans are on a CD that must be copied onto the hard drive of a computer or a zip disc, so that the files on them can be renamed and analysed. (Files burned onto a CD cannot be renamed until they are copied onto another drive or disk).

First you will need to create a main folder where all of the scans for the particular study will be kept. To create this folder on the desktop, click on an ‘empty space’ on the desktop and then go to File – New Folder. Name this folder:

GREAT2DOSCAPNS

If OSIRIX is open when the CD is loaded onto the computer, the file will usually show in the OSIRIX window. If it doesn’t appear, drag the folder from the CD to the hard drive. If it still does not appear in OSIRIX, click “IMPORT” from the OSIRIX file heading and choose the folder with 4 digits. (You may have to wait a few seconds while the program imports all the files). Once the participant’s files are imported, make sure you highlight that participant’s name (in case you have more than 1 participant’s data open). You will now be able to view all the participant’s images. The different thumbnails to the right of the main image allow you to view different ‘series’ of images of the participant (including
topograms).

Select the thigh CT scan, and check that the details on the scan are correct (e.g. patient name, day, right or left leg). The time the scan was taken is also reported on the scan, however the research assistant should record the “real” time, at the time of the scan to avoid errors from hospital clocks or CT scanning equipment. Repeat for the abdominal scan.
Step 2. Finding the Scan(s) to Analyse

You next need to determine the filename of the thigh and abdomen scan. The easiest way to do this is to first export all the images for the participant into Dicom format. To do this, go to the pull-down menu ‘File’ and select ‘Export’ and ‘Export to Dicom’.

Select the (GREAT2DO folder on the desktop and choose the appropriate destination: “baseline”, “6 month” or “12 month” folders as the location you want to export the files to, and click ‘Choose’. Make sure that if you have more than 1 participant’s images open that the correct participant’s name is highlighted in the top window before you click Export (otherwise you will export the wrong person’s scans). All the images that you have open for the participant will then be copied into a folder labelled with the participant’s name. The CT scans should be in a sub-folder (and all have filenames ending in the extension ‘.dcm’). The 2 CT scans of interest (thigh and abdomen) should be in a folder named “GREAT2DO in the folder ‘CT abdomen, CT thigh’.

To check which file(s) correspond to the scan(s) to analyse, complete the following steps:

Go to the pull-down tab ‘File’ and select ‘Delete selected exam’ (make sure the correct participant’s name is highlighted in the top window before you do this). You will be asked ‘Are you sure you want to delete the selected exams?’ Confirm this by clicking OK. Then click ‘Remove the links’ (do not ‘delete the files’). This will remove all the participant’s images from the OSIRIX display. Next, open the individual file to be analysed (that is, one of the 2 files in the scan folder). Make sure you add the filename. This scan will now be the only image open for the participant. Check that it is either a thigh or abdomen CT scan.
Step 3. Renaming the CT Scan(s)

To rename the thigh and abdomen scans so that they can be easily identified and then de-identified, open the study folder on the desktop. Then work your way through the directory to find the particular scans that you now know are the abdomen and thigh scans. Click on the name of this file twice (slowly) – you will now be able to rename it. Rename the file:

Participant ID_timepoint_thigh_DFOV(e.g. G2Do001(b)thigh(DFOV25).dcm)

OR

Participant ID_timepoint_abdo_DFOV (e.g. G2Do001(b)abdo(DFOV48).dcm)
Step 4. Converting the File from ‘.dcm’ to ‘.dcmx’

Before you can analyse a CT scan, it (i.e. the file) needs to be in a format which the analysis program (DICOM NIH Image) can understand. The analysis program will convert the file(s) for you. To open DICOM NIH Image, double-click on the icon labelled ‘DICOM NIH ImageNEW’ on the desktop, and then double-click on the file named ‘NIH Image 1.63’ (note: do not open the older version named ‘NIH Image 1.62’). Ensure one of the DICOM windows are highlighted (to do this just click on any one of the program’s windows). Next, go to the pull-down menu ‘Special’ and then click on ‘Load Macros’. The macros file (‘image macros.txt’) is located under Desktop/DICOM NIH Image NEW/NIH Image 1.63 f/. Loading the macros is necessary for the program to recognise specific commands which have been set up for use with CT scans.

To convert the file, press F1 on the keyboard (if using a laptop you will have to hold down the function ‘fn’ key as you do this; if using a G5 Macintosh running OSX, you will have to hold down the control or option key while pressing F1). A directory tree of the computer will be displayed. Select the options ‘Custom’ and ’16 bit unsigned’. Then ensure the top window (current directory) reads desktop. Using the cursor on the right hand of the directory tree, scroll down until you find the location of the study folder (i.e. GREAT2DO Scans) and double-click on this. Then work your way through the directory tree to double click on the particular CT scan you wish to convert (the file that you just renamed). You will see the CT scan ‘flash’ open and then close again. This means you have successfully converted the file, and a new file has been added to the participant’s folder with the same
filename, except the extension now reads ‘.dcmx’, and not ‘.dcm’. If you get an error message e.g. ‘argument out of range…’ then try repeating the process but with other options selected e.g. ‘16 bit signed’ or ‘8 bit’. If the scans still do not open and show an error message, ask RPA PACS manager to redo the scan files in compatible format.

If you need to convert more than 1 file, hit F1 again (remember to hold ‘fn’ if using a laptop or the control or option key on a G5 computer) to take you back to the directory tree. And repeat as above. You are now ready to analyse the scan(s).

**De-identified Scans**

As analysis is blinded, all scans are copied to the appointed research staff member to assign de-identified numbers to the original files from a computer generated random numbers list. The time-point is excluded in this title but the DFOV must be included.

All files are then copied from USB to the person who is responsible for this task.

A list of original file IDs and corresponding de-identified IDs should be secured.

Each individual file is then relabelled with de-identified ID number, thigh or abdo and appropriate DFOV, e.g. G2Do300_Thigh_DFOV25.dcmx. When this is completed, the abdominal and thigh folders are returned to the person analysing the scans via USB.

When analysis is completed for a specific block of scans, the data sheets are returned to the research assistant to be “re-identified” with original subject ID and time-point. For
thigh scans, the filemaker pro.dbf spreadsheet is also re-identified.

All re-identified files and data analysis sheets are delivered to the appointed research assistant for data entry into the master data sheet.

In summary, there are 3 people involved in this process: the person analysing the scans, the person performing the de-identification and re-identification of subject numbers and the person entering data into the master spreadsheet.
ANALYSING THIGH SCANS

Read all the analysis instructions before you start analysing your first scan.

1. Open DICOM NIH Image 1.63. Click on any one of the program’s windows. Ensure the macros are loaded by going to the pull-down menu ‘Special’ and then click on ‘Load Macros’. The macros file (‘image macros.txt’) is located under Desktop/DICOM NIH Image NEW/NIH Image 1.63 /f. Loading the macros is necessary for the program to recognise specific commands which have been set up for use with CT scans. Open a scan by holding down the space bar and pushing the letter O (or go to File – Open). This will display the file directory tree on the screen.

2. Select the file you wish to analyse by navigating through the directory tree of the hard drive.

3. Open this file by double clicking on its name or clicking on OPEN. (File should be named study.de-identified number.body part.DFOV).

4. Select the correct DFOV as indicated on folder. A cross section of the thigh will appear on the screen. In order to accurately analyse the scan, ‘imperfections’ to the image must be corrected. Some scans will require no correction, but most will.

5. If the scan has the ipsilateral leg or part of the scanner bed touching the cross section of interest (see scan below), then this area must be edited. For accurate editing,
first magnify the image using the magnifying tool located in the top left hand side of the tool section. (Continued on next page)

6. Once the image is magnified to a suitable level (the actual amount is subjective: magnify until you can clearly see the pixels that need to be removed – 4x is generally enough). Click on the eraser tool (fourth from the top on the left hand side) and whilst holding the mouse button down, move the mouse over the ‘offending’ pixels and erase them.

   a. Note: This process can be unreliable if not done carefully. Investigator has to “guess” which pixels to erase as best as possible – there is no better way to complete this process. In order to increase the reliability of this
b. procedure, try to match the border around the entire thigh perimeter (e.g. the same no. of lighter coloured pixels).

c. To save time note that you don’t have to erase all the pixels outside the cross section. As long as there is at least a 1-pixel gap between the peripheral thigh perimeter pixels and the pixels outside the perimeter (i.e. they are not touching one another), the pixels outside the perimeter will not be included in the cross section analysis.

d. Note on the data sheet whether editing of the scan bed or other leg was required (Circle ‘Yes’ or ‘No’). If editing was required, circle one of the numbers to indicate the combined amount/difficulty of the editing (3 = the most difficult/amount of editing, whereas 1 = the least difficult/amount of editing). Obviously this rating is quite subjective but at least it will give you some indication of the amount/difficulty of editing performed at this step, which may be useful when analysing the data.

You can restore the image at any time to its original size by double clicking on the magnifier tool.

7. Remove the ball bearing and associated artefact if ball bearing is inadvertently left on during the cross-sectional scan. *(Typically, scans do not require this step as the protocol is to remove the barium/ball-bearing marker prior to the scan):*
i.e. If the scan exhibits a bright white circular image (barium or ball-bearing marker) on the ‘top’ (periphery) of the cross section this will also have to be edited (e.g. see scan below). Note that this will only be present in baseline scans).

Remove the ball bearing and associated artefact if the ball bearing is
a. First you will need to re-create the thigh border (perimeter) by:

   i. Removing the pixels that are outside what you think is the ‘true’ thigh border.

   ii. Changing the colour (density) of the pixels that you think were affected by the barium/ball-bearing marker to a similar density as the rest of the ‘unaffected’ thigh border.

   iii. Add any pixels that you think are missing due to this artefact. (Try to pick roughly the same colour/density as the rest of the ‘unaffected’ thigh border).

b. If the barium/ball bearing marker is localised to the thigh border and does not protrude into subcutaneous (SC) fat or muscle then this is all the editing that will be required in this step. However, if artefact from the barium/ball-bearing marker does protrude (like ‘rays’) into either SC fat or both SC fat and muscle then further editing is required. i.e. You will need to edit the ‘rays’ from the ball-bearing/barium marker so that:

   i. The densities of pixels in SC fat have density values that fall outside the range for muscle (i.e. outside the range 10-113). Any pixels that fall outside this range will be included as SC fat. Note: Take care when editing SC fat close to muscle. You do not want to change ‘real’
muscle to SC fat (otherwise this will decrease the calculated muscle area and increase the calculated SC fat area).

ii. The densities of pixels which are muscle have density values that fall within the range of muscle (10-113). Note: This step involves a lot of ‘guesswork’, but needs to be done (otherwise values for ‘muscle with holes’ and ‘muscle without holes’ will be underestimated, and, muscle density, SC fat, and IM fat values may also be affected). To aid reliability try to ‘copy’ a section of the muscle that has not been affected by artefact (use the pencil tool). You will need to use a couple of different colours (density values) such that once you have finished editing, the ‘rays’ will hardly be noticeable.
8. Save the edited version of the scan (G2Do.de-identifiedID.EDIT1).

**DO NOT save over the original copy of the scan.**

9. Now press 1. Most of the scan will turn red (see image below).

![Scan Image](image)

10. Magnify around the femur and look at the internal (around bone marrow) and external femur perimeter to see if there are any red pixels that appear to be ‘missing’ and which you think will affect the ‘true’ perimeter values. Select the pencil tool and add red pixels to ‘smooth out’ either or both of these perimeters. Note: These perimeters are not meant to be perfect circles. Very few scans will need any editing at this stage (i.e. only about 1 in 10) and where editing is required only 1 or 2 red pixels will need to be added (In the example above no editing of these perimeters was required).
11. The next step is to calculate the area and perimeter of the total thigh and of the internal and external femur. Do this by selecting the ‘wand tool’ (second from the bottom left), and on the image, click on the bone marrow (the red section in the centre of the limb (1*)), then the bone (the white section surrounding the bone marrow (2*)), and then the muscle/fat area (the large red section surrounding the bone (3*)). The values will appear in the results window. **Note: Make sure that when the thigh perimeter is selected that no pixels outside the thigh perimeter are included (e.g. this may have occurred if you did not leave at least a 1-pixel space between scanner bed pixels and thigh perimeter pixels).**

12. Once the whole thigh is selected, the average density (or attenuation) of the muscle can be calculated.

   a. Go to **analyse** then to **show histogram**

   b. Go to **edit** then to **copy histogram** (you will be copying 256 rows of data that contain the count for each density)

   c. Open **Excel** (average density template), click on the column labelled COUNT (cell B3) and then **paste** the histogram data (in rows 3-258 i.e. density 1 to 256).

   d. The average density value will be displayed. Record this value.

   e. **Do not save any changes to the template.**
- The first column DENSITY already has the range of densities (1-256) entered into it. Do not change the entries in this column.

f. The template has been set up to calculate the average density of muscle (using the density range 10 – 113). Any pixels in the selected cross section that are outside this range (e.g. bone and fat) will not be included in this calculation. Note that some skin and connective tissue in the SC fat may have density values that are included in this calculation. However, this should be the same at all time-points for a patient, so it should not affect any reported changes in average density over time.

g. The template will multiply the "count" column by the "density" column to get a new column, called TOTAL. Then it sums the values in the density range of interest. So for muscle (density range = 10 to 113), it will sum the rows 12 to 115 to get "sum of total" and "sum of count". Then the template will divide "total" sum by "count" sum. The average density for that scan of muscle will be displayed on the template. This is the number that will be entered onto the data analysis sheets. You can also look at "low density muscle" and "high density muscle" using this template just by adjusting the density range used in the calculations.

13. Now go back to the image. Press 2. Select the eraser tool and erase the bone marrow in the centre of the limb (magnify first!).
14. Click on the wand tool and then click on the outside of the muscle border. The results window will display values (4*) – ‘muscle area with holes’ and ‘muscle perimeter with holes’ i.e. for the area you have selected. Note: You may need to re-do this calculation if you notice that:

a. The muscle perimeter you selected is attached to the thigh perimeter (See below).
If this occurs you will need to edit the scan so that there is at least a 1-pixel gap between the thigh perimeter (skin) and ‘real’ muscle perimeter. Do this by erasing the most superficial skin pixels while still leaving at least a 1-pixel thigh perimeter. You should be able to decide which pixels are skin and which are muscle by looking at the ‘original’ scan.

Note on the data sheet whether you needed to edit the muscle border so that it is not touching skin (Circle ‘Yes’ or ‘No’). If editing of the muscle border was necessary assign a rating of the amount of editing required from 1 (edited <5 pixels) to 3 (edited >15 pixels).
b. Do not include other connective tissue (‘red bundles’) that is outside what you think is the periosteum (see scan below). In most scans you will see a small circular ‘bundle’ just outside or on the periosteum. Do not include this ‘bundle’ (It is likely a blood vessel). It may help to look at the original scan when determining what should be included as muscle and what should be left out.

Using the eraser tool, detach the small circular bundle from the periphery of the thigh muscle. It is likely a blood vessel.
UNEDITED AND EDITED THIGH SCANS

Due to the difficulty in determining a consistent method for re-creating the thigh muscle border or the fascial perimeter, GREAT 2 DO thigh scans are calculated via 2 methods: “UNEDITED” (including only editing from the previous steps: erasing the scanner bed, detaching muscle pixels from the skin or detaching muscle from the blood vessel) or “EDITED” (pixels are added to reconstruct the muscle border, but not the fascial perimeter). Up to this step (14), each method is the same.

The selected muscle perimeter often runs deep into the muscle instead of going around (what you think is) the outside of the muscle. This will occur when parts of the muscle have separated. (All it takes is a 1-pixel gap. Un-edited, this results in the ‘muscle area with holes’ being underestimated (and perimeters for ‘muscle with holes’ and ‘muscle without holes’ generally being overestimated). The underestimated ‘muscle area with holes’ results in IMAT being recorded as SC adipose tissue. This problem cannot be completely solved. Therefore the accuracy of IMAT and SC adipose tissue values is compromised. It would be more accurate to compare changes in ‘total fat’.

c. For UNEDITED THIGH SCANS calculation, ‘bundles’ of muscle that fall outside the selected muscle perimeter (but within what you think is the periosteum), will need to be selected separately by clicking on each bundle with the wand tool. The area value(s) displayed for the ‘extra’ muscle bundle(s) in the results window will need to be added to the ‘muscle with holes’ area value to get the total muscle with holes value.
Include all ‘muscle bundles’ that are at least 2 pixels in area.

15. Press 3. As per the ‘muscle with holes’ measure above, select the muscle within the periosteum (by clicking just outside the muscle perimeter). The results window will display the area value and perimeter value(s) for ‘muscle without holes’ (5*). And, as for ‘muscle with holes’, you will need to select individual muscle bundles that fall outside the selected muscle perimeter separately (and add all the area values to calculate the total ‘muscle without holes’).

16. The results are recorded in a window that is similar to the table below.
17. Record the results onto the data sheet and remember to add all the values for the same measure together before entering the final value into Filemaker Pro.

**Table 1. Results Window**

<table>
<thead>
<tr>
<th>Area</th>
<th>Perimeter</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Internal femur</td>
<td></td>
</tr>
<tr>
<td>2. External femur</td>
<td></td>
</tr>
<tr>
<td>3. Total thigh</td>
<td></td>
</tr>
<tr>
<td>4. Muscle with holes</td>
<td>Ignore this measure.</td>
</tr>
<tr>
<td>5. Muscle area</td>
<td>Ignore this measure.</td>
</tr>
</tbody>
</table>

Note that ‘muscle without holes’ may become 6, 7, or 8, …if ‘muscle bundles’ have to be selected separately. Area measures are given in cm² and perimeter measures in cm.

18. **EDITED THIGH SCANS** Repeat steps 2 to 13 (density calculated from step 12 should be the same).

19. If the muscle perimeter runs deep into the muscle where parts of the muscle have separated, the goal is to connect the muscle perimeter with minimal editing by adding pixels with the pencil tool to smooth out the border (see below). The number of pixels added should be recorded on the data sheet.
20. After editing, SAVE AS G2Do.de-identified ID#.edit #

21. EDITED values for ‘muscle with holes’ and ‘muscle without holes’ will be different from UNEDITED values unless the muscle border required no editing. Editing will increase the area of tissue included as IMAT and decrease the tissue area included as subcutaneous fat. This is different from IMAT and subfascial adipose area described by Goodpaster et al.

22. Record values on data sheet under the EDITED column.

23. If a scan is challenging, for reliability do another edit of the same scan (preferably on another day or at least after you edit a different scan first), and save this as ‘G2DoID#.edit#’, then compare the results. If there is greater than 0.3% (e.g. 15/100 variation for values = 50) for any of the following measures – ‘muscle area with holes’, ‘muscle area without holes’, ‘total thigh perimeter’, and ‘total thigh
area’ - between the 2 edits, do a third edit (Note: editing the muscle border may result in the variation of the **perimeter** value for ‘muscle with holes’ and ‘muscle without holes’ between edits to be > 0.3%. As these values are not required in the final analysis this variation is ok – the important thing is area. If the variation for all these measures (except the muscle perimeter) is less than 0.3% between any 2 edits (e.g. edit 1 and 2, or edit 2 and 3), use the average of these 2 particular edits for your final values (to be entered in FileMaker Pro).
Tips for analysis

- The quickest way to re-do the last measure you did is to go to Edit – Undo Measurement.

- To re-do a particular measure, go to Analyse – Redo Measurement and enter the particular measurement you wish to re-do.

- To delete a particular measure, go to Analyse – Delete Measurement and enter the particular measurement you wish to delete.

- To clear all measurements from the results table go to Analyse – Reset.

- The ‘muscle with holes’ and ‘muscle without holes’ perimeter values should be the same.

- When the program calculates a perimeter measure for thigh scans the variation of this calculation is 6/100. You can see this variation by repeatedly selecting e.g. the muscle area with holes (or without holes) and looking at the calculated perimeter value. The value should be exactly the same no matter how many times the program calculates the perimeter, but it will vary by +-6/100.
Scans affected by Artefact

Artefact can appear as ‘streaks’ usually running diagonally down and across from right to left (see image below). It may be due to a metal prothesis (e.g. pin and plate) being in situ in the opposite hip.

Artefact may affect the calculated value for muscle density (attenuation), and area and perimeter values for the internal and external femur, muscle with holes, and muscle without holes. Editing can limit the extent of this affect. However, generally, this type of artefact will not greatly alter the value you calculated for muscle density because although the artefact caused some areas of muscle to have non-muscle density values (meaning these pixels will not be included in the muscle density calculation), most of the ‘missing’ muscle has been relocated to the SC fat (and since the whole cross-section of the thigh is included
in the muscle density calculation these pixels will be included). Similar to analysing other scans, you may need to smooth out the internal and/or external femur perimeter.

After pushing 2 (i.e. just prior to calculating muscle area with holes), the ‘streaks’ or artefact will be more prominent. Importantly, ‘bits’ of muscle will be ‘missing’ (i.e. replaced by black pixels), and in what should be SC fat, there will be bits of muscle (i.e. red pixels). See image below.

![Image of muscle density calculation with streaks and artefacts](image)

Depending on the degree of artefact, if you were to go ahead and select the muscle, in most cases you will find the perimeter of the muscle does not represent the ‘real’ muscle area, i.e., the ‘streaks’ are causing some parts of the muscle perimeter to extend into the SC fat, and other parts of the muscle perimeter to run deeper than it should.

Even for UNEDITED scans, you may need to ‘smooth out’ the muscle perimeter so that when selected, it gives a truer representation of the actual muscle area. This process involves:

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1. Erasing the red streaks/artefact attached to the muscle perimeter that should really be black, i.e. SC fat. Use the original scan as a guide when editing the muscle perimeter (i.e. deciding what is fat and what is muscle). Remember that you only need to leave a 1-pixel gap between the peripheral muscle perimeter pixels and the deepest SC fat pixels.

2. Adding red pixels (muscle) to ‘close off’ the periphery of the muscle perimeter so that when the muscle perimeter is selected, it is continuous and not interrupted by 1 or 2 missing pixels that cause the perimeter to run deep into the muscle where it shouldn’t. (Again, use the original scan to guide you, or scans for the same pt at other time-points).

(However it can depend on the scan: sometimes it is better to skip step 1 above and only perform step 2 i.e. leave the ‘streaks’ of muscle that extend into the SC fat, because this may represent the muscle that is missing from where it actually should be. And thus you will be able to get a value for muscle area without holes that is not underestimated to the same degree than it would have been had you erased all the streaks of muscle that extended into the SC fat. However this may mean that the value for SC fat will be underestimated – can edit twice – first time concerned with ms without holes, and 2nd time concerned with SC fat – although the accuracy and reliability of SC is already limited).

As a result of editing:

To a certain extent it depends on the scan and how you choose to edit but regardless of editing, in nearly all cases of artefact, muscle area without holes will be
underestimated due to the ‘missing muscle’– so IMAT fat will be overestimated. (The greater the artefact the more ‘muscle area without holes’ and IMAT fat will be underestimated and overestimated respectively).

Therefore it is important to record the extent of artefact (i.e. how much you think it affected your results) compared with other scans (assign a rating out of 5 - as a guide, the above scan was given an artefact rating of 3 out of 5). Also note how much editing you performed (e.g. the number of pixels added/deleted). You will then have to decide if the effect of artefact on your results was so great that it warrants some/all values being left out of the data analysis. If you do decide to include the results in your data analysis, by noting the degree of artefact you will be able to determine if an unexpected result may have been somewhat attributable to this artefact.
STEP 4 ANALYSIS USING FILEMARKET PRO

1. Open the master template.

2. Before you enter any data, you must save a copy of the template to enter your data into. (Do not save any changes to the original template). Go to File – Save a copy as and then name the file ‘GREAT2DOuneditedCTscans’. Then go to File – Open – and open the file you just created. Go to window and select the ‘CT analysis master template’. Close this file. The new file you created will now be the only file that the program has open and any data you enter will now be saved under this filename.

3. Select new record from the Records menu.

4. Enter study de-identified ID number. Then enter all the other data into the appropriate fields.

5. The program will calculate the final values that will be analysed later in StatView. These values will be displayed under ‘Results’.

6. To enter data for another patient, select new record from the Records menu again.
7. To print a record, go to **File – print**. Note that you have the option of printing only the ‘current record’ displayed on the screen, or all ‘records being browsed’.

8. A number of files will be de-identified and analysed in groups (Part 1, 2, 3 etc) over the time the trial is continuing. It will save time to enter the UNEDITED data from a completed folder first, then duplicate the original file, then save as ‘GREAT2DO edited CTscans’. This requires caution as all previously entered data are already in the cells and the edited values for ‘muscle with holes’ and ‘muscle without holes’ must be deleted and re-entered. This will change the results for subcutaneous fat and IMAT.

Note:

- At any time you can sort the records e.g. by the patient number so that if you have to come back to a record to enter data for the next time-point or to edit data that you have previously entered you can do so without searching through all the records. To sort records go to the **Records** menu and select **sort**. Then click on the field that you want to sort by (e.g. patient number) and click ‘sort’.

- There is no ‘save’ option. When you close the program, the data just entered is automatically saved.
STEP 5 STATISTICAL ANALYSIS USING STATVIEW

- Enter the data by hand into the StatView template from the printed off Filemaker Pro data sheets. Other variables, such as the ‘time first supine’, and ‘artifact rating’ will also need to be entered from the relevant source.

- The StatView dataset should be updated as additional CT results are known.

- Save the StatView file as nameofstudy.ctscans in dataset transfer format (i.e. with extension .ssd). This allows the file to be opened by either PC or Macintosh computers with StatView installed. Do not save over the original template.

- Proceed with Statistical analyses of records as desired.

If required...to transfer all pt’s data from Filemaker Pro to StatView:

a. In Filemaker Pro, open the data set that you wish to transfer to StatView.

b. Go to File – export records.

c. Choose DBF in pulldown menu (should already be selected).

d. Create a filename (‘G2DoUNEDITED thighs part1) and click ‘save’.
e. Screen will come up showing all the possible variables in the master template which can be transferred. Choose the subset of variables which are applicable for your analyses by highlighting each one and then clicking on MOVE. (Unfortunately you cannot move more than 1 variable at a time). NOTE: Transfer multiple timepoints sequentially in order, as they are required to be in this order for repeated measures ANOVA in StatView. Be sure to include the subject ID and Name variables or you will not know who the data belongs to once it is transferred!

f. These variables will be saved as a DBF file (database format). Open Excel and open this file. The variables you have chosen should appear as a spreadsheet with the variable names as the column headings and the values for each subject in a row (Don’t worry about editing the number of decimal places, column width, variable headings, e.t.c. because you will still have to do this again in StatView).

g. Save the file as an EXCEL 3.0 worksheet. The letters .xls will be appended to the end of the file name you have chosen.

h. Open the Excel file you just created in StatView.

i. A StatView version of this data file will be created. The variable names will have been truncated by DBF and EXCEL conversions. Edit the column headings (variable names) so that they are easily identifiable. Check to see that all the column headings have been transferred and that they are in sequential time-point order. If columns are in a non-desirable order (e.g.
timepoints are not consecutively arranged) you can cut and paste the columns how you wish.

j. Values that were left blank in Filemaker Pro will appear as 0’s in StatView. Delete all the 0’s, otherwise they will be used in calculations.
SUMMARY OF COLLECTED INFORMATION

- Data sheets with values obtained from the analysis performed using NIH Image.

- Printed CT scan results from FileMaker Pro.

- Electronic files will consist of each patients original and edited CT scans (and scout films plus header file), 1 FileMaker pro file (with data for thigh analyses), 1 StatView file (with data for all pts). Note that the interim Excel file that was created when transferring from FileMaker Pro to StatView can be deleted once the StatView file has been created and checked for accuracy).

- You or your supervisor should also have the original CDs, and CT scan data sheets from when the scans were performed (includes information such as the scan date, contrast settings, midpoint of the thigh where the scan was taken, DFOV).
ANALYSING ABDOMINAL CT SCANS

24. Open DICOM NIH Image 1.63. Click on any one of the program’s windows.

Ensure the macros are loaded by going to the pull-down menu ‘Special’ and then click on ‘Load Macros’. The macros file (‘image macros.txt’) is located under Desktop/DICOM NIH Image NEW/NIH Image 1.63 f/. Loading the macros is necessary for the program to recognise specific commands which have been set up for use with CT scans.

25. Open a scan by holding down the space bar and pushing the letter O (or go to File – Open). This will display the file directory tree on the screen. Select the file (scan) you wish to analyse by navigating through the directory tree of the hard drive. Open this file by double clicking on its name or clicking on OPEN. (File should be named G2Do.de-identified ID#.abdo.DFOV.dcm).

26. Select the correct DFOV as indicated on the folder header. A cross section of the abdomen will appear on the screen. In order to accurately analyse the scan, ‘imperfections’ to the image must be corrected.

27. If the scan has part of the scanner bed touching the cross section of interest, (see scan below) then the scanner bed pixels must be removed (so that there is at least a one-pixel gap between the peripheral abdominal skin pixels and scanner bed pixels). For accurate removal, first magnify the image using the magnifying tool located in the top left hand side of the tool section. Click on this tool and then click on the image to magnify around the area that you wish to edit. (Continues on next page)
28. Once the image is magnified to a suitable level (the actual amount is subjective: magnify until you can clearly see the pixels that need to be removed – 4x is generally enough). Click on the eraser tool (fourth from the top on the left hand side) and whilst holding the mouse button down, move the mouse over the ‘offending’ pixels and erase them.

a. Note: This process can be unreliable if not done carefully. For some scans you may need to “guess” which pixels to erase as best as possible – there is no better way to complete this process. In order to increase the reliability of this procedure, try to match the area of abdomen perimeter you
are editing with other areas of the abdomen perimeter unaffected by the scanner bed (e.g. the same no. of lighter coloured pixels).

b. To save time note that you do not have to erase all the pixels outside the cross section. As long as there is at least a 1-pixel gap between the peripheral abdomen perimeter pixels and the pixels outside the perimeter (i.e. they are not touching one another), the pixels outside the perimeter will not be included in the cross section analysis.

You can restore the image at any time to its original size by double clicking on the magnifier tool.

29. Note on the data sheet whether editing of the scan bed was required (Circle ‘Yes’ or ‘No’). If editing was required, circle one of the numbers to indicate the combined amount/difficulty of the editing (3 = the most difficult/amount of editing, whereas 1 = the least difficult/amount of editing. Obviously this rating is quite subjective but at least it will give you some indication of the amount/difficulty of editing performed at this step, which may be useful when analysing the data.

30. Save the edited version of the scan

(G2Do.de-identified ID#.abdo.DFOV.edit1.dcmx).

DO NOT save over the original copy of the scan.
31. Now press 4. Most of the scan will turn red (see image below).

32. The next step is to calculate the area and perimeter of the abdomen (including skin) (1*). Do this by selecting the ‘wand tool’ (second from the bottom left), and on the image, click just outside the abdominal skin (perimeter). The values will appear in the results window. **Note:** Make sure that when the abdominal perimeter is selected that no pixels outside this perimeter are included (e.g. this may have occurred if you did not leave at least a 1-pixel space between scanner bed pixels and abdominal perimeter pixels).
33. Now go back to the image. Press 6. Click on the wand tool and then click just outside the abdominal perimeter. The results window will display the ‘Total Abdominal Fat Without Skin’ value (2*). The program calculates this measure by summing the area within the selected perimeter occupied by pixels with density values in the range of 140-240.

If the program fails to select the abdominal perimeter (without skin), because the abdominal muscle core pixels are attached to the abdominal skin (usually by ‘fissures’ in the subcutaneous fat, i.e. not because muscle and skin are actually connected), then you will need to change the colour (density) of some of the subcutaneous fat pixels (fissures) that are causing this to happen to red. Do this using the pencil tool. Re-calculate ‘Total abdominal fat without skin’ as above. On the data sheet, circle ‘YES’ for ‘Detached Muscle from Skin’ and rate the amount of editing required from 1 (<5 pixels edited) to 3 (>15 pixels edited).

Note: it is unnecessary to smooth-out the perimeter by detaching those ‘fissures’ extending inward from the skin that do not reach the abdominal core of muscle, as the calculation of fat will not be affected.

34. With the abdomen perimeter selected, the average density of fat for the entire abdomen can be calculated.

   a. Go to **analyse** then to **show histogram**
b. Go to **edit** then to **copy histogram** (you will be copying 256 rows of data that contain the count for each density)

c. **Open Excel** (‘Abdomen Fat Density.xls’ located in DICOM NIH ImageNEW folder on the desktop under ‘Instructions’ folder), click on the column labelled **COUNT** (cell B3) and then **paste** the histogram data (in rows 3-258 i.e. density 1 to 256).

d. The average fat density value will be displayed. Record this value.

e. **Do not save any changes to the template.**

f. The first column **DENSITY** already has the range of densities (1-256) entered into it. Do not change the entries in this column.

The template has been set up to calculate the average density of fat (using the density range 140 – 240). Any pixels in the selected cross section that are outside this range (e.g. bone and muscle) will not be included in this calculation. *(Note that some skin pixels, muscle pixels, and abdominal viscera pixels may have density values that are included in this calculation. However, this should be similar across all time-points for a patient, so it should not affect any reported changes in average fat density over time).*

g. The template has been set up to calculate the average density of fat (using the density range 140 – 240). Any pixels in the selected cross section that are outside this range (e.g. bone and muscle) will not be included in this calculation. *(Note that some skin pixels, muscle pixels, and abdominal*
viscera pixels may have density values that are included in this calculation. However, this should be similar across all time-points for a patient, so it should not affect any reported changes in average fat density over time).

h. The template will multiply the "count" column by the "density" column to get a new column, called TOTAL. Then it sums the values in the density range of interest. So for fat (density range = 140 to 240), it will sum the rows 142 to 242 to get "sum of total" and "sum of count". Then the template will divide "total" sum by "count" sum. The average density for that scan of fat will be displayed on the template. This is the number that will be entered onto the data analysis sheet. You can also look at "low density fat" and "high density fat" using this template just by adjusting the density range used in the calculations.

35. The next step is to calculate ‘Visceral Fat’. To do this, select the wand tool and click just outside the abdominal muscle core area. You should now see that the abdominal core is selected (i.e. a complete ‘ring’ of muscle extending from the paraspinal muscles to the anterior abdominal muscles is selected). However, in nearly all scans you will find that the program cannot select this perimeter. This occurs due to the abdominal muscle core perimeter being incomplete (i.e. there are small pixel gaps...
when you look closely at the perimeter – see image below).

You will need to add grey pixels using the pencil tool to complete the abdominal muscle core perimeter.

To overcome this problem you will need to complete the abdominal muscle core perimeter by adding muscle (i.e. grey) pixels. Do this using the pencil tool (magnify first!). Note that this step involves a fair bit of ‘guesswork’ and you may question whether to add pixels at more superficial or deep regions of the abdominal muscle core perimeter. To help you determine this, (and aid the reliability of this editing), only add the minimum number of pixels required to complete the border (e.g. if at one region of the abdominal muscle core perimeter 3 pixels are required to complete the border at its most superficial region, but only 1 pixel is required to complete the border at a deeper location, add the 1 pixel at the deeper location. If both deep and superficial locations require the same number of pixels to complete the perimeter, then add the pixels to where you think would best replicate the perimeter – usually this means adding the pixels superficially).
On the data sheet, circle ‘YES’ for ‘Completed Abdominal Core’, and rate the amount of editing required from 1 (<5 pixels added), to 3 (>15 pixels added).

Once selected, the abdominal muscle core perimeter should appear as a ‘ring’ of muscle (as stated above). This perimeter should by no means be perfectly smooth. As long as it is complete and not attached to abdomen skin pixels, once this perimeter is selected the visceral fat measure will be generated in the results window (3*). Note: it is unnecessary to detach those fissures extending outward into subcutaneous fat that do not reach the skin (see image above), as the densities of these fissures fall outside the density range that the program uses when summing fat area.

36. With the complete abdominal muscle core selected calculate visceral fat density as per steps a to e above.

37. To calculate Subcutaneous Fat subtract ‘Visceral Fat’ from ‘Total Abdominal Fat (without skin)’.

38. To calculate the subcutaneous fat density, proceed as above to select the ‘Total Abdominal Area without skin’ (this time you do not need to worry about any fissures that may be present). Then, to avoid any tissue deep to the subcutaneous fat (e.g. muscle, abdominal viscera, bone, visceral fat) being included, change the colour (density) of any tissue deep to the subcutaneous fat to black (note you do not have to re-colour all the pixels, only those that fall outside the range used for fat,
You can now calculate subcutaneous fat density as per previous fat density calculations above, i.e. with the total abdominal perimeter (without skin) selected,

a. Go to the pull-down tab **analyse** and choose **show histogram**.

b. Go to **edit** then to **copy histogram** (you will be copying 256 rows of data that contain the count for each density)

c. Open **Excel** (average density template), click on the column labelled **COUNT** (cell B3) and then **paste** the histogram data (in rows 3-258 i.e. density 1 to 256).

d. The average fat density value will be displayed. Record this value.

e. **Do not save any changes to the template.**

39. To calculate liver density, use the rope tool to select an area of liver if it is evident in the scan (depending on the level of the scan, the liver may or may not be in the slice). The average density of fat for the selected segment can be calculated.

a. Go to **analyse** then to **show histogram**

b. Go to **edit** then to **copy histogram** (you will be copying 256 rows of data that contain the count for each density)
c. **Open Excel** (average liver density template) click on the column labelled COUNT (cell B3) and then **paste** the histogram data (in rows 3-258 i.e. density 1 to 256).

d. The average liver density value will be displayed. Record this value.

e. **Do not save any changes to the template.**

40. Next, measure the abdominal sagittal length. To do this, first select the ruler tool 5th from the top on the right-hand-side of the tool panel. Then click on the most peripheral trunk skin pixel posterior to the spinous process (magnify first!). This is easily identified in the middle of the posterior abdomen skin perimeter. While holding down the mouse button move the ruler perpendicularly up to the most peripheral anterior abdomen skin pixel – you will have to de-magnify the image first. Note that this line must be completely straight to aid accuracy and reliability of this measure. If after you let go of the mouse button you think that the line is not straight or that you did not draw the line far enough (or you drew it too far), simply move the cursor over the end of the line, hold down the left mouse button and re-position the end of the line to where it should be. Once you are happy with the sagittal line you have drawn go to the pull-down tab ‘Analyse’, and select ‘Measure’. The abdominal sagittal length value will now be displayed in the results table (4*). Note: sometimes the patient’s trunk appears to be rotated (by looking at the angle of the spinous process). This may be due to some rotation of the pt on the scanner bed, but may also be due to a spinal deformity, such as scoliosis. In these
cases, still measure the sagittal length as per above, but note the rotation on the data sheet (as this may affect the ‘true’ abdominal sagittal length).

41. The results for the above measures are recorded in a window that is similar to the table below.

**Table 1. Results Window**

<table>
<thead>
<tr>
<th>Measure</th>
<th>Area</th>
<th>Perimeter (or Length)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Total Abdominal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(with skin)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2. Total Abdominal Fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(without skin)</td>
<td></td>
<td>Ignore this value.</td>
</tr>
<tr>
<td>3. Visceral Fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ignore this value.</td>
</tr>
<tr>
<td>4. Subcutaneous fat area (2 - 3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5. Abdominal Sagittal Length</td>
<td></td>
<td>Ignore this value.</td>
</tr>
</tbody>
</table>

| Total Abdomen Fat Density (w/o skin)         |      |                       |
| Visceral Fat Density                        |      |                       |
| Subcutaneous Fat Density                    |      |                       |
| Liver Fat Density                           |      |                       |
42. Record the results onto the data sheet.

Area measures are given in cm$^2$, perimeter measures in cm, sagittal length in cm.

43. It is also important to record the extent of artefact (i.e. how much you think artefact affected your results) compared with other scans. Artefact usually appears as ‘streaks’ running diagonally across the scan. Artefact changes the density values of the areas affected. In doing so, fat values will usually be increasingly underestimated as artefact increases. This occurs because the density values of fat areas now have density values that fall outside the density range of fat and thus the program does not ‘recognise’ these areas as fat. This is best seen after you press ‘6’ where you will see diagonal ‘streaks’ of pixels coloured grey (i.e. non-fat) that should be coloured red (i.e. as fat). Therefore it is important to assign a rating of the degree of artefact that can used when interpreting changes in fat values across time. As a gross measure, circle a rating between 0 and 5 on the data sheet. As a guide, the scan below was given an artefact rating of 4 out of 5.

Artefact is present in this scan around the arrowhead (mainly in the SC fat area). It may cause all fat values to be underestimated –
44. When a scan requires editing that is more than simply obvious editing of a few pixels, for reliability do another edit of the same scan (Preferably on another day or at least after you edit a different scan first), and save this as ‘edit 2.ID#.Ab’. Once you have completed both edits, compare the results. Use the table on the next page as an indication of an acceptable level of variation between the 1st and 2nd values obtained. If the level of variation of any measure between the 2 edits is outside the ‘max variation’ noted in the table, perform a 3rd edit of the scan. If after 3 edits the variation of any of the measures between the 2 most reliable edits is still greater than the ‘max variation’ consult your supervisor. If the variation of all measures between 2 edits is acceptable enter the average of the 2 values from the 2 edits for all measures into the StatView data entry template.

Note that if the values for a particular measure (perimeter measures only) were different between edits when you did not do any editing that would affect that measure (or measures), calculate (select) the measure a couple of times and enter the most recurring value and not the average of the 2 edits (this is the variation of the program which has been found to be up to 11/100).
Level of Variation (± % change) between Edit 1 and Edit 2 (Using 10 – 17 scans)

<table>
<thead>
<tr>
<th>Measure</th>
<th>Area</th>
<th>Perimeter</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean Variation (%)</td>
<td>Max Variation (%)</td>
</tr>
<tr>
<td>1. Total Abdominal (with skin)</td>
<td>0.005</td>
<td>0.025</td>
</tr>
<tr>
<td>2. Total Abdominal Fat (without skin)</td>
<td>0.021</td>
<td>0.093</td>
</tr>
<tr>
<td>3. Visceral Fat</td>
<td>0.086</td>
<td>0.457</td>
</tr>
<tr>
<td>4. Abdominal Sagittal Length</td>
<td>Ignore this value.</td>
<td>0.117</td>
</tr>
</tbody>
</table>
ANTHROPOMETRY

WAIST CIRCUMFERENCE

Equipment

- Lufkin steel tape measure (W606 PM)

IDF Protocol

- The cross hand technique (left hand under) is used for measuring all girths. The tape should be read at the measurer’s eye level to avoid parallax error and with decimal place in line with the zero. Constant tension is achieved by ensuring that there is no indentation of the skin or gaping of the tape.

- The waist circumference is taken at the mid-point between the lower costal (rib) border and the iliac crest (measured and marked). The measurement is taken at the end of normal expiration with the subject’s arms relaxed at the sides.

ISAK protocol (2006)

- The ISAK waist circumference is located at the narrowest point of the abdomen between the lower costal border (10th rib) and the top of the iliac crest, perpendicular to the long axis of the trunk. If there is no obvious narrowing, the measurement is taken at the mid-point between the lower coastal border and the iliac crest (ie. IDF protocol).

- The subject assumes a relaxed standing position with the arms folded across the
thorax (this also allows clothing to be positioned and held outside the measurement circumference as well). The anthropometrist positions the tape at the target level using the left hand under to read the measurement and then records the number at the end of normal expiration.

**Laser Mark Circumference**

A circumference is recorded (see CT protocol) at the location of the CT scan while the subject is supine, at the mid-point between the lower costal (rib) border and the iliac crest on the left side of the body (measured and marked). When subjects are in standing position, this mark does not usually correspond with the IDF circumference landmark (the mark on the skin at the mid-point between the lower costal border and the iliac crest in supine position is not usually at the same mark on the skin as the mid-point between the lower costal border and the iliac crest when standing). A circumference is also measured where the laser mark is on the skin in standing position. At the baseline scan, the landmark is located from palpation and marking (with ball bearing). At 6 and 12-month scans, this mark is identified by the scanner laser lights at the location of the abdominal CT scan slice.

**Neck Circumference**

The girth around the neck is measured immediately superior to the thyroid cartilage (Adam’s apple). The subject should maintain the head in the Frankfort plane and may be seated or standing. It is important not to pull the tape tight in this region since the tissues are compressible. The tape is held perpendicular to the long axis of the neck, this is not in
a horizontal plane.
PASE SCORING

PASE Score (By Brad Lloyd)

To calculate the PASE score for each activity below, work out the average number of hours spent engaged in each activity per day over the 7 day period and multiply this by the PASE weight.

Examples

1. A participant engages in light sport ‘sometimes (3-4 d)’ for ‘1 but < 2 h’.

3.5 d x 1.5 h = 5.25 h/wk.

5.25 / 7 = 0.75 h/d over the 7 d period.

So PASE score for light sport = 0.75 h/d x 21 = 15.75

<table>
<thead>
<tr>
<th>PASE Activity</th>
<th>Score</th>
<th>PASE Weight</th>
<th>PASE Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle strength/endurance*</td>
<td>h/d</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Strenuous sports*</td>
<td>h/d</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Moderate sports*</td>
<td>h/d</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Light sports*</td>
<td>h/d</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Job involving standing/walking*</td>
<td>h/d</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Walking*</td>
<td>h/d</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Lawn work or yard care</td>
<td></td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Caring for another person</td>
<td></td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>Home repairs</td>
<td></td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Heavy housework</td>
<td></td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Light housework</td>
<td></td>
<td>25</td>
<td></td>
</tr>
<tr>
<td>Outdoor-gardening</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-------------------</td>
<td>----</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>PASE Total</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PASE scores for the activities below are calculated by multiplying the PASE weight by 1 or 0. If the participant engaged in an activity in the last 7 d, multiply the PASE weight by 1. If the participant did not engage in an activity in the last 7 d, multiply the PASE weight by 0. See below.

* determine the average number of hours/day (h/d) over the 7-day period
  
  1= engaged in activity during the previous 7 days
  
  0= did not engage in activity during the previous 7 days
**Paffenbarger Score (BL)**

To calculate the kcal/wk for blocks walked multiply the total number of blocks walked in the previous 7 d by 8. To calculate the kcal/wk for flights climbed multiply the total number of flights climbed in the previous 7 d by 4. To calculate the kcal/wk for light sport, moderate sport, and heavy sport, multiply the total number of minutes spent engaged in each activity over the whole wk by the respective energy expenditure for that activity.

From previous example:

1. A participant engages in light sport ‘sometimes (3-4 d)’ for ‘1 but < 2 h’.

   3.5 d x 1.5 h = 5.25 h/wk.

   5.25 x 60 = 315 min/wk

   315 x 5 = 1575 kcal/wk

<table>
<thead>
<tr>
<th>Activity</th>
<th>Energy Expenditure</th>
<th>Calculation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blocks walked</td>
<td>X 8 kcal / block</td>
<td>= kcal</td>
</tr>
<tr>
<td>Flights climbed</td>
<td>X 4 kcal / flight</td>
<td>= kcal</td>
</tr>
<tr>
<td>Minutes light sport / recreation</td>
<td>X 5 kcal / min</td>
<td>= kcal</td>
</tr>
<tr>
<td>Minutes moderate sport / recreation or muscle strength</td>
<td>X 7.5 kcal / min</td>
<td>= kcal</td>
</tr>
<tr>
<td>Minutes heavy sport / recreation</td>
<td>x 10 kcal / min</td>
<td>= kcal</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>kcal/wk</td>
</tr>
</tbody>
</table>

**NOTE for PASE**

1. Walking – has to be outdoors.

2. Hip exercise/physiotherapy exercise/stretching exercise/seated calisthenics – do not count as muscle strength/endurance. If you think the exercise has a similar EE as ‘light sport’ then include this as ‘light sport’ (e.g. doing weights, light cycling).
3. DO NOT include study exercise in estimate of activity for any question

4. Please remember that if you answer ‘never’ to the first part of Q2 then you should leave Q’s 2a and 2b blank and move onto Q3.

5. Q 2a. Walking To work out the average number of hours per day walked over a 7 day period:
   - Take the average of how many days walked (e.g 1-2) and times this by the average of the number of hours the patient walked per day that they walked (e.g. <1 hour).
   - E.g. Walked ‘seldom’ (1-2 days per week) for less than 1 hour per day = 1.5 x 0.5 hours/day over a 7 day period.
   - If ticked ‘more than 4 hours’ – take this as 4 hours.
   [Note: If exact values are given by RA use these values. E.g. Walked 7 days for 2 hours each day = 2 hour/day over a 7 day period].

6. Q 2b. Walking The distance the patient walked given by RA is per day that the patient walked (unless written otherwise).
   - E.g. If ticked less than 1 mile and walked ‘seldom’ (1-2 days per week), then the patient walked 0.5 mile X 1.5 days = 0.75 miles per week.
   - E.g. If written 4 blocks and walked ‘sometimes’ (3-4 days per week), then the patient walked 4 blocks X 3.5 days = 14 blocks per week.
   - If ticked ‘more than 4 miles’ – takes this as 4 miles.
   [Note: If exact values are given by RA use these values. E.g. Walked 2 blocks per day, 7 day per week = 2 blocks X 7 days = 14 blocks/week.]
7. Q 3. Please record the total number of flights/steps climbed up in a week. Do not include stairs descended.

Note: If exact value is given by RA use this value, otherwise take the average of what the RA has ticked.

If ticked more than 4 flights – take this as 4 flights.

8. Q’s 4. Light sport, 5. Moderate sport, 6. Strenuous sport, 7. Ms. Strength/endurance Work out the average number of hours per day over a 7 day period as per Q 2a.

Do not include ROM exercise as ‘light sport’.

Pilates = ‘light sport’
APPENDIX C. ASSESSMENT PROTOCOLS (ASSESSMENT B)

ASSESSMENT B PROTOCOLS
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<th>Section No.</th>
<th>Page No.</th>
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</thead>
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<tr>
<td>2. Bioelectrical Impedance Analysis</td>
<td></td>
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<tr>
<td>3. Heart Rate Variability</td>
<td></td>
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<tr>
<td>4. Resting Metabolic Rate</td>
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<td>5. Sensory Testing</td>
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<tr>
<td>6. Ankle / Brachial Index</td>
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<tr>
<td>7. Orthostatic Hypotension</td>
<td></td>
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<tr>
<td>8. Blood Test #1 (Fasting)</td>
<td></td>
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<tr>
<td>9. Standardized Meal</td>
<td></td>
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<tr>
<td>10. Demographics</td>
<td></td>
</tr>
<tr>
<td>11. Geriatric Depression Scale</td>
<td></td>
</tr>
<tr>
<td>12. 24h Food Recall</td>
<td></td>
</tr>
<tr>
<td>13. Self-Efficacy Questionnaire</td>
<td></td>
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<tr>
<td>14. NHANES Questionnaire</td>
<td></td>
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<tr>
<td>15. Trail Making Test</td>
<td></td>
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<tr>
<td>16. Modified Mini-mental Exam</td>
<td></td>
</tr>
<tr>
<td>17. Blood Test #2 (Pre-exercise)</td>
<td></td>
</tr>
<tr>
<td>18. Strength Testing (1RM)</td>
<td></td>
</tr>
<tr>
<td>19. Blood Test #3 (Post-exercise)</td>
<td></td>
</tr>
</tbody>
</table>
20. 6 Minute Walk Test

21. Power & Endurance Testing

22. Muscle Biopsy
ANTHROPOMETRY

Equipment

- Weighing Scale (AND HW-100k & SECA Wedderburn (>100 kgs)

- Free weights of known mass (range x kgs, x kgs)

Calibration of Scale

- The site staff must ensure that calibration of the weighing scale is performed following the instructions outlined by the manufacturer's user manual. The frequency of calibration must be as recommended by the manufacturer of the scale.

- Three objects of known weight (eg, dumbbells which have been accurately weighed on a force platform) are EACH placed on the weighing scale on three separate occasions, and the weight to the nearest 0.1kg as displayed by the weighing scale recorded.

The calibration factor to be used for correcting the subject weight is then obtained by following the steps below:

- The average of the three attempts for EACH of the three known weights is calculated

- The ratio of the scale average to each of the known weights is calculated

  e.g. Scale weight averages = 5.1 kg, 10.5, 20.7 kg
Known weights= 4.9 kg, 10.1kg, 20.3 kg
Ratios=5.1/4.9; 10.5/10.1; 20.7/20.3

The average of these 3 ratios is the calibration factor.

- Each measured weight of the subject is divided by the average calibration factor to obtain the TRUE WEIGHT, which is entered into the source document.

- The calibration factor may change during the course of the study and it is important that site staff maintain a log of the date/time that each calibration is undertaken. It is strongly recommended that the calibration factors are part of the calibration log and kept with the weighing scale.

Subject Preparation

- When the subject arrives, ask them to go to the bathroom to relieve themselves whether they feel that they need to or not. They will be lying down for an extended period of time and won’t have the opportunity to go to the bathroom.

- Have the subject change into the gown, removing all garments of clothing (including shoes and socks) and leaving their underwear on. Instruct the subject not to tie the gown up at the back as this will be uncomfortable to lie on for the hour. Leave the room while the subject changes.
Body Weight

- Body weight is recorded three times while the subject is wearing only a robe (with a measured weight) and no shoes.

- Any unusual conditions should be noted (e.g. presence of a cast or other non-removable appliance such as a brace, amputation).

- The subject should step on and off the scale for EACH of the three attempts, whenever possible.

- All three weights are recorded, corrected with the calibration factor as described above, and entered onto the data sheet.

Note:

- For RMR, body mass in the robe minus the weight of the robe is the entered measurement.
BIOELECTRICAL IMPEDANCE ANALYSIS

Equipment

- BIA Analyzer (RJL Systems, Inc., Clinton, MI, USA)

Purpose

BIA will be used to evaluate body composition (RJL Systems, Inc., Clinton, MI). A low-level electrical current is passed through the subject’s body via electrodes placed on the right hand and foot. Impedance (opposition to flow of the current) is measured by the BIA analyzer to estimate the individual’s total body water (TBW). Because of the relatively high water (73%) and electrolyte content of fat free mass (FFM), it offers less impedance to electrical current than fat, which is anhydrous and a poor conductor of electrical current. Thus, individuals with a larger FFM and TBW content will have less resistance to current than those with less FFM and greater body fat.

Subject preparation

- Avoid ingesting food or fluids for 12 hours prior to the test (present in a fasted state).
- Avoid consumption of alcohol for 12 hours prior to testing.
- Avoid exercise, strenuous exertion, or taking a sauna 8 hours prior to testing.
• Subject should not be wet from sweat or urine.

• Subject should not have a fever or be in shock.

Environmental considerations

• The exam area should be comfortable and free of drafts and portable heaters.

Calibration

• Calibrate before each test using 500-ohm resistor. Resistance should be between 495-505 ohms (usually 502 ohms). Record resistance.

• Maximum total test time (including placement and removal of electrodes) = 5 minutes

• Maximum time BIA Analyser is on for = 1 minute

Procedure

1. Record the patient’s naked weight, height, age and gender. Naked weight is calculated by taking away the weight of the gown from the measured weight taken with the gown on.

Example Weight of person + gown = 80.41kg
Weight of gown = 0.39kg

Naked Weight = 80.41kg – 0.39kg
               = 80.02kg

2. The patient should remove their right shoe and sock. Generally the test is completed on the right side of the body. If for some reason the test cannot be completed on the right side, conduct the test on the left side. (Subsequent tests must be conducted on the same side as the first test).

3. Lay the subject in a supine position with arms 30 degrees away from the body, and the legs not touching.

4. Clean the electrode sites with alcohol to remove any dry skin or lotion.

5. Place a signal electrode on the *proximal interphalangeal joint of the middle finger* of the right hand and attach the *black clip with the red lead*.

6. Place the detecting electrode edge on the *dorsal aspect of the wrist* along an imaginary line bisecting the styloid process of the ulna and attach the *red clip with the red lead*.

7. Place a signal electrode over the base of the proximal phalange of the second toe of the right foot and attach the black clip with the black lead.

8. Place the detecting electrode edge on the *anterior aspect of the ankle* along an imaginary line bisecting the medial malleolus and attach the *red clip with the black lead*.

9. Turn the analyser on and make sure the subject refrains from moving. Record the
Resistance and Reactance. Do this three times.

10. Remove and dispose of the electrodes.

**BIA Equation**

Fat free mass [FFM] in (kg) is calculated using the following equation:

$$-4.03 + 0.734 \left( \frac{Ht^2}{R} \right) + 0.116 \,(\text{weight}) + 0.096 \,(X_c) + 0.984 \,(\text{Sex})$$

Where:

- $Ht =$ height in cm
- $R =$ resistance in $\Omega$
- weight is in kg
- $X_c =$ reactance in $\Omega$
- $\text{Sex} =$ 0 for women or 1 for men
RESTING METABOLIC RATE

Equipment

- Ultima PFX, Medgraphics, Minnesota.
- BreezeSuite software.
- Electrodes
- Pnuemotach
- Medgraphics mask

RMR MEASUREMENT

Baseline assessments are performed before initiation of resistance exercise. Two more measurements are done at 6 and 12 months assessments. Each subject should have been transported by motor vehicle to the testing site to ensure minimal activity before RMR determination. Subjects should have been asked to avoid exercise or the ingestion of food, fluids or alcohol for 12 hours prior to the test. Additionally subjects should have had the last training session no less than 48 hours prior to the procedure to avoid the effect of excess post-exercise O2 consumption (EPOC). [1, 2, 3]

Room preparation

- Place metabolic cart next to desk against wall
- Place the foot of the bed against the southern wall of the room to allow the sample tube to reach from behind the head of the patient
- Tape the tube to the bed head if necessary to prevent pulling of the mask
- Turn off light

RMR

After preparation of the equipment and software, RMR is measured with the participants lying supine for 60 min while breathing through a mask assuring an air tight seal. The ambient room temperature should be above 15° Celsius and the patient should be provided with blankets if needed to guarantee a thermo neutral state; the room should be darkened and noise kept to a minimum. The first 30 min of measurements should be considered a resting and a wash out period. The last 30 min will be considered for the actual calculation of the RMR.

Medgraphics Equipment and Software preparation

1. Remind the patient whether they need to visit the bathroom prior to the test.

2. Turn Ultima PFX “on” via the wall switch (white cord) at least 40 min before use.
   Wait until the red light on the Ultima PFX turns from red to green. This indicates that it is ready for use.

3. On the computer screen (desktop screen), select the program “Breeze”.

4. The window which appears in front of you when you first open the program is the ‘Patient’ screen. Select the ‘New’ option at the bottom of the window.

5. Enter in patient’s last, middle and first names, gender race and Date of Birth in the
boxes provided.

6. Press ‘Add visit’. This information is only entered at the first visit, and is retrievable subsequent visits. To retrieve, when the ‘Patient’ screen is open, select the patients file from the list present, press ‘add visit’.

7. Enter in the patient’s height (from Assessment A) and weight (Assessment B).

8. Select **GX Vac**

9. Wait until the red coloured numbers next to “GX Vac” turn into a green “READY”. This takes 10 minutes.

10. Select **CALIBRATE**

    This calibrates the pneumotach.

11. You will need to enter the temperature, humidity and barometric pressure at bottom of window/screen PRIOR to calibrating. Room temperature (°C) and humidity (%) are obtained from the temperature and humidity gauge (placed on the table). The barometric pressure (hPa) is obtained from the Bankstown airport Website: http://www.bom.gov.au/products/IDN65092/IDN65092.94765.shtml
12. Attach pneumotach to the blue end of the 3L calibration syringe. Remove the gas analyser from the front of the Ultima system and attach it to the pneumotach/syringe configuration. (NOTE: the gas analyser is attached to the pneumotach correctly; the notch on the gas analyser is at opposite sides to the notch on the pneumotach).

13. Select “Zero flow” (whilst holding your palm over the end of the pneumotach). If there a caution message that the ‘flow is out of range’, check correct configuration of the syringe/pneumotach/gas analyser configuration and retry. If there was no caution message, this mean the ‘zero flow’ was successful.

14. When ready, you will be asked to calibrate different flow rates using the known volume of air in the syringe. Press ‘start’ and then pull syringe pistol in and out - at a speed to match the lines on the graph displayed on the screen. Do this at five different speeds.

15. To re-do or reset (if you make a mistake): select “Stop”, then “Start” – and try calibrating again.

16. If calibration is successful, ‘calibration successful’ will appear on the top right hand corner of the screen. If the calibration was unsuccessful, ‘calibration unsuccessful’ will appear in the same space. You will need to retry until ‘calibration successful’ appears.

17. Select “OK” when done. This will close the calibration window.

18. The gas cylinders are located at the back of the cart. Turn handles on both gas
cylinders in a counter-clockwise direction to open cylinders. You do not need to open the knobs all the way. They only need to be turned 90 degrees from the starting position. (Do not touch the knobs where indicated by signs ‘DO NOT TOUCH!’).

19. Return the gas analyser into the Ultima PFX (with the 2 pins on top).

20. Select AUTO CAL. This is the ‘Calibration of gases’.

21. A caution message ‘Calibrating Gas Analysers’ will appear while auto calibrating the gas cylinders. A summary window will appear once the calibration is complete, indicating that the calibration was successful.

22. Select “OK”.

23. Turn gases off completely (twist knobs clockwise) when calibration is complete. If left open, the gases will be depleted.

24. Select Tab at the bottom of the screen – Gas Exchange)

The ‘settings’ page will be the page appearing on the screen.

25. Enter the details of the test you will be conducting. In this case it will be ‘Metabolic - DARE’.

26. Enter physician and technician details in the appropriate places.

27. Select the ‘Test’ tab. At this point the page displays a blank data section (located in the top portion of the screen with variables such as \( V_{O2} \), \( VCO_2 \) RER and HR) and
two blank graphs.


29. Explain the placement of the mask and its purpose.

30. Place the mask on the patients face while in the seated position.

31. Let the patient know that the data acquisition will go for 60 minutes, where they are needed to stay as still and as relaxed as possible. Sleeping is not permitted; they will be gently woken if they are seen to be falling asleep.

32. Press the \textbf{START} button located on the top left hand corner of the screen. This will start the collection of the data from the mask into the Medgraphics system. The empty data screen and graphs will now have information appearing.

33. At the end of the 60 minute period, stop the test.

NOTE: Wearing the mask is uncomfortable, and this time should not be prolonged unnecessarily.

RMR calculation (use naked body weight in calculations)

The final RMR value will be determined as follows:

1. Using the functions available in the software, the measurement window will be adjusted to the last 30 min. This procedure will provide a mean value for the last 30 min which will be used as a reference later.

2. The data points provided by the software will be exported to a datasheet in Excel and the coefficient of variation CV (SD/mean) of each 3 min block will be calculated for
VO2 and VCO2.

3. Additionally the minute to minute variability (%) of the VO2 and VCO2 data points will also be calculated.

4. The 5 min period with a min-min variability <10% and the lowest CV will be considered the RMR value.

5. The values obtained at step 1 and 4 should be compared. The value in 4 should be lower than 1, confirming that the result corresponds to a stable period close to the basal activity and not a result coming from a stable peak.

Steps 2 to 4 should be done in order to determine a steady state period of gas exchange defined by a 5-minute interval during which VO2 and VCO2 vary by <10%. [4] A 3-minute interval can be considered clinically acceptable in ambulatory patients whenever the 5-min period is difficult to achieve. [5] The validity of the measurements must be verified by at least 2 essential parameters: evaluation of the RQ and documentation that steady state has been achieved. The RQ should be within the physiologic range of 0.67 to 1.3. [4, 6]

**Fat Oxidation Calculation**

Once the RMR has been calculated (see above) the amount of fat oxidized per day (both absolute g/day and relative g.kg\(^{-1}\).day\(^{-1}\) or g.kg\(^{-1}\).FFM.day\(^{-1}\)) can be calculated.

1. Insert the average VO2 (L.min\(^{-1}\)) and VCO2 (L.min\(^{-1}\)) from the calculated RMR period into the equation of Frayn (1983): [7]

\[
\text{Fat oxidation (g/min)} = 1.67(\text{VO2}) - 1.67(\text{VCO2})
\]
2. Multiply by 1440 (i.e. number of minutes in a day) to get total grams of fat oxidized per day.

3. Divide by naked body weight (kg) and/or fat free mass (FFM) calculated from the BIA to determine the relative daily fat oxidation rate (i.e. g.kg\(^{-1}\).day\(^{-1}\)).

4. Example: Subject 1 (BM = 98kg, FFM = 68 kg) has resting VO\(_2\) = 0.283 L.min\(^{-1}\), VCO\(_2\) = 0.221 L.min\(^{-1}\), RER = 0.78

   Fat oxidation (g/min) = 1.67 × 0.283 – 1.67 × 0.221 = 0.104
   Fat oxidation (g/day) = 0.104 × 1440 = 149.8
   Fat oxidation (g.kg\(^{-1}\).day\(^{-1}\)) = 149.8 ÷ 98 = 1.529
   Fat oxidation (g.kgFFM\(^{-1}\).day\(^{-1}\)) = 149.8 ÷ 68 = 2.203

Data Extraction from Medgraphics

- Open Patient file
- Select Patient
- Select a visit (should be either resting or treadmill: select resting) double click
- You are now in “Visit Demographics”
- Select “GX” tab (bottom of screen)
- You are now in “Settings”
- Select “Test” tab
- You are now looking at the data in spreadsheet and/or graph form
- Select the data on the spreadsheet ➔ Right-click ➔ copy ➔ paste into
Excel spreadsheet for further analysis.

If further data is required that is not displayed in the columns of the spreadsheet

- Click of “Tools”
- Select “Options”
- In the “Test” tab go to “configuration”
- In the drop-down list select “RMR Analysis (Raw)”
- In the “Averaging” box select “Unaveraged” and click “OK”
- Click on any column heading, a drop down list will appear, scroll through the list and select the data you want.
- Copy and paste into Excel.

Environment data extraction from Medgraphics

All environmental data (ambient temperature, relative humidity and barometric pressure) typed in for each test is saved by Medgraphics. To extract this data:

- Click on the “Calibration” button (top of screen)
- You are now in the pneumotach calibration screen
- Click on the “Cal Log” button (bottom left of screen)
- From the list double click on the test that is required and all environmental data will be there

Possible outliers and spurious data

Some RMR data may have RER values >1. Some possible explanations for this are:

1. Bad calibration of Medgraphics
2. Patient is hyperventilating resulting in CO2 being blown off. This increases
the RER via a non-metabolic source of CO2. Some reasons for hyperventilation are:

i. Anxiety or stress

ii. A reaction to wearing the mask

iii. Obese patients lying on their back can experience dyspnoea

iv. Patients with mild COPD who suffer from dyspnoea

2. Patient may fall asleep. If they suffer from sleep apnoea the patient will not breathe for periods of 20-60s followed by a period hyperventilation.

Monitor patient closely to prevent sleep.

4. Some patients may have rapid but shallow breathing. The Medgraphics has a default setting for tidal volume (Vt) of 180ml. Any breathe less than this will not be shown on the screen resulting in gaps as large as 2 minutes. The default value can be changed retrospectively in the software to include all breathes. Go to the “settings” page to change Vt default setting before loading the file.

5. The data output on the screen needs to be monitored in order to observe any large gaps between breathes. Check patient is awake and mask is properly positioned.

**Bland-Altmann analyses of fat oxidation methods**

Data of the first 20 subjects (55 files) in G2D study were used to look at differences between different equations from the literature and the Medgraphics output for fat oxidation rates. Equations used were Frayn (1983)7, Jequier et al. (1987) [8] and Consolazio et al. (1963)9. These were also compared to the Medgraphics output.

Note: the 3 equations are very similar. The Frayn (1983) equation was therefore selected
as it is the most cited.
REFERENCES


9. Consolazio CF, Johnson RE, Pecora LJ. Physiological measurements of metabolic
BLOOD TEST #1 (FASTING)

Blood sample preparation, analysis, storage and shipment

- Blood Insulin, Glucose, Total cholesterol, LDL, HDL, triglycerides

- Blood should be collected on a 10 ml serum tube (gel tube or clot activated) which is labelled with subjects name, study ID number, sample type (Ins, Glu, Chol, etc.), date and visit number (ie. Baseline = Visit 1; 6 months = Visit 2; 12 months = Visit 3).

- Record the time sample is drawn, and the time it is spun.

- Tubes should be left to clot at room temperature for 30 minutes. Do not allow clotted samples to sit for more than 1 hour (if possible). Spin the tube in a refrigerated centrifuge (H107, Sorvall centrifuge, 3400rpm, 10min at 4°) and leave it in on ice until collection.

Full blood count and blood HbA1c samples (Purple top)

- Samples should be collected in a 10 ml EDTA (purple top) tube,

- Samples must be clearly labelled with subjects name, study ID number, sample type (ie. FBC + HbA1c) and identified as to which visit they represent (ie. Baseline = Visit 1; 6 months = Visit 2; 12 months = Visit 3)

- Samples can be stored on ice with the previous sample until time of pickup by courier.
Shipment procedure

- Samples will be picked up by a courier and transported on dry ice.
- Samples must be accompanied by a spreadsheet detailing the subject initials, study ID, number, sex, date of birth, date of collection and time of collection. The spreadsheet will be provided by the Laboratory.

Delivery should be organized prior to the visit by contacting DHM courier on 9855 5200

Blood test results

Blood results are available electronically and via the mail within 1-3 days of blood collection. To view the results electronically, visit http://www.dhm.com.au "Online Services for Doctors"
"Webster"
"Log-in here"
Username: XXXXXX
Password: XXXXXX

Serum C-peptide (Red top)

- Serum C-peptide should be collected in a 10 ml serum (red top) tube after the
subject has fasted for 12 hours.

- The tube must be labelled with subjects name, study ID number, date and visit number (ie. Baseline = Visit 1; 6 months = Visit 2; 12 months = Visit 3).

- The tube should be left to clot at room temperature for 30 minutes. Do not allow clotted samples to sit for more than 1 hour (if possible).

- Centrifuge in a refrigerated centrifuge (found in H107, Sorvall centrifuge, 3400rpm, 10 min at 4°) and pipette 3ml of serum that you transfer into a 4ml plastic tube. The tube must be labeled with subject name, study ID number.

- Freeze it in liquid nitrogen, and store it in the -20° freezer in H block, room H107 until collection.

- The rest of the serum should be transferred to 1.5ml eppendorfs (0.5ml per eppendorf) and labeled with subjects name, study ID number and type of sample (spare sample 1, 2, etc.). These tubes should be placed inside a GREAT2DO freezer box, and stored in –80 freezr in H block, room H108 until analysis.

**CRP Analysis**

CRP analyses are performed by Bernhard Baune’s laboratory at the University of Adelaide, Adelaide SA. Organise 1 eppendorf containing serum from each participant, at each time point to be analysed for CRP, and place them inside a cryogenic box to prepare for shipping. Samples should be shipped with an accompanying list to help the laboratory identify the samples inside. Organise a courier to transport the samples. The following
courier is recommended http://www.worldcourier.com/locations/australia.

Serum samples should be shipped to the following address:

Prof. Bernhard Baune

Psychiatric Neuroscience Laboratory

Attention: Dr. Catharine Jawahar / Dr. Emily Jaehne

Level 4, Medical School South

University of Adelaide

Frome Road

Adelaide – 5005

Tel: 61 8 8222 5141

Fax: 61 8 8222 2774

**Human C-reactive Protein Instant ELISA (eBIOSCIENCE)**

**Description**

The human C-reactive protein Instant ELISA is an enzyme-linked immunosorbent assay for the quantitative detection of human C-reactive protein. The human C-reactive protein Instant ELISA is for research use only. Not for diagnostic or therapeutic procedures.
3 Principles of the Test

An anti-human C-reactive protein polyclonal coating antibody is adsorbed onto microwells. Human C-reactive protein present in the sample or standard binds to antibodies adsorbed to the microwells; an HRP-conjugated monoclonal anti-human C-reactive protein antibody binds to human C-reactive protein captured by the first antibody. Following incubation unbound enzyme conjugated anti-human C-reactive protein is removed during a wash step and substrate solution reactive with HRP is added to the wells.

A coloured product is formed in proportion to the amount of soluble human C-reactive protein present in the sample. The reaction is terminated by addition of acid and absorbance is measured at 450 nm. A standard curve is prepared from seven human C-reactive protein standard dilutions and human C-reactive protein sample concentration determined.

Sensitivity: 3.0 pg/ml

Sensitivity limit is comparable to other high sensitivity ones:

hsCRP Human ELISA (BioVendor) 0.02 μg/ml

IBL Immuno-biological laboratories CRP high sensitive ELISA 0.124 ng/ml

SI unit: mg/l

For comparison:

1. Haider et al. C-reactive protein is expressed and secreted by peripheral blood
mononuclear cells. Clinical & Experimental Immunology. 2006; 146:533-539. 

http://ajpendo.physiology.org/content/293/4/E1030.full (Table 1)


**Expected Values**

A panel of 8 sera from randomly selected healthy donors (males and females) was tested for human C-reactive protein. The detected human C-reactive protein levels ranged between 136 and 800 ng/ml with a mean level of 381 ng/ml and a standard deviation of 214 ng/ml. (136 ng/ml = 0.136 mg/l)

**Coefficient of Variation**

Absorbance values from duplicates are allowed to be less than 20%.
Table 1: Intra- and inter-assay CV in %

<table>
<thead>
<tr>
<th></th>
<th>Intra-assay CV (%)</th>
<th>Inter-assay CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plate</td>
<td>6.3</td>
<td>24.5</td>
</tr>
<tr>
<td>Plate</td>
<td>2.3</td>
<td></td>
</tr>
<tr>
<td>Plate</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>Plate</td>
<td>4.8</td>
<td></td>
</tr>
<tr>
<td>Plate</td>
<td>5.6</td>
<td></td>
</tr>
<tr>
<td>Plate</td>
<td>6.4</td>
<td></td>
</tr>
</tbody>
</table>
Serum adiponectin

Collection and storage

• Serum adiponectin should be collected in a 10 ml serum (red top) tube after the subject has fasted for 12 hours.

• Each tube must be labelled with subjects name, study ID number, sample type (ie. Adiponectin), date and visit number (ie. Baseline = Visit 1; 6 months = Visit 2; 12 months = Visit 3).

• Tubes should be left to clot at room temperature for 30-60 minutes. Do not allow clotted samples to sit for more than 1 hour (if possible).

• Centrifuge in a refrigerated centrifuge in a refrigerated centrifuge (found in H107, Sorvall centrifuge, 3400rpm, 10min at 4°) and pipette 0.5ml of serum into 5 different 1.5 ml microfuge (Eppendorf) tubes. Each tube must be labelled with subjects name, study ID number and type of sample (adiponectin). Pipette the rest of the serum in different Eppendorfs (0.5ml per Eppendorf) and label it with subjects name, study ID number and type of sample (spare sample 1, 2, etc.).

• Store samples at 4°C until all samples from subject are prepared.

• Store all samples for each subject together in -80°C freezer in GREAT 2 Do Freezer boxes until time of analysis in batches.
Shipment procedure

- Samples will be picked up by a courier and transported on dry ice.

- Samples must be accompanied by a spreadsheet detailing the subject initials, study ID number, sex, date of birth, date of collection and time of collection. The spreadsheet will be provided by the Laboratory as a PDF file with all the information except the ones above that will need to be filed.

- Samples should be shipped with an accompanying list to help the laboratory identify the samples inside. Organise a courier to transport the samples. The following courier is recommended
  
  http://www.worldcourier.com/locations/australia. Serum samples should be shipped to the following address:

  Prof. Bernhard Baune.

  School of Medicine and Dentistry,
  
  James Cook University (Townsville, QLD, Australia)

Human Adiponectin Immunoassay

Introduction

The Quantikine Human Total Adiponectin Immunoassay is a 4.5 hour solid-phase enzyme-linked immunosorbent assay (ELISA) designed to measure total (low, middle, and high molecular weight) human Adiponectin in cell culture supernates, serum, and plasma. It contains NS0-expressed recombinant human adiponectin and has been shown to accurately quantitate the recombinant factor. The human adiponectin Immunoassay is for research use
only. Not for diagnostic or therapeutic procedures.

**Principle of the assay**

This assay employs the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for the Adiponectin globular domain has been pre-coated onto a microplate. Standards and samples are pipetted into the wells and any Adiponectin present is bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked monoclonal antibody specific for the Adiponectin globular domain is added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution is added to the wells and color develops in proportion to the amount of Adiponectin bound in the initial step. The color development is stopped and the intensity of the color is measured.

**Sensitivity**

Eighty assays were evaluated and the minimum detectable dose (MDD) of Adiponectin ranged from 0.079 - 0.891 ng/mL. The mean MDD was 0.246 ng/mL.

**Sample values**

Serum samples drawn from apparently healthy volunteers were evaluated for the presence of adiponectin in this assay.

<table>
<thead>
<tr>
<th>Sample Type</th>
<th>Mean (ng/mL)</th>
<th>Range (ng/mL)</th>
<th>Standard Deviation (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum (n=60) 6641</td>
<td>6641</td>
<td>865 - 21,424</td>
<td>3665</td>
</tr>
</tbody>
</table>
Precision

Intra-assay Precision (Precision within an assay): Three samples of known concentration were tested twenty times on one plate to assess intra-assay precision.

Inter-assay Precision (Precision between assays): Three samples of known concentration were tested in forty separate assays to assess

Inter-assay precision.

<table>
<thead>
<tr>
<th></th>
<th>Intra-assay Precision</th>
<th>Inter-assay Precision</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>n</td>
<td>20</td>
<td>20</td>
</tr>
<tr>
<td>Mean (ng/mL)</td>
<td>19.8</td>
<td>69.9</td>
</tr>
<tr>
<td>Standard Deviation (ng/mL)</td>
<td>0.50</td>
<td>2.40</td>
</tr>
<tr>
<td>CV%</td>
<td>2.5</td>
<td>3.4</td>
</tr>
</tbody>
</table>
DEMOGRAPHICS

Gender

☐ Male

☐ Female

Race / Ethnic Background

What is your ethnic background?

☐ Caucasian

☐ Asian

☐ Aboriginal

☐ Indian

☐ Middle East

☐ Black

☐ Other ____________________

Marital Status

Are you married, widowed, divorced, separated, never married?

☐ Married / Defacto

☐ Widowed

☐ Divorced

☐ Single / Never Married
Residence

In what type of accommodation do you live?  
- House (own)
- House (rented)
- Unit (own)
- Unit (rent)
- Retirement Village
- Hostel

How long have you lived at this address?  
- Nursing Home
- Board / Rooming House

___________ Years

___________ Months

Living Situation

With whom do you live?  
- Alone
- Spouse / Partner
Total number of people in the household

☐ Family

☐ Paid Carer

☐ Friend

☐ Other Residents

__________ People

**Education**

What is the highest grade or year of school you completed?

☐ Never / Kindergarten

☐ Primary School

☐ High School

☐ Tertiary / Undergraduate

☐ Post Graduate

Year 1 2 3 4 5 6 7
8 9 10
11 12 13 14 15 16 17 18 19 20

**Work**

Do you currently work for pay either for yourself or someone else?

☐ Yes (__________ hours / week)

☐ No
Do you currently work as a volunteer? □ Yes (_________ hours / week)
□ No

**Annual Income**

In what range is your annual income? □ < $15,000
□ $15,000 - $30,000
□ > $30,000

**Private Health Insurance**

Do you have private health insurance? □ Yes
□ No

**Hospital Admissions**

During the past 12 months, how many different times did you stay in hospital overnight? □ Number of times
□ Number of days in hospital

**Smoking**
Have you ever smoked cigarettes, cigars or a pipe on a daily basis?  
☐ Yes (__________ number / day)  
☐ No

Do you currently smoke at least 1 cigarette, cigar or pipe per day?  
☐ Yes  
☐ No

Alcohol  
During the past 30 days, about how many days did you drink any alcoholic beverages (beer, wine, spirits)?  
☐ Almost every day  
☐ 3-4 times a week  
☐ Once or twice a week  
☐ 2-3 times a month  
☐ Once a month  
☐ None
GERIATRIC DEPRESSION SCALE

SCORING INSTRUCTIONS

1. USE THE TRANSPARENCY TEMPLATE WITH ALL THE NON-DEPRESSED ANSWERS BLACKENED.

2. PLACE TRANSPARENCY OVER QUESTIONNAIRE; ALL “DEPRESSED” ANSWERS WHICH ARE CHECKED WILL SHOW THROUGH THE CLEAR BOXES.

3. COUNT THE NUMBER OF CHECKED DEPRESSED ANSWERS.

4. THIS IS THE SCORE OF THE GDS (RANGE 0-30)

TOTAL SCORE AS WELL AS CATEGORICAL SCORE SHOULD BE ENTERED INTO THE DATABASE:

- 0-9 = NORMAL
- 10-19 = MILD DEPRESSIVE SYMPTOMS
- 20-30 = SEVERE DEPRESSIVE SYMPTOMS
TRAIL MAKING TEST A

Hand the participant the “Trail Making-Sample A” Sheet and a pencil with an eraser.

Say to the participant:

“On this page are some numbers. Begin at number 1 (point to 1) and draw a line to number 2 (point to 2), 2 to 3 (point to 3), 3 to 4 (point to 4), 4 to 5 (point to 5), and so on in order, until you reach the end (point to the circle marked “End”). Draw the lines as fast as you can. Ready? Begin.”

If the participant makes a mistake point out the error and explain it. If necessary guide the participant’s hand through the trail, eraser end down. Then say “Now you try it,” and repeat the original directions starting with “Begin at number 1…” Repeat instructions with guidance twice.

If the participant completes the sample item correctly and shows that he/she understands the task say, “Good! Let’s try the next one.” If the participant still does not understand, terminate Trail Making Test A and go on to Trail Making Test B.

Hand the participant the “Trail Making Test A” Sheet.

Start timing as soon as the instruction is given to begin. Allow a maximum of 300 seconds for the task. WATCH CLOSELY IN ORDER TO CATCH ANY ERRORS AS THEY ARE MADE. If the participant makes an error, identify it immediately, draw a perpendicular line through the incorrect line and tell him/her to proceed from the number where the mistake
occurred. DO NOT STOP TIMING.

If the participant goes over the 300 seconds, stop and go to the next cognitive function test.

Record time taken on the sheet.
TRAIL MAKING TEST B

Hand the participant the “Trail Making Sample B” Sheet and a pencil with an eraser.

Say to the participant:

“On this page are some numbers and letters. Begin at number 1 (point to 1) and draw a line to A (point to A), A to 2 (point to 2), 2 to B (point to B), 3 to C (point to C), and so on in order, until you reach the end (point to the circle marked “End”). Remember, first you have a number (point to 1), then a letter (point to A), then a number (point to 2), then a letter (point to B) and so on. Draw the lines as fast as you can. Ready? Begin.”

If the participant makes a mistake explain the rules in exactly the same way you did for the previous test.

Hand the participant the “Trail Making Test B” Sheet.

Start timing according to the same instruction given for the previous test. If the participant goes over 300 seconds, stop and go to the next cognitive function test.
TRAIL MAKING TEST A SCORING SHEET

☐ NOT DONE

Number of circles connected (maximum 25): __________

Total time (maximum 300 seconds): __________

Errors: __________

TRAIL MAKING TEST B SCORING SHEET

☐ NOT DONE

Number of circles connected (maximum 25): __________

Total time (maximum 300 seconds): __________

Errors: __________
TRAIL MAKING Part B

SAMPLE

```
Begin
1

D

End

4

A

B

2

C

3
```
MODIFIED MINI MENTAL STATUS (3MS) EXAMINATION

ADMINISTRATION AND SCORING

A summary form for the administration and scoring of the 3MS is presented in the Appendix and can be reproduced on one side of a standard (8.5 in. x 11 in.) sheet of paper. 3MS is a revision of the MMS that includes four additional items (date and place of birth, word fluency, similarities, and delayed recall of words) to sample a wider range of cognitive abilities an expended range of scores from 0-30 to 30-100. On the back side of the same sheet, CLOSE YOUR EYES (all in capital letters, approximately 12 in. high) can be printed in the upper part, and two intersecting pentagons (each side 1 in, long) can be drawn in the lower part. Enough blank space is left to record the participant's drawing and writing.

Testing procedures and scoring criteria that either do not differ from the original MMS or are self-evident in the summary form are not repeated here. Clarifications, important aspects of administration, and comments on the differences between the MMS and the 3MS are presented. Instructions enclosed in quotation marks and printed in capital letters should be follow verbatim.

Date and Place of Birth

Assign one point each to the year, month, and date, City or town, and state of birth. This item is added to provide some measure of the subject's recall of personal information that one can assume to have been overlearned.
Registration

"I SHALL SAY THREE WORDS FOR YOU TO REMEMBER. REPEAT THEM AFTER I HAVE SAID ALL THREE WORDS SHIRT BROWN HONESTY."

If a person is tested repeatedly, the alternatives of "shoes, black, modesty" and "socks, blue, char in." May be used in successive test sessions. However, whether or not the three alternate forms are comparable has yet to be determined.

The MMS procedure permits the use of the names of any three objects, thus allowing wide variations in item difficulty. The 3MS procedure specifies the three words to reduce the variation. The inclusion in the 3MS of a low frequency abstract word, honesty, is intended to broaden the range of difficulty.

Mental Reversal

First establish the subject's ability to recite in the forward direction, coaching him or her once if needed. Then ask the subject to recite in the reverse direction. Score for the number of elements in correct relative position. Score 0, if after being coached, the subject is still unable to recite in the usual direction.

The relatively easy item of counting backward from 5 to 1 is added to introduce the task and to extend the lower range of the test.

The corresponding MMS item of "Attention and Calculation" permits two choices of
testing: either by spelling "world" backward or by five serial subtractions of 7. However, the equivalence between the two alternatives in the composition of mental operations has not been demonstrated. The serial subtractions are more difficult and are more affected by the subject's educational background; therefore. This alternative is eliminated from the 3MS.

**First Recall**

First ask, "WHAT ARE THE THREE WORDS THAT I ASKED YOU TO REMEMBER?"

For each word not recalled, provide a category cue (e.g., "something to wear"); if the subject still cannot give the correct answer, provide three choices (e.g., "shoes, shirt, socks"). Use only the specified cues and choices. If the subject does not give the correct answer from the three choices, score 0 and provide the correct answer.

The MMS gives credit only for unaided recall. To extend the lower range of the test, the 3MS also gives credit for correct responses after the subject has received category-cueing and after being given multiple choices.

**Temporal Orientation**

The MMS dichotomises the response to each of the five subitems as correct or incorrect. The 3MS assigns scores according to the closeness of the response to the correct answer. Graded scoring of temporal orientation has been found to be highly sensitive for detecting abnormal mental decline in old persons.'
Temporal orientation is scored in a negative manner. For example, most nondemented persons know the year; assigning 8 points for the year means that not knowing the year will be penalised for up to 8 points.

**Spatial Orientation**

For the last subitem, ask, "ARE WE IN A HOSPITAL OR OFFICE BUILDING OR HOME?" If the correct answer is not among those three choices, substitute the correct answer for the second choice, office building.

The MMS asks for the name of the hospital, but reporting the hospital's name has a high memory component and may not be applicable in some circumstances, such as when a subject is tested in his or her home. The 3MS procedure simply provides three alternatives for the subject to choose from. The MMS item for floor is eliminated because the correct identification of the floor is pan influenced by the total number of floors in a building.

**Naming**

Point to a pan of your own body and ask the subject name it. Score 0 if the subject cannot name it ready gives an incorrect name. Do not wait for the subject to mentally search for the name. Body parts are used to ensure equal familiarity b, subjects. According to the Kucera-Francis word count the frequencies of occurrence in approximately important words for "shoulder," "chin," "forehead;" bow," and "knuckle" are 61, 27, 16, 10, and 3,
restively. The corresponding frequencies for the MMS w of "watch" and "pencil" are 81 and 34, respective:

**Four-Legged**

Ask, "WHAT ANIMALS HAVE FOUR LEGS?" allow 30 seconds for the response. If the subject gives no response in 10 seconds, the question once.

The first time an incorrect answer is provided, say “I WANT FOUR-LEGGED ANIMALS." Do not correct subsequent errors. Score for the number of correct responses, up to 10. This item is added because fluency of retrieval from specified category has been demonstrated to be sensitive in differentiating between normal and early-dementia states.

**Similarities**

Ask, "IN WHAT WAY ARE AN ARM AND A LEG I ALIKE?" If the subject fails to give an answer that worth 2 points, assign the appropriate score of 1 or 0, do coach the subject by saying that an arm and a leg either limbs or parts of the body. Do not coach for the, sequent two subitems. This item is added to sample abstraction or conceptual thinking that is relatively unrelated to category retrieval but that is impaired in dementia.

**Repetition**

First say, “REPEAT WHAT I SAY, 'I WOULD L TO GO HOME/OUT.” Pronounce the individual word clearly but with the normal tempo of a spoken sentence (i.e., without
artificial slowing or pausing after forward). Use "home" in the sentence if the subject is at home; otherwise, use "out."

Next say, "NOW REPEAT, 'NO IFS, ANDS, OR BUTS.' "Again, use the normal tempo of a spoken sentence. Assign 1 point each for "no ifs," "ands," "buts." Give no credit if the subject misses the "s." The first sentence is added to extend the lower range of the test and to help establish the subject's mental set repeating.

**Read and Obey "Close Your Eyes"**

Hold up the piece of paper on which the command printed and say, "PLEASE DO THIS." If the subject not close his or her eyes within 5 seconds, prompt him or her by pointing to the sentence and saying, "READ AND DO WHAT THIS SAYS." If the subject has already read the sentence aloud spontaneously, simply say, "DO WHAT THIS SAYS." Allow 5 seconds for the response. Assign a score of 1 if the subject reads the sentence either spontaneously or after the examiner's request, but does not close the eyes.

**Writing**

For this and the following item, provide the subject a soft (No. 2) pencil with an eraser attached. Ask the subject to write, "I would like to go home/out." Repeat the sentence, word by word if necessary, but a maximum of 1 minute after the first reading of the sentence for the response. Either printing or cursive writing is allowed. Assign 1 point for each correct word, but give no credit for "I." Each word needs to be completely correct to earn 1 point. DO not penalise self-corrected errors. If the writing is
ambiguous, judge whether or not the word can be readily recognised in isolation. The MMS calls for a written sentence generated by the subject and gives a score of 1 or 0 for the whole product. The subject may fail because he or she is unable to generate a sentence or unable to write or both. Recent reports indicate that the inability to write is the more limiting component for this item, and the loss of the ability to write is associated with a higher familial incidence of dementia. The 3MS item more specifically measures the ability to write a standard dictated sentence, and it permits a range of scores from 0 to 5.

**Copying two Intersecting Pentagons.**

Allow 1 minute for copying. In scoring, do not penalise for self-corrected errors, tremors, minor gaps, or overshoots. For each five-sided enclosure, assign a score of 4 unless the longest side is more than twice the length of the shortest side, in which case assigned a score of 3. A non-pentagon enclosed figure is given 2 points. Two or more line segments that do not form an enclosure are given 1 point. A four-cornered intersection is given 2 points. An intersection with other than four corners receives 1 point. The 0-10 graded scoring for this item in the 3MS replaces the 0-1 dichotomous scoring of the MMS. In the MMS only this one point is given to a nonverbal task.

**Three-stage Command**

Hold up a piece of white paper in plain view of the Subject but out of his or her reach and say, "TAKE THIS PAPER WITH YOUR LEFT [for a left-handed person, Say RIGHT] HAND, FOLD IT IN HALF, AND HAND BACK TO ME."
After saying the whole command, hold the paper Within reach of the subject. Do not repeat any part of the command. Do not give visual cues for the subject to return the paper, such as keeping a hand in a ready-receive posture.

The first part of the command asks the subject to use the nonpreferred hand in order to avoid crediting 1 point by default. The third part of the command is revised from the MMS for ease of administration.

**Second Recall**

Administer this item even if the subject has a score of 0 on the first recall. Test and score in the same way as with the first recall. The second recall is added to test the subject's memory after a longer interval than the first recall, and it is expected to extend the ceiling of the test. The second recall may also help differentiate dementia of the Alzheimer type from other forms of dementia. Although the distinction between cortical dementia and subcortical dementia has been questioned, patients with dementia of the Alzheimer type show a clearly faster rate of forgetting between two recall tests than do patients with Huntington's disease.
Read and Obey "Close Your Eyes" Hold up the piece of paper on which the comma printed and say, "PLEASE DO THIS." If the subject ("Where were you born?")

<table>
<thead>
<tr>
<th>1. “Where were you born?”</th>
<th>Record responses</th>
<th>Correct answer</th>
<th>Error / refused</th>
</tr>
</thead>
<tbody>
<tr>
<td>City / town</td>
<td>_______________</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>State / county</td>
<td>_______________</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. “When were you born?”</th>
<th>Record responses</th>
<th>Correct answer</th>
<th>Error / refused</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day</td>
<td>_______________</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Month</td>
<td>_______________</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Year</td>
<td>_______________</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

3. “I am going to say three words for you to remember. Repeat them after I have said all three words: Socks, blue, charity.”

Do not repeat the words for the participant until after the first trial. The participant may give the words in any order. If there are errors on the first trial, repeat the items up to three times until they are learned.

<table>
<thead>
<tr>
<th>First trial only:</th>
<th>Correct answer</th>
<th>Error / refused</th>
</tr>
</thead>
</table>
a. Socks 1 0
b. Blue 1 0
c. Charity 1 0
d. number of presentations necessary for the participant to repeat the sequence (choose 0-3)

4. “Count from 1 to 5.”

☐ Able to count forward

☐ Unable to count forward (if unable to count forward, say “1-2-3-4-5”)

“Now count backwards from 5 to 1.”

Record the responses in the order given:

First number __________ Accurate Answer

1 1-2 errors

Second number __________

0 > 2 errors
Third number

Fourth number

Fifth number

3MS Page 1, Score: ________
5. “Spell ‘world’.”

☐ Able to spell

☐ Unable to spell (say “It’s spelled W-O-R-L-D”)

“Now spell ‘world’ backwards.” Examples (not only possibilities):

Record the letters in the order given:  5 DLROW

4  DLORW, DLWRO, DROW, DLOW, DRLOW

First letter

Second letter  

Third letter  

Fourth letter  

5th letter

Fifth letter  0  No response
6. “What three words did I ask you to remember earlier?”

The words may be repeated in any order

If the participant cannot give the correct answer after a category cue, provide the three choices listed.

If the participant still cannot give the correct answer from the 3 choices, mark 0 and provide the correct answer.

<table>
<thead>
<tr>
<th>a. Socks</th>
<th>3 spontaneous recall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 after “Something to wear”</td>
</tr>
<tr>
<td></td>
<td>1 after “Was it shirt, shoes or socks?”</td>
</tr>
<tr>
<td></td>
<td>0 still incorrect / refused (provide correct answer)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>b. Blue</th>
<th>3 spontaneous recall</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 after “A colour”</td>
</tr>
<tr>
<td></td>
<td>1 after “Was it blue, black or brown?”</td>
</tr>
<tr>
<td></td>
<td>0 still incorrect / refused (provide correct answer)</td>
</tr>
</tbody>
</table>
c. Charity

3 spontaneous recall

2 after “A good, personal quality”

1 after “Was it honesty, charity or modesty?”

0 still incorrect / refused (provide correct answer)

3MS Page 2, Score: __________
7. **What is today’s date?** Record response. Enter ‘X’ if no response. Probe for the month, day or year if it is not volunteered.

<table>
<thead>
<tr>
<th></th>
<th>2</th>
<th>Accurate or within 5 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month</td>
<td>1</td>
<td>Missed by 6 days to 1 month</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Missed &gt; 1 month</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>Accurate</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Missed by 1-2 days</td>
</tr>
<tr>
<td>Day</td>
<td>1</td>
<td>Missed by 3-5 days</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Missed by &gt; 5 days</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>Accurate</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>Missed by or within 1 year</td>
</tr>
<tr>
<td>Year</td>
<td>2</td>
<td>Missed by or within 2-5 years</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>Missed by &gt; 5 years</td>
</tr>
</tbody>
</table>
8. “What is the day of the week?”

Record answer in error. Correct Error / refus
Enter ‘X’ if no response answer refused

Day of the week _______________

9. “What season of the year is it?”

Record answer in error. Correct Error / refus
Enter ‘X’ if no response answer refused

Season _______________

10. “What state are we in?”

Record answer in error. Correct Error / refus
Enter ‘X’ if no response answer refused

State _______________

11. “What county (suburb) are we in?”

Record answer in error. Correct Error / refus
Enter ‘X’ if no response answer refused

County _______________
12. “What city/town are we in?”

Record answer in error. Correct answer Error / refused

Enter ‘X’ if no response

City/town ______________ 1 0

13. “Are we in a store, medical clinic (hospital) or home?”

Correct answer Error / refused

If the correct answer is not among the three alternatives (eg university), substitute is for the middle alternative.

If the participant states that none is correct, ask them to make the best choice of the three options.

14. Point to the part of your own body and ask the participant to name it. Score 0 is the participant cannot name it within 2 seconds or gives an incorrect name. Do not wait for the participant to mentally search for the name.

Correct answer Error / refused

a. forehead: “What do you call this part of the face?” 1 0

968
b. chin: “… And this part?” 1 0

c. shoulder: “… And this part of the body?” 1 0

d. elbow: “… And this part?” 1 0

e. knuckle: “… And this part?” 1 0

15. “What animals have four legs? Tell me as many as you can.”

Discontinue after 30 seconds. Count all the correct response. If the participant gives no response in 10 seconds, and there are at least 10 seconds of remaining time, gently remind (once only) “What (other) animals have four legs?” The first time an incorrect answer is provided, say “I want four legged animals”. Do not correct subsequent errors.
Introduce by saying: “An apple and a banana are alike in that they are both fruit.”
16. “In what way are an arm and a leg alike?”
Response:

If the participant fails to give an answer that is worth 2 points mark the appropriate score of 1 or 0. If the answer is not worth 2 points, coach the participant by saying “An arm and leg are both limbs or extremities.” Do not coach questions 17 & 18.

2    limbs, extremities, parts of the body
1    lesser correct answer (eg both bend, have joint or bones, long, move)
0    error (eg states differences, useful, gives unrelated answer) / refused

17. “In what way are laughing and crying alike?”
Response:

Do not coach.

2    (expressions of) feelings, emotions
1    lesser correct answer (eg sounds, expressions, involve the mouth)
0    error (eg produces tears, states differences, gives unrelated answer, sometime you laugh, sometime you cry) / refused

18. “In what way are eating and sleeping alike?”

2    necessary bodily functions, essential for life
1 lesser correct answer (eg bodily functions, relaxing, “good for you”, refreshing, enjoyable daily activities, “I like both”)

3 error (eg states differences, gives unrelated answer) “I don’t know” / refused

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<tr>
<td>2</td>
<td>1</td>
<td></td>
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<tr>
<td>1</td>
<td>2 words missed or wrong</td>
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<tr>
<td>0</td>
<td>3 or more words missed or wrong words / refused</td>
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19. “Repeat exactly what I say: ‘He would like to go home.’” Response:

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<tr>
<td>2</td>
<td>correct</td>
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<tr>
<td>1</td>
<td>1 or 2 words missed or wrong</td>
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<tr>
<td>0</td>
<td>3 or more words missed or wrong</td>
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20. “Now request: ‘No ifs ands or buts.’”

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<tr>
<td>a. no ifs</td>
<td>1</td>
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<tr>
<td>b. ands</td>
<td>1</td>
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</table>
21. Hold up Worksheet 1 and say “Please do this.”

If the participant does not close his / her eyes within 5 seconds, prompt by pointing to the sentence and saying “Read and do what this says.” If the participant has already read the sentence aloud spontaneously, simply say, “Do what this says.”

Allow 5 seconds, for the response. Mark 1 if the participant read the sentence aloud, either spontaneously or after your request, but does not close his / her eyes. As soon as the participant closes his / her eyes, say “Thanks, You can open your eyes now.”
22. I would like to have a sample of your handwriting. Write ‘He would like to go home.’”

Hand the participant Worksheet 2 and a #2 pencil with eraser. If necessary, repeat the sentence word by word as the participant writes. Allow a maximum of 1 minute after the first reading of the sentence for the second response. If at the end of 1 minute the subject is still writing, consider allowing him / her to finish for the sake of rapport and morale, but mark the 1 minute point on the product using the scoring, and do not credit points finished after 1 minute.

Either printing or cursive writing is allowed. Assign 1 point for each correct word, but no credit for “He.” For each word, mark 0 if there are spelling errors, or incorrect mixed capitalisations (all letter printed in uppercase is permissible). Do not penalize for self corrected errors.

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<thead>
<tr>
<th></th>
<th>correct</th>
<th>error / refused</th>
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<tr>
<td>a. would</td>
<td>1</td>
<td>0</td>
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<tr>
<td>b. like</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>c. to</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>d. go</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>e. home</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
23. “Here is a drawing. Please copy the drawing onto this piece of paper.”

Hand the participant Worksheet 3. For right-handed participants, present the sample on their left side. For left-handed, present the sample on their right side. Allow 1 minute for copying. In scoring, do not penalize for self correct errors, tremors, minor gaps or overshoots. If at the end of 1 minute he / she is still working on the task, consider allowing him / her to finish for sake of rapport and morale. Do mark the 12 minute point on the product during scoring, but do not credit parts finished after 1 minute. If the subject attempts more than 1 drawing due to dissatisfaction with the first one, score the better product completed within one minute.

4 5 approximately equal sides
3 5 sides, but longest : shortest side is >2:1
a. pentagon 1
2 nonpentagon enclosed figure
1 2 or more lines, not an enclosure
0 less than 2 lines / refused
<p>| | |</p>
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<tr>
<td>4</td>
<td>5 approximately equal sides</td>
</tr>
<tr>
<td>3</td>
<td>5 sides, but longest : shortest side is &gt;2:1</td>
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<tr>
<td>a.</td>
<td>pentagon 2</td>
</tr>
<tr>
<td>2</td>
<td>nonpentagon enclosed figure</td>
</tr>
<tr>
<td>1</td>
<td>2 or more lines, not an enclosure</td>
</tr>
<tr>
<td>0</td>
<td>less than 2 lines / refused</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>b.</td>
<td>intersection</td>
</tr>
<tr>
<td>2</td>
<td>4-cornered enclosure</td>
</tr>
<tr>
<td>1</td>
<td>other than 4-cornered enclosure</td>
</tr>
<tr>
<td>0</td>
<td>no enclosure / refused</td>
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</table>
24. Hold up Worksheet 2 in plain view of the participant but out of his / her reach, and say:

“Take this paper with you left (right for left-handed person) hand, fold it in half, and hand it back to me.”

After saying the whole command, hold the paper within reach of the participant. Do not give visual cues for him / her to take or return the paper. He / She may hand it back with either hand. Do not repeat any part of the command. (“Sorry I cannot repeat. Just do what I think I asked you to do.”) If it is desirable to oblige for sake of maintaining a fragile rapport, score according to responses executed before the repat presentation of the command. He / She may fold the paper with both hands and may hand back the paper with either hand.

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<thead>
<tr>
<th></th>
<th>correct</th>
<th>error / refused</th>
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<tbody>
<tr>
<td>a. takes paper in correct hand</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>b. folds paper in half once</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>c. hands paper back</td>
<td>1</td>
<td>0</td>
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3MS Page 7, Score: __________
25. “What three words did I ask you to remember earlier?”

a. socks
   3 spontaneous recall
   2 after “Something to wear”
   1 after “Was it shirt, shoes or socks?”
   0 still incorrect / refused (provide correct answer)

b. blue
   3 spontaneous recall
   2 after “A colour”
   1 after “Was it blue, black or brown?”
   0 still incorrect / refused (provide correct answer)

c. charity
   3 spontaneous recall
   2 after “A good, personal quality”
   1 after “Was it honesty, charity or modesty?”
   0 still incorrect / refused (provide correct answer)

3MS Page 8, Score: __________
Total Score (maximum 100): __________
INTERVENTION AND SHAM EXERCISE GUIDELINES

RANDOMISATION PROCEDURE

After Assessment B is completed, a follow-up phone call is made to the patient to ascertain how the biopsy site is healing. Ask the patient if there is any bleeding, swelling, inflammation, significant redness or heat in the surrounding tissues, masses (or lumps) under the skin, opening of the skin edges, oozing of fluid from the incision or significant pain or numbness near the site.

If the site is healing well, ask the patient if they are still willing to participate in the program. If the answer is yes, let them know that they will receive a call from Shelley to let them know what time on Monday they will have their first session at the Harbord Diggers.

The Research Assistant (Kylie) will email Angela Lange (alan5625@mail.usyd.edu.au) with the following details:

Patient’s Name,

Gender,

Whether or insulin dependent or non-insulin dependent

Angela will email Shelley with the randomisation information and email the RA to advise that the subject has been randomised and the date of randomisation.
Shelley will call the patient back and let them know what time on the Monday they will meet at the Diggers.

Subjects are randomised after the entire second baseline assessment has been completed to either the:

Experimental PRT group

OR

SHAM exercise group

Randomisation is at the level of the individual patient, and will be stratified by gender and use or non-use of insulin and carried out in blocks of 4. Written informed consent will be required prior to any testing or randomisation. The list will be generated and maintained by a research assistant not otherwise involved in the study. Assignments will be placed in sealed opaque envelopes and designated “Blue Group” for Experimental or “Green Group” for SHAM exercise. The sequential treatment assignments are based on a computer-generated randomisation scheme (by using the Web site www.randomization.com set up by Dr Gerard E. Dallal). **The subject will open these envelopes after completion of all baseline testing.** Subjects who dropout prior to completion of baseline testing will not be randomized.

**Experimental PRT Group:**

Subjects in the experimental group will receive high intensity (~80% of 1 repetition maximum) PRT of 7 exercises for the major muscle groups, 3 days per week at Freshwater Rehabilitation at Harbord Diggers Memorial Club or at the STRONG Clinic, Balmain
Hospital for 12 months (see Progressive Resistance Training Guidelines).

**SHAM Group:**

Subjects in the SHAM group will receive low intensity, non-progressive training of 6 similar exercises for the major muscle groups, 3 days per week at Freshwater Rehabilitation at Harbord Diggers Memorial Club for 12 months.

**PRT GUIDELINES**

Subjects in the experimental group will participate in high-intensity, progressive resistance training 3 days per week for 12 months under the supervision of an exercise physiologist. High intensity progressive resistance training is defined as training with 80% of the maximal weight (1RM) that can be lifted in good form. On the 3 days of the first week, the loads are 50%, 60% and 70% of the baseline 1RM. The target training intensity will then be maintained at approximately 80% of the most recently determined 1RM for each machine by progressively increasing the loads utilized as tolerated by the subject.

Strength is re-tested every 4 weeks to establish a new 1RM. After the strength test, 1 set of exercises at the new weight can be performed to complete the training for that day. On all other days, 3 sets of 8 repetitions of each exercise are performed at the target load calculated for that day.

The 1RM tests at baseline and follow-up testing (6 and 12 months) are blind to the trainer; therefore loads must be established by the trainer on the training equipment, independent
of the assessment strength tests.

The Borg scale of perceived exertion should be used to rate effort during a lift. On this scale from 6-20, a rating of 15-18 (Hard to Very Hard) is equivalent to 80% of maximum lifting capacity in studies conducted in young and older adults, and is therefore an appropriate training goal. The technique is as follows:

As soon as the subject performs the lift with the first weight selected, he/she should be asked to rate how difficult it was to lift

If it was given a score less than 15, than the next higher weight available can be used until the appropriate range is reached

If a weight that is too heavy is selected, as long as proper form, breathing and speed of lifting are adhered to, the only thing that can happen is that they will be unable to cover the full range of motion or complete a full set of repetitions

Older adults, particularly older men and women, rarely, if ever, voluntarily chose weights that are too heavy. On the other hand, there is a great tendency to choose weights that are far too light to be optimally therapeutic.

Warm up

The warm up for strength training is to do 4 reps at lowest load on the machine at slow velocity.

Cool down
Training sessions average 60 min and end with 5 min of stretching.

**PRT**

PRT is comprised of dynamic contractions of large upper and lower body muscle groups using pneumatic-resistance training equipment (Keiser Sports Health Equipment Inc., Fresno, CA) at Freshwater Health and Fitness, Harbord Diggers Memorial Club and at the STRONG Clinic, Balmain Hospital.

With each piece of strength training equipment, the following protocol will be used:

The subject will be placed on the piece of equipment and the settings recorded to ensure proper biomechanics with each training exercise and testing session.

The subject will be shown how each piece of strength training equipment works, what muscle group it isolates and where this muscle group is located.

It will be explained and demonstrated to the subjects why emphasis is placed on proper breathing technique (exhaling on exertion, avoidance of Valsalva manoeuvre).

The settings for each equipment position are recorded on the data sheet.

The subject performs 3 sets of 8 repetitions on each machine. Each repetition is to be as fast as possible for the concentric phase and approximately 4 seconds in the eccentric phase, with a 2-3 seconds rest between repetitions and 60-90 seconds rest between sets.
The subject will be encouraged to discuss with the trainer any problems which arise before, during and after each training session regarding muscle soreness, dizziness, light headedness or any discomfort of any kind.

The order may be dictated by:

The set up of the room

The number of trainers available to supervise

The time it takes to get on and off the machines

The general level of frailty of the group, and

Other practical issues

Alternating upper and lower body exercises is preferred in order to limit fatigue in particular muscle groups that may impair performance of subsequent exercises.

Preferred order:

Leg press

Chest press

Hip abduction

Knee extension

Seated row

Hip flexion

Hip extension

SEATED LEG PRESS (BILATERAL)

Machine set up
Move the seat to the recorded position

Assist the subject onto the machine by backing up towards the seat and sitting down first; then assist or observe as the legs are lifted up onto the foot plates

**Movement performance**

The subject’s feet should be placed at the bottom of each foot plate, with the heel resting on the rubber “lip” at the bottom of the foot plate; or if joint pain is encountered, a position allowing pain free movement.

Extra caution should be used for those subjects who have chronic lower back discomfort, ensuring that they are not twisting the spine and are keeping their back, neck, and head against the padded seat.

The subject may stabilise the upper body by using hand grips on each side of the seat, making sure that his/her thumbs are not touching the force control knobs. The subject’s shoulders and neck should be relaxed.

The subjects should then be instructed to push both legs simultaneously so that the concentric phase is performed as fast as possible, hold the muscle in the contracted state for 1 second and then slowly allow the legs to control the return of the weight back to the starting position over approximately 3-4 seconds. The subject should not allow the footplates to snap back rapidly or move the feet off the footplates before the machine has completely returned to the resting position.
It is important that you communicate to the subject that the knees travel in line with the toes, and that they do not drift medially (which is common in subjects with arthritis or weak ligaments around the knee)

The push should be generated through the whole foot particularly the heel, not through the forefoot/toes, to ensure activation of the gluteus and hamstring muscles, not just the plantar flexors/quads. You may show the subject where the active muscles are, and have him/her place their hand on these muscle groups to feel them contracting as they are doing the movement correctly.

The subject should push until the knees are just short of being “locked” in full extension; that is there should be a very slight bend at the knee. Subjects who have osteoarthritis may have limited extension and may not achieve this full range of motion. A subject whose knees are correctly positioned (not locked) will have to use muscle force to keep the footplate out. When the knees are locked, no muscle force is being used, and the bones of the leg are keeping the footplate up. This should be explained and demonstrated explicitly so the subject knows what it feels like to perform the exercise correctly (versus incorrectly). The subject must not lift his/her buttocks off the seat excessively to accomplish a lift.

**CHEST PRESS**

**Machine set up**

Adjust the height of the seat such so the subject’s forearms run parallel with the floor.
Record this setting in the source document.

Adjust arm levers (if possible) to the comfort level of the subject and note position. This may depend on the joint limitations and ROM of the rotator cuff.

**Movement performance**

Subject should sit upright facing forward with lower back pressed against the back pad. The feet should rest in a position that does not exert pressure on the foot pedals on the older model Keiser equipment.

While gripping the handles, excessive extension of the wrist should be avoided throughout the range.

The subject should then be instructed to push to full range without locking the elbow so that the concentric phase is performed as fast as possible, hold the muscle in the contracted state for 1 second and then slowly allow the arms to control the return of the weight back to the starting position over approximately 3 - 4 seconds.

Good form is working through full range of motion determined in the unweighted position. The shoulders should not be elevated to compensate for the effort.

**HIP ABDUCTION**

**Machine set up**

Adjust the height of the platform.

Set the starting dial at 2 on the side of the movement leg that is being worked as the prime mover.
Movement performance

Subject should stand upright facing towards the dial on the machine with the hip pad resting just above the knee on the outside leg that will be used for the exercise.

The support leg should be fully extended and positioned so that the forefoot is protruding slightly off the footplate, and the support leg is cantered in front of the machine dial. (With the foot completely on the footplate, the padded bar is not long enough to fully reach the exercising thigh and allow it to move freely out to the side without hitting the footplate. This is the reason the foot of the support leg must be moved forward so that the toes hang off the footplate).

The subject’s hands should be both grasping the handlebars on either side of the machine lightly to provide balance. This may be challenging for frail subjects due to the need to stand on one leg, and move the foot forward as described above. The subject’s hands should always be on the grips for this exercise for stability.

The subject’s back should remain straight and motionless throughout the exercise.

The subject should move the working leg out to the side as fast as possible without bending at the waist or rotating the trunk, and then slowly return to the starting position.

Toes must not be turned out during the movement; they should be positioned directly forward with the ankle in neutral position throughout (no dorsiflexion or extension). This is the most common error made in this exercise.

Good form is working to or near full range of motion on the dial (established with an unloaded repetition).

Repeat for the other leg, moving the dial to “2” on the side of the movement leg.
KNEE EXTENSION

Machine set up
Move backrest position, pad and range limiter.

Movement Performance
The subject’s hands should be resting lightly on the grips.
Similarly, the subject’s shoulders and neck should be as relaxed as possible.
The subject should then be instructed to straighten his/her legs without any ballistic movement as fast as possible, keeping the ankle in neutral position (90° of flexion), hold the muscle in the contracted state for 1 second and then slowly allow the legs to control the return of the weight back to the starting position over approximately 3 - 4 seconds.
Good form is working to full extension (determined in the unweighted position) and not arching the back more than very minimally or lifting the thigh off the seat.

SEATED ROW

Machine set up
Adjust the seat height and chest pad.
Good form is working through full or within 50 of full range of motion determined in the unweighted position.

Movement performance
The subject’s hands should be resting lightly on the grips.

The chest should remain in contact with the pad, the back should remain straight and motionless and arching the back and neck should be avoided.

Using the wide grip, the handles should move to the level or if possible behind the chest pad while contracting the shoulder blades together and down. The subject pulls the handles as fast as possible in concentric phase, holds for a second and then slowly returns the weight over 3–4 seconds to resting position.

**HIP FLEXION**

**Machine set up**

Adjust the height of the platform and the pad rest (if possible).

Set the starting dial at 2.

**Movement performance**

Subject should stand upright facing sideways to the dial on the machine with the hip pad resting just above the knee on the front of the leg that will be used for the exercise.

The support leg should be fully extended, and positioned on the footplate.

The subject’s hands should be resting on either side of the machine lightly to provide balance. This may be challenging for frail subjects due to the need to stand on one leg, and move the foot forward as described above.

The subject’s back should remain straight and motionless throughout the exercise.

The subject should move the working leg as fast as possible without bending at the waist.
or rotating the trunk, and then return to the starting position.

Good form is working through full range of motion determined during a slow unloaded repetition.

Repeat for the other leg adjusting to the “2” position on the other side

**SHAM TRAINING GUIDELINES**

The SHAM training intervention consists of exercises that are modified so as to remove the essential elements leading to physiological adaptations. The exercise serves as an ideal “control” activity, because it is offered under supervision, by the same staff, and in the same location as the PRT. Subjects will not be told which of the two forms of exercise is hypothesized to be the preferred one for the outcomes being studied. Exercises are performed on 8 of the 9 following Keiser Pneumatic Resistance Machines and choice of machine may be varied.

**Warm-Up**

There is no warm-up for the SHAM group.

**Cool Down**

Training sessions end with 5 minutes of stretching.

**Seated Leg Press (bilateral)**

**Machine Setup**
• Assist the subject onto the machine by backing up towards the seat and sitting down first; then assist or observe as the legs are lifted up onto the footplates.

• Move the seat to a position where the hips and knees are bent at approximately 90°. The seat may be moved while the subject is seated, as long as they are stabilised by you and warned that the seat is going to move slowly.

• If subjects cannot flex hips to 90° due to hip pain or abdominal girth, move the seat back to a tolerable position.

• Record the final seat position from the numbered plate in the source document.

Movement Performance

• Subjects’ feet should be placed at the bottom of each foot plate, with the heel resting on the rubber “lip” at the bottom of the foot plate; or if joint pain is encountered, a position allowing pain free movement.

• Extra caution should be used for those subjects who have chronic lower back discomfort, ensuring that they are not twisting the spine and are keeping their back, neck, and head against the padded seat.

• The subject may stabilise the upper body by using handgrips on each side of the seat, making sure that his/her thumb is not touching the force control knob accidentally. The subject’s shoulders and neck should be relaxed.

• The subject should then be instructed to push both legs forward simultaneously and to control the return of the weight back to a resting state.
• It is important that you communicate to the subject that the knees travel in line with the toes, and that they do not drift medially (which is common in subjects with arthritis or weak ligaments around the knee).

• The push should be generated through the whole foot, particularly the heel, not through the forefoot/ toes, to ensure activation of the gluteus and hamstring muscles, not just the plantar flexors/quads. You may show the subject where the active muscle area.

• The subject should push until the knees are just short of being “locked” in full extension; that is there should be a very slight bend at the knee.

• Subjects who have osteoarthritis may have limited extension and may not achieve this full range of motion. A subject whose knees are correctly positioned (not locked) will have to use muscle force to keep the footplate out. When the knees are locked, no muscle force is being used, and the bones of the leg are keeping the footplate up. This should be explained and demonstrated explicitly so the subject knows what it feels like to perform the exercise correctly (versus incorrectly).

• Excessive movement of the buttocks completely rising up off the seat is not considered good form but slight movements are tolerated.

Chest Press

Machine Setup

• Adjust the height of the seat such so the subject’s forearms run parallel with the floor. Record this setting in the source document.

• Range of motion should be determined in the unweighted position
• Adjust arm levers to the comfort level of the subject and note position. This may depend on the joint limitations and ROM of the rotator cuff. The range limiter will be set at 3 for most subjects.

**Movement Performance**

• Subject should sit upright facing forward with the back pressed against the back pad.

• The position while gripping the handles should avoid excessive extension of the wrist throughout the range.

• Subject should push to full range without locking the elbows and then slowly allow the arms to control the return of the weight back to resting position.

• The shoulders should not be elevated to compensate for the effort.

**Knee Extension**

**Machine Setup**

• Move backrest position so that back and upper legs of the subject are fully supported after the subject is assisted onto the machine.

• The pad should rest just behind the subject’s knee in the popliteal fossa; the subject’s back should be securely supported by the backrest.

• Record the final seat position number in the source document from the numbered plate or notches on the back rest.
With the subject well positioned in the seat, move the weighted bar position so that it sits just above the malleoli (ankle) level and the foot can still dorsiflex below the weighted bar. Record the position number of the bar in the source document. This may be recorded to the nearest 0.5 (e.g. 3.5) if it is between 2 engraved numbers on the machine.

Start position is always 90° of knee flexion, to avoid overstretching of the patellar tendon that may cause knee pain. Adjust by pulling out the knob on the range limiter until the correct number appears in the window. No limitation on extension range is imposed during strength testing or training however. Unscrew the range-limiting knob and leave it off the machine. Most subjects will have full extension short of this. Record the start and end positions of the range limiter in the source document.

Movement Performance

The subject’s hands should be resting lightly on the grips, making sure that his/her thumb is not touching the force control accidentally.

Similarly, the subject’s shoulders and neck should be as relaxed as possible.

The subject should then be instructed to straighten his/her legs without any ballistic movement as far as possible, keeping the ankle in neutral position (90° of flexion), and then control the return of the weight back to a resting state.

Failure is defined as not reaching full extension.

Do not allow subjects to arch their backs more than very minimally or lift their thigh off the seat to qualify as “good form”.
Seated Row

Machine Setup

- Adjust the seat height so that xiphoid process is positioned in the middle of the chest pad then record this position.
- Adjust the chest pad so that arms are comfortable at full extension and record this position.
- Range of motion should be determined in the unweighted position and recorded.
- Wide grip will be used for 1RM testing, although in training wide grip is used for the PRT group and narrow grip for the SHAM group.

Movement Performance

- The subject’s hands should be resting lightly on the grips, making sure that his/her thumbs are not touching the force control accidentally.
- The chest should remain in contact with the pad, the back should remain straight and motionless and arching the back and neck should be avoided.
- The handles should move to the level or if possible behind the chest pad while contracting the shoulder blades together and then slowly allow their arms to control the return of the weight back to resting position.
- Failure is defined as not reaching within 50 of the recorded full extension (derived from the unweighted range).
Knee Flexion

Machine Setup

- Move backrest position so that back and upper legs of the subject are fully supported after the subject is assisted onto the machine.
- Note the lever position so that ankles just hang over the edge of the foot padding.
- Record the position number of the bar in the source document. This may be recorded to the nearest 0.5 (e.g. 3.5) if it is between 2 engraved numbers on the machine.
- Ensure that upper legs are held firmly in place by the padding and clicked into place.
- Start position is maintained at -10° of knee flexion. Adjust by pulling out the knob on the range limiter until the correct number appears in the window.
- Unscrew the range limiting knob and leave it off the machine. Record the start and end positions of the range limiter in the source document.

Movement Performance

- The subject’s hands should be resting lightly on the grips.
- The subject’s shoulders and neck should be relaxed.
- The subject should then be instructed to bend his/her legs without any ballistic movement as far as possible, keeping the ankle in neutral position, and then allow the legs to control the return of the weight back to an extended position.
- Failure is defined as not reaching full flexion.
- Do not allow the subject to arch the back more than very minimally to qualify as "good form".

- The subject may need to be reminded to reposition on the seat to ensure the lower back is in contact with the back pad.
6 MINUTE WALK TEST

SIX MINUTE WALK TEST

Equipment
- Measure Meter
- Stopwatch

Purpose
The six minute walk is a proxy for overall cardiovascular endurance capacity (aerobic capacity). In addition to cardiovascular efficiency, however, in the elderly subject it may be determined by muscle strength and endurance, balance, orthopaedic or neurologic abnormalities, and other problems. It works best as an estimate of aerobic capacity in individuals who cannot run, so that variations in walking velocity describe most of the possible range of function. Therefore it is very appropriate in very frail or elderly volunteers as well as healthy elderly.

Preparing the volunteer
Volunteer should be wearing normal, low-heeled walking shoes, comfortable clothing, eye glasses and hearing aides, if any. They should have been offered to use the restroom prior to starting the test. If an assistive device is normally used for walking, the person should use this during the test, and the device used should be recorded on the data sheet. The same assistive device should be used at all timepoints if possible, unless the person has advanced
to a higher level device (e.g. walker instead of a cane) due to changing medical condition. If the volunteer rarely uses a cane, do not use it during the testing.

**Environmental considerations**

This test requires a long open circuit around which the volunteer can walk continuously for six minutes. Long circular or square corridors around the perimeter of a building without many turns are ideal. All testing should be done indoors rather than outdoors, as there are too many uncontrolled variables in outdoor areas. The path should be free of clutter and all other traffic should be closed off if possible during the testing. No steps, inclines, doors, or other obstacles should be in the path of the volunteer, and lighting and ventilation should be adequate.

**Protocol**

The person should be instructed that they are to “cover as much ground as possible in six minutes” by “walking as fast as they can the entire time”. They must be encouraged and reminded of the task at least every 30 seconds during the test or they will tend to slow down. Line up the Measure Meter (with the dial reset to read 000) with the volunteer’s feet on the starting line. Prior to beginning the test, ascertain that the volunteer’s pulse rate, breathing rate, and blood pressure are in their normal range. Say “1,2,3, GO!” and begin the stopwatch. Follow closely behind the volunteer with the Measure Meter, attempting to follow their path as closely as possible without getting in their way or influencing their gait speed. The number of metres travelled at the end of 6 minutes is recorded to the nearest foot from the wheel. Use standardized statements such as:
• “Keep Going!”
• “You’re Doing Well!”
• “Keep up the Good Work”

If the volunteer needs to stop to rest during the test, the watch continues to run, and they should be instructed to start back up again as soon as they are able.

If they develop angina during the test, or any other symptoms which seem severe, the test should be terminated immediately and emergency medical help should be contacted. However, shortness of breath, fatigue, and slight muscle or joint pain are not unusual and are not an indication for stopping the test. If claudication occurs, the person may need to stop momentarily, but can go on as soon as they feel able.

Record if an assistive device used, the number of stops made during the test, any symptoms which developed during the test, reason for stopping prematurely, if any, and the total distance covered in 6 minutes to the nearest 0.1 metre. This test is only performed once.

Common problems/questions
The volunteer should be well rested prior to beginning this test, as it requires physical stamina and mental alertness. The exact wording above should be used to instruct the volunteer so that consistency is maintained. The volunteer is not allowed to break into a run; if this happens, stop the test and begin again. If a chair is anticipated to be needed for rest stops, a second examiner can follow closely behind the timer with a wheelchair which
can be positioned behind the volunteer as needed. If a volunteer can only ambulate by pushing themselves in a wheelchair, the test can be conducted in this way, but no assistance in moving the wheelchair from anyone else is allowed.
POWER TESTING

Equipment
Keiser pneumatic resistance training equipment (Keiser Sports Health Equipment, Inc., Fresno, CA) with K400 electronics is used for muscle endurance testing (in C-Block). The compressor should be turned on at both the power point and the distribution box 2-3 hours prior to use.

Purpose
- This test measures the ability of muscles to generate force (movement) quickly.
- Force, velocity, and power will be assessed using a single explosive contraction at 20, 40, 50, 60, 70, 80, 90, and 100% of the subject’s most recently measured 1RM or, at baseline, the better of the two 1RM measurements using the Keiser Leg Press Machine.

Five exercises will be tested: bilateral horizontal leg press, seated chest press, bilateral knee extension, seated row, and seated bilateral knee flexion. Keiser A400 software calculates work and power during the concentric phase of the repetition by sampling the system pressure (force) and position (via ultrasonic position transducers) at a rate of 400 times per second. Accuracy of system pressure and position are reported by the manufacturer to be within 1%. Power (Watts) and velocity (cm/sec) are calculated as the average respective value between 5% and 95% of the concentric phase of the repetition to eliminate noisy data at the beginning and end points of motion.
The highest average power produced throughout the loads tested will be recorded as the peak power.

Additional power testing at follow-up test periods

- To assess potential change in peak velocity capacity the subject will perform an ‘extra’ lift at the load during which peak velocity was demonstrated at baseline.
- Power testing must follow 1RM testing when performed at each timepoint, as the loads are set based on the results of the 1RM testing.
- Power testing should be done in an unfatigued state at each timepoint.

Protocol

- Demonstrate movement (fast concentric/slow eccentric).
- Prior to starting the test, explain the purpose of the test to the subject and how it will be achieved. E.g. “The purpose of this test is to measure how powerful muscles are in your legs. This means how quickly your muscles can generate force, so this time I will ask you to push the weight as fast as you can. However, I still want you to slowly return the weight to the starting position. Similar to the maximum strength test, you will start with a light weight and then move onto heavier weights.” (Avoid saying something like “You should be able to push the lighter weights faster than you can push the heavier weights”).
- Subject will be instructed to push the footplate as fast as possible and slowly return it for one time only at each of the workloads and will be verbally cued. “1, 2, 3, GO!!”
• To improve coordination of breathing and exertion, subjects may be instructed to inhale on the count of “1”, exhale on the count of “2”, inhale again on the count of “3”, and exhale with rapid exertion on “GO!”

• A rest period of 30-60 seconds will be taken between repetitions.

• Ensure subject is in the correct starting position for the exercise (see 1RM testing).

• Allow one ‘practice’ trial at 20% 1RM and record the results from the motion the real time display on the computer panel. The force, work, and power will be available on the time computer display panel. (Distance moved is also shown, but is not needed for the POWER test). The velocity will need to be taken from of motion the data file downloaded onto the computer at the conclusion of the test (see below for A420 software instructions), as it is not shown on the real time display window.

• If the subject’s baseline 20% 1RM is less than the minimal resistance of machine, use the minimal resistance possible on the machine. If the subject’s 1RM was so low that the machine’s lowest resistance is greater than some of the lighter loads e.g. 20, 40% 1RM then you can only do those loads that the machine will allow. If the subject’s 1RM is the lowest resistance that the machine allows then the subject can only be tested at 100% 1RM. Allow the subject 3 trials at this load, with 1-min rest between each one. Record force, work, and power for each trial, (the highest power achieved out of the 3 attempts will be recorded as their peak power).

• Next, set the machine resistance at 20% of the most recent 1RM and continue with heavier loads.
• Assess the subject at each %1RM (40, 50, 60, 70, 80, 90, and 100%), right up to 100%1RM even if you think they achieved their peak power at a lighter load. For subjects whose power is still increasing at 100% of the 1RM, additional loads must be used at 10% increments (110%, 120%, etc.) until a drop in Power is seen. This will be a very unusual, but possible occurrence.

• Record the force, velocity, work, and power at each % 1RM on the source document (record the attempt where the highest power was achieved out of the 2 attempts at 20% 1RM as the “20%” value when the source document).

• Allow 30 seconds rest after the trial at 20%, and 60 seconds rest after each trial at heavier loads (RPE scorings of 15+)
ENDURANCE TESTING

Equipment

Keiser pneumatic resistance training equipment (Keiser Sports Health Equipment, Inc., Fresno, CA) with K400 electronics is used for muscle endurance testing (in C-Block). The compressor should be turned on at both the power point and the distribution box 2-3 hours prior to use.

Purpose

- Muscle endurance is a test of sub-maximal muscle performance. Analogous to a sub-maximal aerobic capacity test, the same workload is used at baseline and final testing, and the performance relative to this fixed workload is used to determine adaptation to the intervention.

Types of Endurance testing

ABSOLUTE ENDURANCE

- 90% of the subject’s best baseline 1RM will be used as the workload at all timepoints. If they cannot complete 1 repetition, load will be decreased to 80%1RM. The adjusted load will be used at all subsequent timepoints as well.
RELATIVE ENDURANCE

- 90% of the subjects current 1RM will be used as the workload. If they cannot complete 1 repetition, load will be decreased to 80%1RM. The adjusted load will be used at all subsequent timepoints as well.

PLEASE NOTE:
Assessors for the GREAT2DO study will measure RELATIVE ENDURANCE.
However, ABSOLUTE ENDURANCE has been measured in a subset of participants. These participants will have this noted on their assessment/data testing sheets. Participants MUST be undergo the same type of endurance testing at ALL timepoints. Ie. If absolute endurance was measured at baseline or six months, absolute endurance must be measured at 12 months. There is provision for both relative and absolute muscle endurance data entry within the outcomes database.

Protocol

- Muscle endurance will be assessed on leg press, chest press, knee extension, seated row, and knee flexion.

- 90% of the subjects previously determined 1RM (best of 2 baseline 1 RM)s) will be used as the workload. If they cannot complete 1 repetition, load will be decreased to 80%1RM. The adjusted load will be used at all subsequent timepoints as well.

- Keiser Machine display should be set on “Position Mode” so that the range of motion bar can be seen to evaluate the completeness of lift.
• The examiner will perform sample continuous repetitions at the desired cadence to full range of motion, describing the “mistakes” of pauses, incomplete range of motion and bad form.

• First the subject is asked to perform a full range of motion with the machine set to minimum resistance possible. For the leg press, this is the resistance which is necessary to keep the footplates up against gravity. This range of motion lift may be repeated 2 times to correctly ascertain the range of motion.

• The subject will be instructed to perform as many consecutive repetitions as possible through their full range of motion using good form.

• Repetitions will be performed at the cadence of approx. 2 seconds concentric, 3 seconds eccentric, with no rest at the fully extended/flexed position or between repetitions. Rest is defined as a visual pause in the motion as assessed subjectively by the examiner.

• Test is terminated when subject performs a lift and the moving bar is short of the arrowhead marking the point of full range of motion or pauses at any point in the lifts, or uses bad form (other than minor deviations such as slight use of accessory muscles or arching of the back.

• The total number of complete repetitions, the total work performed, as well as the velocity and power generated during the first and last complete repetitions for each exercise will be recorded on the data sheet. Note that if a repetition is stopped halfway, this is not the last complete repetition. The previous full repetition is used to record the work, velocity and power.
• Post training assessment of muscle endurance at 6 and 12 months will be performed using 90% of the subject's baseline 1RM. If 80%1RM as used at baseline, 80%1RM will also be used during post training assessments.