LIFESTYLE INTERVENTION EFFECTS ON OVERWEIGHT ADULTS WITH KNEE OSTEOARTHRITIS

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A thesis submitted in fulfilment of the requirement for the degree of
Doctorate of Philosophy

THE UNIVERSITY OF SYDNEY

Sydney School of Health Sciences
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30th June 2024

STUDENT DECLARATION

I, Yareni Guerrero Ayala, hereby declare that the work contained within this thesis is my own and has not been submitted to any other university of institution for any higher degree.

I, Yareni Guerrero, hereby declare that that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material from any other source, except where due acknowledgement is made.

I, Yareni Guerrero Ayala. acknowledge that if my candidature is successful, this thesis will be lodged with the University Librarian and made available for immediate public use.

Yareni Guerrero Ayala

30th of June 2024

SUPERVISOR STATEMENT

I certify that the thesis entitled "Lifestyle intervention effects on overweight adults with knee osteoarthritis", submitted by Yareni Guerrero Ayala in fulfilment of the degree of Doctor of Philosophy, is ready for submission.

Professor Maria Fiatarone Singh

30th June 2024

AUTHORSHIP STATEMENT

This chapter was published in The Journal of the Australian Physiotherapy Association Volume 61 Issue 4 in October 2015. https://doi.org/10.1016/j.jphys.2015.05.020

The co-authors of the paper "Train High Eat Low for Osteoarthritis Study (THE LO Study): Protocol for a Randomised controlled trial" confirm that Yareni Guerrero Ayala has made the following contributions:

- Conception and design of the research
- Conduct and management of study
- Writing of the paper and critical appraisal of the content

As the primary supervisor for the candidate upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Maria Fiatarone Singh

30 June 2024

ACKNOWLEDGMENTS

Throughout this candidature, I have received boundless love and support from numerous family members, colleagues, and friends. While I am deeply grateful to all of them, there are a few whom I wish to acknowledge in detail:

To my primary supervisor, Professor Maria A. Fiatarone Singh. Thank you for believing in me and staying alongside until the last minute. I am beyond fortunate to have had the opportunity to learn from such an extraordinary but humble woman. Your amazing dedication and care as a clinician, accompanied by your rigorous scientific work, are invaluable.

To my associate supervisor, Associate Professor Suzi Edwards. Just a day before withdrawal from my candidature, I decided to raise my hand and ask for help… you were there… and the end of this story is a happy ending. Learning with you was like a HIIT training session, everything was intense and fast with short periods of break but well rewarded. Thank you for your patience and the knowledge shared with me.

To my associate supervisor, Associate Professor Milena Simic. Thank you for all the support and guidance in this project, always providing a clear perspective, encouraging and inspiring me to be the best I can be.

To all the 110 participants of THE LO Study who made this project happened. I thoroughly enjoyed meeting every one of you and thank you for volunteering your precious time and energy. A very special thank you to the wonderful team of Fit for Your Life research team: Dr. Guy Wilson, Dr. Michael Inskip, Kenneth Daniel, Isabel Shish. I feel very privileged to have worked, laughed, and shared cakes with you all.

To Associate Professor Yorgi Mavros. I am glad you never agreed to be my supervisor, then I have the best mentor and friend far beyond this candidature. Countless times you gave me the best advice, and so much I learned from you. I will miss “the double shot cap” alongside a nice walk chatting with you.

To my parents, Martha Patricia Ayala and Jose Fred Guerrero, the first and always people who believe in me. Dad, thank you for showing me the path of love, science, and wisdom. Mom, the power and courage are in your soul, thank you for always supporting, encouraging, and cheering me up, and making me feel that there are no limits to my dreams.

To my siblings, Marisol Guerrero and Cesar Guerrero, countless calls with laughs and tears with both of you. Thank you because we always stick together; if not… may the force be with you.

To my love, Victor Quiroz, the support you have always gave me in all my crazy ideas, and this is just another of them. From the very first day, without even knowing what I wanted, you were by my side on that “Open Day at the University of Sydney” when I decided to embark on this journey. Today, we close the page of a chapter with you always next to me. Thank you for the unconditional love and support you have always given, for taking care of Sophia and Maxima during my long absences. I will be enormously grateful to you. Love you.

DEDICATION

With all my love to Sophia Victora and Maxima Luciana

…never ever give up.

Con todo mi amor para Sophia Victoria y Máxima Luciana

*...nunca se den por vencidas***.**

Because the light of the wisdom will guide you to the maximus victorious…

Porque la luz de la sabiduría siempre las guiará a la máxima victoria…

PREFACE

This PhD thesis journey took longer than expected both for circumstantial but for personal reasons as well. I was able to weave together a comprehensive knowledge base of the relationship between biomechanics, 3D motion analysis, musculoskeletal and chronic conditions, metabolic health and get a great and deep understanding of ageing and how to approach older adults with complex co-morbidities, I learned potential applications of biomechanical analysis to optimise clinical guidance and improve the lifestyle of people. I learned the huge potential and important role of exercise, most specifically the resistance training and behavioral changes needed to counteract the disability and deterioration in health of older adults. I was humbled by the opportunity to strategically manage a huge RCT study including staff and students' coordination. Overall, one of the greatest opportunities this project had for me was the opportunity to learn from the most humble and privileged supervisors, they supported me from the first day until the last minute of my candidature. They had faith in me when I did lost hope. They taught me to recognise mistakes, how to say NO when I can't do anymore, how to ask for help, they fully supported me during many transitions in my family life and health. They trusted in me when I wasn't sure… these and many more things you also learn in a PhD.

PUBLICATIONS AND PRESENTATIONS

Peer-reviewed journal publications

Chapter 3 of this thesis was published in the Journal of Physiotherapy and can be viewed in Appendix .As the first author of this manuscript, I was responsible for the design, collection and extraction of data, and drafting and editing the final manuscript, with contributions from my supervisors to all aspects.

Guerrero, Yareni, Najeebullah Soomro, Guy Wilson, Yian Dam, Jacinda Meiklejohn, Kylie Simpson, Richard Smith, et al. "Train High Eat Low for Osteoarthritis Study (THE LO Study): Protocol for a Randomized Controlled Trial." *Journal of Physiotherapy* 61, no. 4 (October 2015): 217. https://doi.org/10.1016/j.jphys.2015.05.020.

Conference proceedings

Parts of this thesis were presented at national and international conferences

Guerrero Y, (2017) Progressive Resistance Training in Osteoarthritis, Exercise is Medicine [podium]. *American College of Sports Medicine Annual Meeting and World Congress on Exercise is Medicine – Denver, Colorado, USA.*

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CHAPTER 1. Introduction

1.1. Musculoskeletal Health Status

Musculoskeletal health is critical for mobility, as well as the ability to maintain social, financial, and functional independence across the lifespan. The enormous impact of impaired musculoskeletal health is globally recognised. The Global Burden of Disease (GBD) study defines 150 different musculoskeletal conditions, and osteoarthritis (OA) leads the list along with low back pain as a contribution to disability.[1] The World Health Organization (WHO), as part of their *"World Report of Aging and Health"* highlighted the serious implications for disability, reduced quality of life and mortality posed by musculoskeletal impairments.[2] Notably, these musculoskeletal conditions disproportionately affect indigenous and lower-income communities which were historically were perceived as being minimally impacted by such conditions.[3]

The negative impact of musculoskeletal disease is particularly evident when it occurs in the context of multimorbidity (the presence of multiple chronic conditions at the same time). It has been shown that multimorbidity adversely affects the physical and mental aspects of health-related quality of life, and this is exacerbated when one of those conditions is a musculoskeletal impairment.[4] When the musculoskeletal condition is osteoarthritis, this has significant financial implications, impacting long-term labour force participation as well as the cost of the illness itself.[5] Therefore, it is critical to improve our ability to understand the pathophysiology, as well as prevent and manage the disability associated with osteoarthritis, given its substantial impacts on individual quality of life and societal burden.

1.2. Osteoarthritis

Osteoarthritis (OA) is the one of the most common musculoskeletal conditions amongst adults globally. It is a chronic disease marked by an imbalance between degradation and synthesis of articular cartilage. It is characterised by pathophysiological and mechanical changes to the entire joint and peri-articular structures, including bone, cartilage, ligaments, and muscles. This includes degradation and cartilage volume loss, osteophyte formation, synovial inflammation, and reduction of space between bones (identified as joint space narrowing on radiography.[6–8]

Consequently, the pathology of this complex OA process leads to pain, stiffness, swelling and loss of normal joint function.[7,8] Reduced quality of life and psychological impairments are additional important factors to be considered.[6,7,9] The latest report of the Australian Institute of Health and Welfare (AIHW) in December 2023 revealed that people aged over 45 with OA (compared to age- and sex-matched peers without OA) were significantly more commonly diagnosed with eight of nine comorbidities: back problems [38% vs. 23%], mental conditions [31% vs. 20%] osteoporosis or osteopenia [22.3% vs. 6%], heart, stroke and vascular disease[18% vs. 9%]; asthma [18.3% vs. 10.6%], diabetes [15.4% vs. 9.6%], chronic obstructive pulmonary disease (COPD) [9% vs. 3.7%], cancer [6% vs. 3%], and kidney disease [3.85 vs 1.5%].[10] This multimorbidity likely reflects shared lifestyle and

genetic predisposition to these conditions, as well as changes in mobility and physical activity patterns arising after the onset of OA.

Due to the combination of ageing and increases in the prevalence of obesity, OA is becoming more prevalent, with estimates of 250 million people affected globally currently,[5,7,11] According to the most recent report of the Australian Bureau of Statistics (ABS), just under 2.2 million Australians live with this condition.[12] The cost of OA in Australia during 2020-2021 exceeded $4 billion AUD.[10] The number of people affected by 2032 is expected to increase by 58% due to population ageing and obesity increases.[4–6] Notably, OA is recognised as a significant component of the global burden of disease among individuals aged 50 years and over.[1,7] Therefore, efforts to lessen this growing global impact require a detailed understanding of the potentially modifiable elements of the complex pathophysiology of OA.

1.3. Knee Osteoarthritis

The tibiofemoral joint at the knee is one of the joints most frequently affected by OA.[8,12] From 1990 to 2019, there was a substantial increase in the prevalence of knee OA globally: 120% in women and 135% in men.[3] Compared with other health-related conditions, knee OA amongst Australians is the condition with the highest years of life with disability (YLD) for both sexes: 36, 244 YLD for females and 23,440 YLD for males.[3] To improve quality of life in the later stage of knee OA disease, knee joint replacement is indicated, yet it is estimated that in Australia this expensive procedure will not be financially sustainable beyond 2030.[3] In 2003, the rate of total knee replacements in Australia was 123 per 100,000 persons; by 2013 it had increased to 213 and it is estimated to reach 250 procedures/100,000 persons in 2030 at an estimated cost of $1.38 billion AUD to the healthcare system.[6] Therefore, there is great interest in non-surgical management of knee OA by lifestyle interventions that may have the potential slow the progression of this disease, such as interventions that target a reduction in the knee joint load imbalance during gait, reduce obesity-overweight and inflammation, increase bone density, muscle strength, and physical activity levels and/or reduce additional comorbidities that adversely impact the physical and psychological health of individuals with knee OA.[10,13–1]

1.4. Knee Joint Loading

Amongst the potentially modifiable risk factors for knee OA structural progression, excessive imbalance of load across the medial and lateral compartment of the joint during walking[13–15] is one of the most critical. Dynamic knee joint loading is correlated to a static alignment.[16] In heathy adults, the maximum joint force at the knee during walking has been estimated to be in the range of 2-4 times body weight. For example, Morrison et al., 1970,[17] estimated the load of an average of 12 subjects to be 3.03 times body weight. While walking, those compressive forces are not equally distributed across the medial and lateral joint compartments,[18–20] as approximately 70% of this total load mainly passes through the medial plateau of the tibial condyle,[18] Therefore, estimating the joint load over the medial side during walking is extremely relevant to individuals with medial knee OA. Lifestyle interventions with a potential to modify this imbalanced and excessive medial loading have been explored with some positive results and is the topic of a systematic review in **Chapter 2**.

1.5. Knee Adduction Moment to measure knee joint load distribution.

The Knee Adduction Moment (KAM) has been shown to be a reliable[28] and valid[29] proxy of medial joint load distribution during gait in people with medial knee OA.[21] It is a surrogate measure, well-suited to predicting the force acting at the tibiofemoral joint throughout the whole stance phase of the gait cycle or the medial force during the early stance phase.[21,22] While walking, the force vector of the ground reaction force in conjunction with the lever arm from the knee joint centre create an adduction moment (KAM). In a computer simulation study, it was observed that a higher magnitude of this moment could predict the progression of medial knee OA, as shown by Schipplein and Andriacchi in 1991.[23] Subsequently, other investigators reported significant relationships between KAM and radiographic knee OA disease severity,[24] and strong relationships to lower limb alignment[20,25] and bone mineral density on the proximal tibia.[25,26] Miyazaki and colleagues 2002[14] showed that baseline KAM could predict radiographic OA progression after six years follow-up. One of the most recent systematic reviews in this field has confirmed that the KAM is positively associated with OA disease progression.[21]

This growing recognition of the importance of joint forces to knee OA progression was accompanied by the proliferation of three-dimensional (3D) motion systems as a critical tool to perform gait analysis for both clinical and research purposes. The external forces and moments acting through the lower limbs can be measured in a 3D motion system laboratory

utilising optoelectrical cameras to capture motion synchronised with floor-mounted force platforms to measure ground reaction forces. Thus, by inverse dynamic calculations it is possible to estimate internal forces and moments acting through muscles and joints.

1.6. Lifestyle Interventions as Potential Programs to Modify Knee Loading and Clinical Symptoms

In other chronic diseases, such as type 2 diabetes, intensive lifestyle modifications including diet, exercise routines, increases in incidental physical activity and behavioral change have proven effective for both prevention and treatment.[27] Such lifestyle modification has also been shown to benefit clinical symptoms in knee OA in several large RCTs.[28] The first of these, the Arthritis, Diet and Activity Promotion Trial (ADAPT), demonstrated improvements of self-reported measures of function and pain and in performance measures of mobility in the combined weight loss and low-moderate intensity exercise group compared to weight loss alone, exercise alone, or general advice control.

Among non-pharmacological interventions, weight loss and exercise are key strategies that can effectively alleviate symptoms and improve the quality of life for individuals with knee OA.

Resistance training strengthens the muscles around the knee, particularly the quadriceps, which is crucial for joint stabilization and function.[9] Bandak et al., 2022,[56] demonstrated that combining exercise with education about osteoarthritis yielded comparable benefits to saline injections, which are often used as temporary pain relief for OA. Their randomised controlled trial showed that a structured exercise and education

program significantly improved patients' pain and function over a 12-month period, emphasizing the long-term value of non-invasive treatments over short-term pharmacological solutions. Furthermore, Bandak et al., 2022[56] also pointed to the psychological benefits of such interventions, as patients reported better understanding and management of their condition when they received education alongside physical therapy.

In addition, exercise, when combined with dietary modifications designed to reduce caloric intake, such interventions can enhance weight loss outcomes and mitigate knee OA progression. Such an approach underscores the need for tailored, multifaceted treatment plans that incorporate both diet and physical activity to manage the complex role of obesity and joint degeneration in knee osteoarthritis.[45]

Obesity is a well-established risk factor that increases the mechanical load on the knee joint, while also contributing to systemic inflammation, both of which accelerate disease progression.[44,57] Current research strongly advocates for the use of weight loss and exercise as primary interventions to manage knee OA, as these approaches can effectively reduce joint stress, lower inflammation, and improve overall functionality.

Weight loss of 5-10% has been linked to substantial reductions in knee pain and functional limitations in overweight and obese individuals with knee OA.[57]

A combined strategy of weight loss through dietary modifications and structured exercise interventions has been shown to significantly enhance outcomes in terms of pain relief and mobility improvements.[45] These findings support the view that exercise, when combined with weight management and patient education, offers a holistic, cost-effective, and sustainable approach to managing knee OA.[38]

However, despite these published data, the effectiveness of exercise as a therapeutic approach for pain relief and physical function improvement in individuals with knee osteoarthritis (OA) remains not fully resolved. For example, Holden et al. 2023,[58] conducted a systematic review and meta-analysis, focusing on individual participant data to determine the moderating factors influencing exercise outcomes for OA patients. Their findings indicate that although exercise has been commonly recommended, it may not be universally effective across all patient subgroups, it is also important to consider that pain is multifactorial variable, dependant on not just one mechanism. The variability in response suggests that factors beyond the general recommendation of exercise need to be considered when prescribing exercise as a therapeutic intervention for knee OA. This meta-analysis underscores the importance of personalized treatment strategies, highlighting that patient-specific variables must be considered to optimize therapeutic exercise outcomes.

The majority of knee OA affects the medial tibiofemoral compartment[29,30] and is often associated with varus malalignment[18,31] that increases the loading on the medial side of the

joint.[16,32] This significantly increases risk and progression of OA.[14,21] Computational simulation has demonstrated that altering walking patterns via medial thrust gait could reduce KAM by 32%.[33,34] Barrios and David 2010[16] reduced the KAM in healthy young subjects with varus knee alignment through real-time feedback (but not in OA). The primary theoretical rationale behind gait retraining is that by adopting new gait patterns as a habitual way of walking, reductions in knee adduction moment (KAM) can be observed immediately. This suggests that participants must actively and consciously modify their gait patterns during the intervention. This also supports the feasibility of conducting single-session studies, as the adoption of gait adaptations can yield immediate results.

In fact, a systematic review by one of our team members (MS) demonstrated that some gait modifications, increasing the foot progression angle (toe-out) and lateral trunk lean in RCTs[35–37] with no longer than 6 weeks of duration could decrease KAM significantly. Thus, gait retraining interventions have to potential to alter the KAM. To date only short-term interventions utilising a variety of different strategies have been implemented, and thus the optimal gait retraining modality, dose, and duration remain to be defined and verified in clinical cohorts. The practical challenge lies in the long-term implementation of these modifications on a daily and routine basis, which requires a motor learning process and behavioural support strategy to adopt and adhere to the new gait pattern over the long-term. Without long-term interventions, therefore, it is not possible to determine the actual effectiveness of the intervention as a strategy for mitigation of disease progression

Exercise is beneficial for general health as well as OA symptoms. An extensive systematic review of 54 RCTs[38] demonstrated high quality evidence for pain reduction (12 points on a scale of 0-100 [95% Confidence Intervals (CI) 10,15 points]) and moderate quality evidence in physical function improvements by (10 points on a scale from 0-100 [95% CIs 8, 13 points]). Segal et al.2010[39,40] reported that women with knee OA and low quadriceps strength also had a 65% higher risk of radiographic progression of disease. A systematic review co-authored by one of our research team (MAFS) on progressive resistance training (PRT) in patients with OA demonstrated improvements in muscle strength, self-reported measures of pain and physical function and performance as well as improved co-morbidities.[41] In the RCT Resistance Exercise And Cartilage Health (**REACH**)[42] conducted by one of our team (MAFS), significant increases in muscle strength (48.7%; range -33.0 to 124.0%) and knee symptoms such as pain and self-reported physical function (-27.6 ± 37.6%) were found in women with OA randomised to a high intensity PRT program for 6 months.

Resistance training aims to reduce KAM by strengthening the muscles of the lower limbs, specifically the quadriceps and adductors, to improve pelvic stability and overall lower limb strength. Unlike gait retraining, resistance training does not produce immediate effects, as muscle strengthening is achieved progressively over time. There is substantial evidence indicating that resistance training requires prolonged intervention periods to be effective. For example, gait retraining interventions typically ranged from 4 to 6 weeks in 3 out of 4 studies, with only one study extending to 16 weeks. Resistance training interventions, however, were

no shorter than 10 weeks, with durations ranging from 10 to 72 weeks, which is sufficient time to see robust strength gains and their potential impact, if any, on KAM.

Nutritional interventions may also improve knee OA symptoms. Robust evidence has shown benefits of weight reduction directly acting to decrease joint load.[13,43–45]However, the dietary advice in the Arthritis Australia brochure is limited.[46] Generic lifestyle prescriptions of a "healthy diet/increased activity level" are insufficient and unrealistic[47] in a cohort that is often significantly overweight and markedly impaired in mobility and activity level due to lower extremity pain. The results achieved in ADAPT[43] and IDEA[44] studies may not be generalisable given the intense, long-term behavioral intervention applied in these RCTs and the use of 2 meal replacement shakes/day in which is likely non-sustainable long-term outside of a supervised RCT setting.

Despite the evidence outlined above for some promising lifestyle approaches to date, there is yet no cure for knee OA, nor demonstration that any intervention can slow the progression of cartilage degeneration. Current international clinical guidelines emphasise non-invasive strategies as core treatments for clinical symptoms such as pain, stiffness and disability in early stages of knee OA, with specific attention given to educational programs, exercise, and weight reduction when necessary.[48–5] However no specific and detailed exercise recommendations are universally recommended, in fact, poor replicability of knee OA exercise programs has been highlighted as an issue by Bartholdy et all., 2019.[52]

As part of the current Australian clinical guidelines such as The Royal Australian College of General Practitioners (RACGP),[55] regular exercise is recommended for relieving pain and improving function in people with knee and/or hip AO. Exercise is also recommended as it targets other comorbidities and overall health. For knee OA, land-based exercise such as muscle strengthening, walking and Tai Chi are strongly recommended; other land-based exercise that could be considered for some people with knee OA include stationary cycling and Hatha yoga. The best land-based exercise for people with hip OA has not yet been determined because of limited research. In addition, attention should be paid to strategies to enhance exercise adoption and adherence (specific prescription and supervision, written materials, logbooks, text message reminders, etc).

As noted above, musculoskeletal health is vital to ensure the capacity to engage in physical activity and sustain mobility and quality of life with advancing age. Promotion of physical activity is an essential strategy to reduce risk of other non-communicable chronic diseases. The WHO has targeted obesity and physical inactivity as two of the major risks for premature mortality globally. Given the rising prevalence of knee OA as a cause of mobility impairment, there is a need to refine a specific model of care to target the clinical symptoms such as pain and disability, as well to reduce the KAM to potentially slow down the progression of medial knee OA. We do not yet have a consensus from existing literature as to how we can best mitigate the abnormal joint forces that initiate and cause progression of the cartilage destruction and other pathology of the joint in knee OA.

Thus, the overall aim of this thesis was first to review the clinical trials to date which have targeted KAM as an outcome in individuals with knee OA. Secondly, we aimed to conduct a randomised controlled trial of potentially effective isolated and combined lifestyle interventions designed to address the risk factors for knee OA progression in a clinical cohort. These interventions were hypothesised to have a positive impact on clinical symptoms: pain and physical function, mediated in part via beneficial alterations in biomechanical forces of the knee joint.

1.7. Thesis Outline

This thesis is presented in six chapters, each one can be read independently and one of them is published as a manuscript in a peer-reviewed scientific journal as part of this candidature. This thesis provides an overview of lifestyle interventions that could modify the abnormal joint load over the medial side of the knee in patients with medial knee OA as well as the challenges faced in the conduct of 3D motion analysis in this cohort to meet the most updated standards published by the Australia and New Zealand Clinical Motion Analysis Group.[53]

Chapter One Provides an introduction and background of the topics covered in the present thesis and provides a background on the relevance of gait analysis to evaluate joint loading in patients with medial knee OA.

Chapter Two Consists of a systematic review of randomised controlled trials of lifestyle interventions targeting KAM in individuals with knee OA. This chapter reflects the complexity and large variations of methodology employed to deliver exercise, restricted calorie diets and\ or gait modifications; all of them with the aim to reduce the knee joint loading.

Chapter Three Includes an article published at *The Journal of Physiotherapy* in 2015: "Train High Eat Low for Osteoarthritis (THELO Study): Protocol for a randomised controlled trial"; This manuscript describes in detail the protocol implemented between 2011 to 2018 in 110 overweight / obese patients diagnosed with medial knee OA. The primary purpose of the study was to reduce the knee joint loading thus, potentially slow down the progression of disease.

Chapter Four Presents a test-retest reliability study of three-dimensional kinematic gait parameters and anthropometric measurements obtained during the *Train High Eat Low for Osteoarthritis (THE LO) Study*. The goal of this chapter was to evaluate the precise methodology and quality control implemented during the motion data collection. The reasons for the ultimate inability to analyse the primary biomechanical outcomes of THE LO trial are described.

Chapter Five Secondary outcomes of THE LO Study are presented. Self-reported pain and physical function attributed to knee OA were evaluated via the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) questionnaire.[54]

Chapter Six Summarises the main findings of this thesis, discusses the limitations, practical implications, and future directions of lifestyle interventions in individuals with knee OA.

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CHAPTER 2

Effects of Lifestyle Intervention on Knee Adduction Moment in Individuals with Knee Osteoarthritis: Systematic Review of Randomised Controlled Trials

2.1. Introduction

Osteoarthritis (OA) is the most common form of arthritis. According to the Australian Bureau of Statistics (ABS 2019), 2.2 million (9.3%) people in Australia reported having this condition. The knee is one of the joints most commonly affected by this condition and the prevalence of knee OA has increased sharply in recent years.[1–3] It is the most common cause of disability in older adults.[4,5] There is no cure for this condition and the best option to reduce the burden of disease is to target risk factors for disease progression.

Knee biomechanics during gait are relevant outcomes to identify the risk of knee OA progression. The Knee Adduction Moment (KAM) represents the medial compartment knee joint loading during walking in patients with knee OA.[6] Increased KAM is associated with increased knee joint forces on the medial compartment of the tibiofemoral joint.[7–9] It is also significantly correlated with the proximal tibial bone mineral distribution between the medial and lateral tibia plateaus.[10] During the gait cycle, once the foot contacts the ground and the ground reaction force (GRF) vector acts in equal magnitude and opposite direction the force applied, individuals with medial knee OA tend to shift the knee medially away from the centre of the gravity. The KAM is the resultant force component created when the GRF passes through the medial side of the knee and is related to the perpendicular distance from that load vector to the centre of the joint. The KAM is a reliable[11] and valid[12] measurement to estimate joint load during gait

in patients with medial knee OA.[6] Several studies have now identified elevated KAM as predictive of the severity and risk of progression of knee OA.[13,14]

Consequently, lifestyle interventions which could be used to reduce the load over the medial side of the knee in patients with medial knee OA have great relevance. There is yet no consensus on the best way to reduce KAM 1st peak, as many different approaches have been used in the literature to date with variable effectiveness. For example, dietary weight loss has been shown a slight reduction in KAM only in people who achieved not less than 10% weight reduction in comparison to people who achieved small weight reduction (2.5%) over 18 months.[15,16] Exercise interventions have shown positive changes in pain, physical function and strength in knee OA,[17] and theoretically as muscles improve in strength, they could stabilise the joint and reduce KAM, but this has not been observed in studies to date.[18,19] Gait retraining (such as such as altering the foot angle or leaning the truck laterally while walking) is an emerging lifestyle intervention to reduce joint loading by reducing the magnitude of KAM,[20–22] however, the feasibility of gait retraining to be implemented clinically over the long term in individuals with knee OA outside of experimental lab settings has not been confirmed.

To our knowledge, there has been no comprehensive review of all these potential non-surgical lifestyle interventions, applied singly or in combination, to define their effectiveness in modifying KAM and related clinical symptoms of OA. Therefore, our objective was to systematically review the published literature to identify all randomised

controlled trials of lifestyle interventions (excluding surgical or artefacts interventions) that aimed to modify the knee adduction moment in people with knee OA.

2.2. Methods

2.2.1. Study Design

We conducted a systematic literature review, investigating the effects of any lifestyle intervention on KAM as a risk factor for progression of knee osteoarthritis (OA). This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)[23] and was prospectively registered at PROSPERO (registration number: CRD42015024013).

2.2.2. Search Strategies and Search Terms

A comprehensive search of online sources was conducted on 31st of August 2021 and updated for the final time on November 2023 to identify eligible randomised controlled trials (RCTs) using six different databases from inception to the date of the final search: Web of Science (1992), MEDLINE (1966), Scopus (2004), CINAHL(Complete) (1961), EMBASE (1972), and SPORT Discus (1985), accessed via the University of Sydney computerised library database platforms.

The following terms and strings were utilised:

Osteoarthritis OR arthrosis AND Knee OR tibiofemoral joint OR knee joint AND Biomechanic* OR “Biomechanic parameters” OR “3D motion analysis” OR “3D analysis” OR “Three-dimensional motion analysis” OR kinetic* OR kinematic* OR “Gait analysis”. AND Exercise* OR Training* OR “Therapeutic Exercise” OR Resistance* OR “Resistance training” OR “Physical therapy” OR “Progressive resistance training” OR “Strength conditioning” OR “Weight lifting” OR “Muscle strength increment” OR “aerobic exercise” OR “aerobic training” OR “ circuit training” OR lifestyle intervention* OR Gait retraining* OR “Gait modification” OR “Gait intervention” OR “Toe in” OR “Toe out” OR “Trunk lean” OR Diet* OR “deficit caloric” OR “weight lost* weight program” OR “weight reduction” OR dietary weight loss” AND Randomised Control Trial OR exp clinical trial OR exp placebos OR random assignment* OR control groups OR cross-over studies OR clinical trial.pt. OR (crossover or cross-over or cross over).tw. OR (random* or placebo* or "clinical trial*"). OR ((singl* or doubl* or trebl* or tripl*) adj1 (blind* or mask*)).ab,ti. OR Systematic review.tw,pt. OR exp Systematic review/ OR Systematic review*.tw,pt.

2.2.3. Inclusion/Exclusion Criteria

Inclusion criteria were:

1) The study was a randomised controlled trial (RCT).

2) The RCT was reported in a full-length, published manuscript in a peer reviewed journal format and in English language.

3) RCTs must have been implemented in adults with tibiofemoral osteoarthritis symptoms in at least in one limb, clinically confirmed according to the American College of Rheumatology (ACR)[24] and/or by any kind of validated imaging study (radiographic, MRI) or arthroscopy.

4) Only RCTs which implemented any lifestyle interventions (e.g., physical therapy defined as any exercise or set of exercises aiming to reduce the KAM with the exception of massage or electrophysical therapies; any type of exercise modality, diet modifications, weight loss programs, gait modifications, gait programs or gait retraining) in the form of an intervention or exposure with any type of supervision (e.g., supervised/unsupervised/ group or individual sessions); and in any type of facility (e.g., clinics, gyms, hospital, home-based, universities, research clinics or home-based) and any frequency, intensity or volume.

5) The intervention length must have been at least two sessions of training/counselling delivering the treatment with a minimum of one day between sessions; and must have had one initial biomechanical assessment prior to intervention and a final evaluation post intervention.

6) All trials must have had a comparator group with any kind of control condition (e.g., waiting list, no intervention, usual medical care, other lifestyle intervention, or usual guidelines recommendations) or placebo or sham activity considered to be less effective than the experimental intervention (e.g., gentle exercise that will not promote increments of their current physical activity levels and or modifications of gait patterns), walking with no modification strategies, usual diet) if it did not promote increases in their current physical activity levels.

7) All studies must have included the KAM assessment during gait as one of their outcomes analysed in a 3D motion analysis system.

Exclusion criteria were:

1) Participants were under 18 years of age.
2) Adults had any other type of arthritis (rheumatoid arthritis), joint injury, injection, or surgery within the past six months, or knee replacement on index knee.
3) Interventions consisted of only one training or counselling session (i.e., acute exposure studies).
4) Studies included pharmacological, surgical, footwear or assistive device interventions.

2.2.4. Study Selection and Data Extraction

Three authors (MFS, YG, MS) prepared and planed the search strategy which was registered prospectively in PROSPERO. One author (YG) conducted the computerised database searches. After having removed duplicates automatically using Endnote X20 citation manager system,[25] all papers identified were screened by first author (YG), initially by title, then by abstract. Remaining papers were screened in full text following above exclusion and inclusion criteria. Two authors (YG and MS) screened papers accepted for inclusion in the review. Any disagreement was solved by consensus or in consultation with a third investigator according to their expertise (MFS and/or SE).

Quality assessment of all eligible articles was performed guided by Physiotherapy Evidence Database (PEDro)[26] to determine the risk of bias.

Author (YG) organised and extracted data from selected studies, with accuracy checked by a second investigator (SE and/or MFS). Trials were divided into three different groups according to intervention strategy: a) Gait Retraining, b) Exercise and c) Diet. Data extracted from studies included the following four key areas:

Study Characteristics: Study design, blinding process, obesity inclusion, assessment time points, sample size, length intervention, intervention characteristics (type of intervention, supervision, protocol,) knee OA diagnosis, inclusion/exclusion criteria.

Baseline Cohort Characteristics (divided by intervention/control groups): gender, age, body mass index (BMI), mass, OA severity; pain and self-reported physical function scores via Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[27]

Biomechanical assessment characteristics: a) 3D motion capture data specifications: KAM 1st peak, 3D motion capture system, force platform system, marker set, filtering, joint coordinate system, joint angles definition, joint moment calculation, 3D modelling, reliability test. b) Experimental task design: for gait testing (footwear, gait speed

methods, statistical adjustment) for KAM and any other kinetic/ kinematic variable tested.

Research findings: Relevant findings reported for adherence, dropout rate, all biomechanical outcomes, OA symptoms (pain, stiffness, disability via validated assessment scales.

2.3. Results

2.3.1. Studies Retrieved

The search strategy identified a total of 2,325 articles, while another two articles were identified manually by reviewing citations of retrieved articles. Figure 2.1 shows the PRISMA flowchart[23] of the trial selection process. After excluding duplicates electronically with EndNote X20[25] 1,522 articles remained for title and abstract analysis and studies not meeting the eligibility criteria were excluded. The main reasons for exclusions were the absence of KAM measure as one of its variables (*n*=23), non-RCTs (*n*=11), or interventions implementing artefacts such as insoles (*n*=4). Following a full-text screening of 49 studies, the final sample consisted of 11 studies.[18,19,28–36]

Figure 2.1PRISMA flow chart

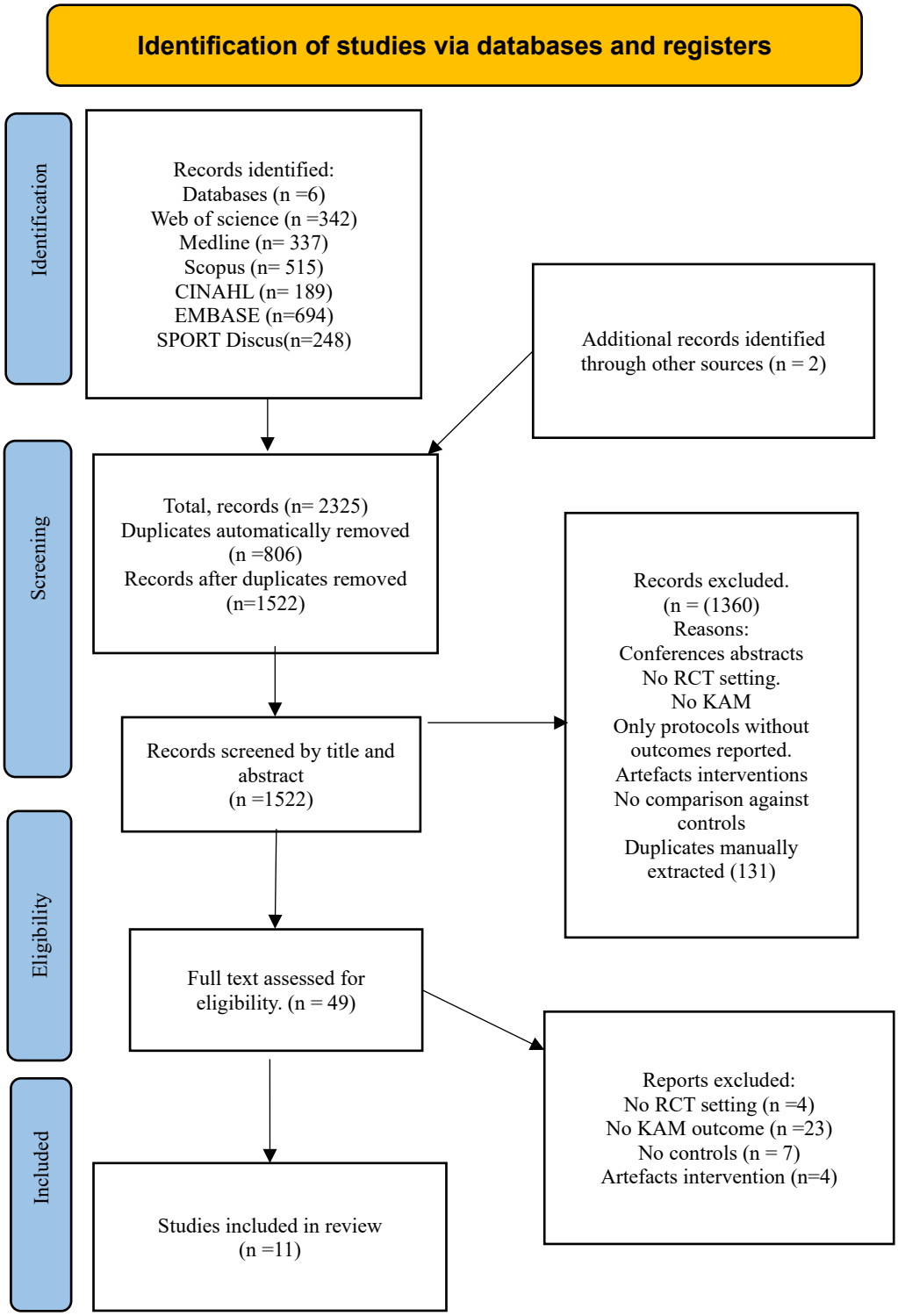


Figure based on PRISMA flow chart for reporting systematic reviews.
n=number, RCT= randomised controlled trial, KAM= knee adduction moment

2.3.2. Study General Characteristics

2.3.2.1. Risk of Bias and Quality Assurance

As shown in Table 2.1, overall, the quality of the RCTs included ranged from 7 to 9 out of 11 points on the PEDro quality assurance scale[26,37,38] The most common deficiencies were the lack of blinding of participants (8/10),[19,28–31,33–36] and/or therapists (11/11),[19,28–36,39] criteria which are difficult or impossible to implement in exercise or gait retraining trials). Four of them[19,29,30,39] did not reach the 85% of participation threshold at the completion of the intervention.

As shown in Figure 2.2, four RCT studies[30,34–36] included inactive control groups (usual clinical care or 'avoid any exercise intervention' without any further indication); another four studies[28,31–33] had active controls prescribing only walking without further instructions to their control groups (although it was prescribed at same facilities with equal number of sessions and duration as the active intervention. Cho et al., 2015[19] implemented a 'sham control group' by applying a hot pack to the affected knees for 20 minutes and transcutaneous electrical nerve stimulation (TENS) at 80 to 120 Hz for 15 minutes. Foroughi et al., 2018[39] designed a 'sham exercise group' with low resistance strength training without progression. Messier et al., 2020[29] provided an 'active control group' by prescribing exercise (aerobic and resistance training) alone. These sham and active exercise groups were set to not impact KAM, justifying their choice as control groups for KAM outcome.[40,41]

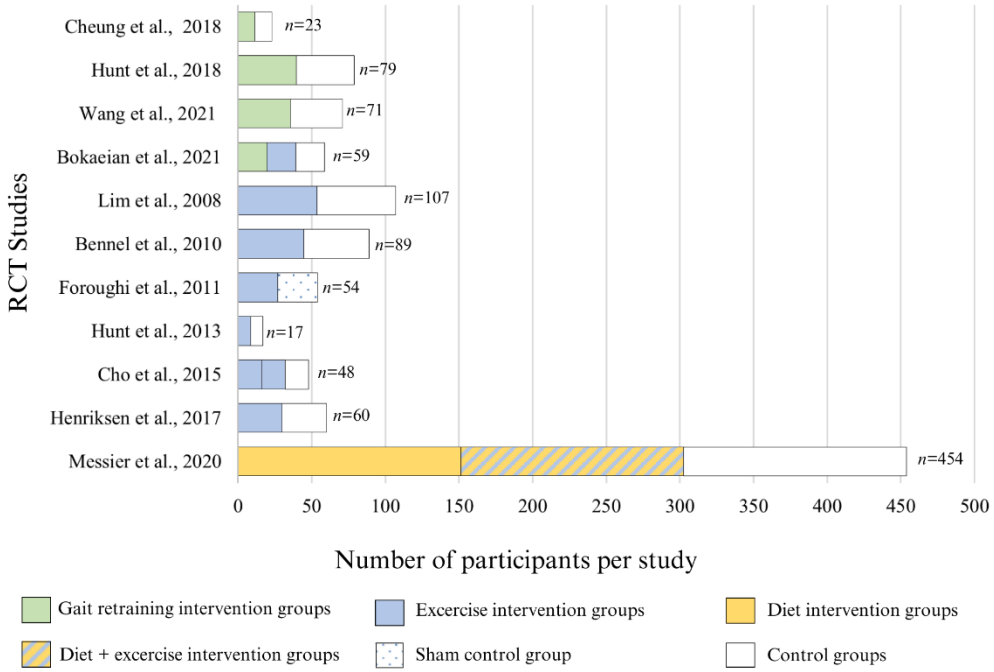
Table 2.1 PEDro scale for quality assurance

PEDro scale	Cheung 2018[31]	Hunt 2018[28]	Wang 2021[32]	Bokaeian 2021[33]	Lim 2008[35]	Bennell 2010[35]	Foroughi 2011[18]	Hunt 2013[36]	Cho 2015[19]	Henriksen 2017[30]	Messier 2020[29]
Study design	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT	RCT
Eligibility criteria specified	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Random allocation	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Concealed allocation	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Similar groups at baseline	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Participants blinded	x	x	yes	x	x	x	yes	x	x	x	x
Therapist blinded	x	x	x	x	x	x	x	x	x	x	x
Assessors blinded	yes	yes	x	yes	yes	yes	yes	yes	x	yes	yes
At least 85% of outcomes obtained	yes	yes	yes	yes	yes	yes	x	yes	x	x	yes
Outcomes analysed with "intention to treat"	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Between-group statistical comparisons reported	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Point measures, and measures of at least variability	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes
Score out of 11	9/11	9/11	9/11	9/11	9/11	9/11	9/11	9/11	7/11	8/11	9/11

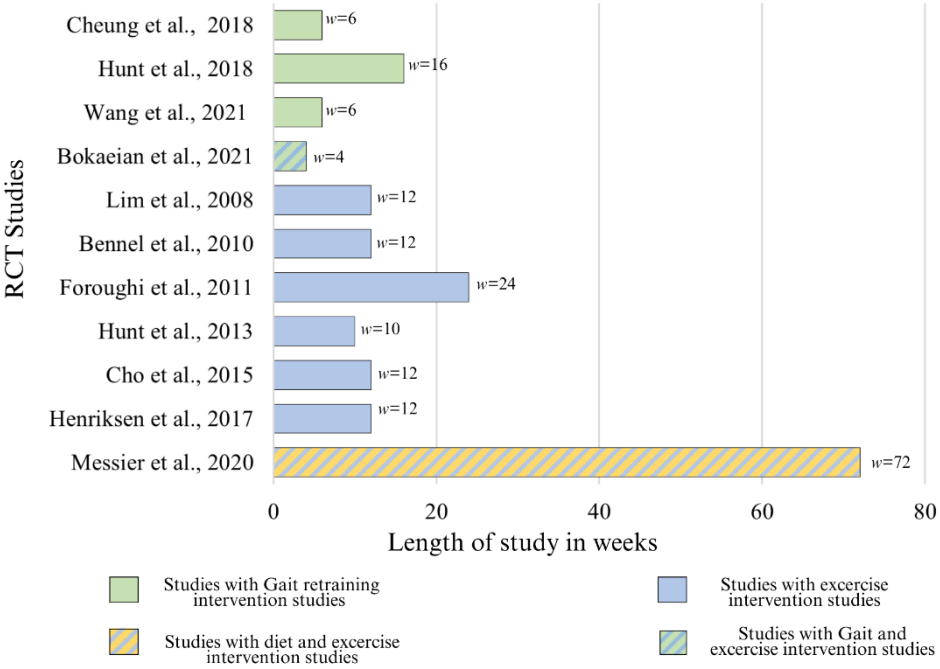
PEDro scale: Physiotherapy Evidence Database for methodological quality of clinical trials[37]
yes: Study met the specific criteria. x: Study did not meet the specific criteria.
RCT: randomised controlled trial

The median intervention length was 12 weeks (range: 4-72 weeks). The median sample size was 60 participants (range:17 to 454 participants). Out of the 11 clinical trials, 3 of them included gait retraining vs. control interventions (2 arms of study analyses);[28,31,32] another 5 included exercise vs. control interventions (2 arms of study analyses);[18,19,30,34–36] one included 2 different modalities of exercises vs. control interventions (3 arms of study analyses), another one included exercise, gait retraining and control groups (3 arms of study analyses); and one included diet, diet + exercise and control (exercise) groups (3 arms of study analyses).[29]

Figure 2.2 Graphic visualisation of a) Number of participants and b) RCT duration in weeks



a) Number of participants per study



b) Intervention length per study

2.3.2.2. Participant Characteristics

A total of 1,061 participants shown in Figure 2.2 were initially enrolled across the 11 trials (individual study sample size ranged from 17 to 454 participants). The mean age of all groups ranged from 54.9 years old [±5.0 Standard Deviation (SD)] to 71.2 years old (±7.0 SD). Sixty-nine percent of participants were women. Two studies were exclusively designed for women.[18,19] The rationale for this in the trial of Foroughi et al. 2011[18] was that women are weaker and have lower limb muscle mass at all ages compared to men, thus they are mechanically disadvantaged compared to men at the same level of body mass. All studies except for one[30] implemented the Kellgren and Lawrence scale[42] to diagnose severity of knee OA. One study included as part of their eligible criteria only participants with bilateral knee OA [19] at any joint location, six studies [28,31,32,34–36] recruited only participants with knee OA at the medial section of the knee whereas four of them included participants with lateral and/or medial and lateral knee OA. Foroughi et. al., 2011[40] included participants with medial and lateral OA in their study, with an initial analysis conducted on a subset of participants with only medial knee OA[18] (for the purpose of this review we will further refer to the study with only medial knee OA as both reported similar outcomes.

2.3.3. Interventions

2.3.3.1. Gait Retraining Interventions

Studies with gait retraining [28,31–33] interventions (*n*=4) ranged from 23 to 79 (mean of 58 ± 24.7) participants in total (Table 2.2). All of them set a participation restriction for patients with a BMI no greater than ≥34 kg/m^2. They all used "only walking" without any strategy, modification, or further indication for their control group and all of them used same facilities, number of sessions and staff to deliver their control strategy.

Hunt et. al., 2018[28] implemented the gait retraining strategy of toe out (15°) during stance phase while walking on a treadmill progressing from 20 to 45 minutes with mirror guided biofeedback. Bokaeian et. al., 2021[33] used a medial thrust walking strategy during the stance phase of the gait cycle (protocol of Fregly et al., 2007)[43] on treadmill with verbal feedback immediately followed by two yoga postures (Goddess Squat and Warrior Lunge) each practiced 3 times for 30 seconds with a 40-second rest interval (a total of 3 min of active yoga practice). Due to the small total volume of active yoga positions implemented, for the purpose of this review we decided to classify this intervention within the gait retraining subgroup of trials for analysis and description purposes. This study. (Bokaeian et. al., 2021)[33] also implemented an exercise intervention described in exercise interventions section below.

Cheung et. al., 2018,[31] and Wang et. al.,[32] implemented the protocol designed by Shull et al., 2013,[44] with individualised gait pattern adaptations. In both trials, while participants were walking on a treadmill, they could see on a screen in front of them the KAM magnitude in real-time. Next, they chose the most comfortable and achievable strategy such as increasing or decreasing foot progression angles (toes pointing in/out) or hip adduction/adduction rotations or trunk sway during the stance phase of the gait cycle if KAM was reduced. Thus, participants had the opportunity to self-select their most comfortable and beneficial strategy.

All four RCTs with gait retraining interventions implemented a system with real-time visual or verbal feedback to guide participants to maintain their strategy during the session. All of them had fully supervised sessions in a clinic/facility, once a week (Cheung et al., 2018[31] and Wang et al. 2021[32]), three times a week (Bokaeian et. Al., 2021),[33] or once every fortnight (Hunt et al., 2013).[36] In all four studies, recommendation was given to implement the targeted gait strategy in daily activities post-training when possible, during the duration of intervention, however no monitoring strategy (in any of the 4 studies) was described to log post-training gait pattern practice/implementation.

2.3.3.2. Exercise Interventions

Exercise intervention general characteristics are shown in Table 2.3. The eight studies that had exercise as at least one of their interventions ranged from 17 to 454 participants; one of them was a short-term intervention (4 weeks);[33] five of them were mid-term

interventions (10 to 12 weeks)[19,30,34–36] and two of them were long-term interventions (6 and 18 months).[18,29]

All exercise interventions included resistance training, varying from a single muscle group to several lower limb muscles groups (quadriceps, hamstrings, adductors and abductors). across a range of intensities and equipment modalities. Three studies targeted knee extensor muscles only,[19,33,34] using resistance elastic bands and or ankle cuffs at a comfortable intensity to achieve 10 continuous repetitions. Bennell et. al., 2010[35] targeted hip adductor and abductor muscles with resistance elastic bands (3 sets of 10 repetitions at moderate intensity). Foroughi et. al., 2011[18] trained 5 lower limb muscle groups at 80% of the one repetition maximum (1RM), with a planned progression of 3% every session after each interim (fortnightly) 1RM so as to maintain the desired intensity using pneumatic machines (Keiser). This was the only study to employ high intensity PRT. Hunt et. al., 2013[36] trained 5 lower limb muscles with ankle cuffs, adjusting resistance when participants were able to perform 3 sets of 10 repetitions. In Henriksen et. al., 2017,[30] the strategy was circuit training including 10 minutes of aerobic warm up at 10-15/20 using the Borg Rating of Perceived Exertion (RPE)[45] scale, followed by core and lower limb exercises with a progression from easiest to most difficult to perform exercises. Messier et. al., 2020[29] had two arms with exercise interventions: Diet + Exercise and Exercise (control group). Both arms implemented the same exercise program, which was a combination of aerobic, strength and flexibility exercises. The sessions included 15 minutes of aerobic training mainly (walking or cycling) immediately before and after 1 or 2 sets with 10 to 12 repetitions of leg extensors, leg flexors, leg press and calf rases, and chess press (TheraBand's were used at home-based

sessions) then 10-minute stretch session to cool down. Intensity for aerobic components were set between 50%-70% of HR reserve. Cho et. al., 2015[19] had two different exercise arm interventions (in addition to the control group which received 15 minutes of TENS at 80 to 120 Hz); one targeting quadriceps strengthening while the other group implemented a proprioceptive/balance training program. No hypothesis in regard to hypothesised group superiority was described in the publication.

2.3.3.3. Diet Intervention

The one dietary intervention is shown in table 2.4. Messier et. al., 2020[29] included two different RCT arms with a diet intervention (diet, and diet + exercise group) with the same diet protocol of up to 2 meal replacement shakes per day with an energy intake deficit of 800-1000 kcal per day, aiming for a weight reduction of 10 to 15% of baseline body weight. If participants reached their goal, they had the option to continue losing weight or a switch to a maintenance program. A strong behavioural change support system was used to sustain the intervention.

Table 2.2 General Characteristics of RCTs with Gait Retraining interventions.

Citation	Assessment	Control intervention	Knee OA Gait Retraining Intervention			Diagnosis: KL scale	Inclusion criteria
			Type	*Supervision*	*Details*		
Cheung et al., 2018	0 w 7 w 26 w	Walking on treadmill No further instructions	GaitRe: • ↑ or↓ foot progression angle. • Hip add/rot • Trunk sway.	Facility-based All sessions supervised	*Frequency:* 1 * week *Intensity*: Feedback progressively reduced. Implementation of new gait pattern daily. *Time:* Progressive increments up to 30 min*session. *Type*: Walking on treadmill. Protocol based on Barrios 2010 & Hall 2017. Real-time KAM displayed on screen. Freely adaptation of strategies to lower their KAM	•Medial tibiofemoral OA •I, II	• Knee pain 1day*week over 8 weeks prior to participation • ≥45 to ≤80 years • Walk unaided at least 60 min • BMI ≤35 kg/m²
Hunt et al., 2018	0 w 16 w 20 w	Walking on treadmill No further instructions	GaitRe: Toe out 15°	Facility based. Session 1: one-on-one Session 2-8: 3:1 ratio. Same trainer and rehabilitation facility all times	*Frequency:* 8 supervised training sessions at w:1,2,4,6,8,10,12,15 *Intensity*: Feedback progressively reduced. *Time:* Progressive increments from 20 min-40 min at w15 *Type:*15° more toe-out than the self-selected the baseline Mirror-guided biofeedback of performance placing a piece of tape to guide participants of foot angle while walking on a treadmill	Medial tibiofemoral OA II, III, IV	•Osteophytes on X-ray • Joint space narrower in medial tibiofemoral compartment compared to the lateral • Pain >6 months • Ave. knee pain of at least 3/10 over a month prior to initial screening

Citation	Assessment	Control intervention	Knee OA Gait Retraining Intervention			Diagnosis: KL scale	Inclusion criteria
			Type	***Supervision***	***Details***		
Wang et al., 2021	0 w 7 w	Walking on treadmill No further instructions Shoes identical as intervention.	GaitRe via real-time feedback	Facility-based supervision: (Both groups)	Frequency: 1*week *Intensity:* Feedback progressively removed Implement new pattern on daily activities was advised *Time:* Progressive increments by 3 min each session up to 30 min over six sessions *Type:* KAM modulation based on Shull 2013 & Cheung (2018). KAM curve displayed in real time on a tablet while walking on a regular self-paced treadmill. Intent to adjust the foot progression angle to reduce the KAM peak by 20% from the BL. Same pair of shoes with an internal sensor device (gyroscope and accelerometer) at all sessions.	Medial tibiofemoral OA I, II	• Self-reported knee pain at least 1d*week • Aged >40 to <70 years old • Able to walk unaided for at least 60 min
Bokaeian et al., 2021	0 w 4 w 8 w	Walking on treadmill No further instructions	Yoga+GaitRe (medial thrust) Knee muscle strengthening (described in exercise Table2.3)	Physiotherapist supervision at all sessions All groups received thermotherapy with a hot pack for 20 min.	*YogaMT* *Frequency*: 3*week *Intensity*: Based on RPE Scale *Time*: 20 min*GaitRet+ 3*30sec holding yoga positions intervals of*40sec rest *Type*: Medial thrust gait: walk with slight hip internal rotation and knee flexion (20°) at their selected speed on the treadmill. 2. Goddess squat: Feet in approx. 45° external rotation and shoulder-width apart. Squatted down to 30° (or 60° to 80° of knee flexion and from hands on hips to arms	Unilateral or bilateral tibiofemoral OA II, III	• Between 45 and 76 years old • Knee pain ≥30 on 100-mm VAS scale • Pain for more than a month • Ability to walk without assistive devices

Citation	Assessment	Control intervention	Knee OA Gait Retraining Intervention			Diagnosis: KL scale	Inclusion criteria
			Type	***Supervision***	***Details***		
					overhead for progressions) 3. Lunge position with affected knee forward bending down at 90° (hands on hips to arms overhead for progressions *KMS Group*: Details on exercise table		

KL scale Kellgren & Lawerence radiographic severity scale for knee Osteoarthritis 0-IV where IV indicates worst [42],

RPE= Borg Rating of Perceived Exertion Scale[45]

GaitRe: gait retraining intervention; OA: osteoarthritis; w: weeks, m: months, d: day; min: minutes; sec: seconds; reps: repetitions, BMI: body mass index; kg: kilograms; TKR: total knee replacement; YogaMT: Yoga plus gait retraining (medial thrust); VAS: visual analogue scale; KMS: knee muscle strengthening.

Table 2.3 General Characteristics of RCTs with Exercise interventions

Citation	Assessment	Control intervention	Knee OA Exercise Intervention			Diagnosis: KL scale	Inclusion criteria
			Type	*Supervision*	*Details*		
Lim et al., 2008	0 w 13 w	Instructed to avoid any exercise programs	Quadriceps strengthening	6 experienced physiotherapists Home-based + 7 supervised sessions (w:1, 2, 3, 4, 5, 7, & 10).	*Frequency:* 5*w 2 rest days self-determined by participants symptoms. *Intensity:* Loads progressed when participants could comfortably achieve previous dosage *Time*: 2-3 sets*10 reps *Type:* 1.Seated knee extension 90° to 0° of knee flexion 2. Inner range knee extension -supine lying 30° to 0° knee flexion 3. Straight leg raises in supine lying (or elbow-supported supine lying position) 4. Isometric knee extension at 30° knee flexion 5. Isometric knee extension at 60° knee flexion in sitting position).	Medial tibiofemoral OA II, III, IV	•OA in at least 1 joint fulfilling ACR criteria • Medial knee pain, medial compartment osteophytes, & medial joint space narrowing greater than lateral joint space narrowing
Bennell et al., 2010	0 w 13w	Usual clinical management	Hip adductor/ abductor strengthening	Physiotherapist with 15.6 yrs. (10.10 years of clinical experience and research studies Home-based with 7 sessions 30-min in w1, 15-minutes*w	*Frequency:* 5*w *Intensity:* 10RM moderate resistance adjusted on session *Time: 3* sets*10 reps *Type:* 1 & 2. Unilateral hip abduction & adduction- standing with ankle cuff weights 3 & 4. Unilateral hip abduction & adduction standing with moderate resistance bands 5.Isometric hip abduction. Unipedal stance, opposite limb in 90 degrees of hip & knee flexion performed bilaterally	Medial knee OA & valgus alignment II, III, IV	• ≥50 Years old • At least one knee fulfilling ACR criteria • Ave knee pain >3 on an 0-11 scale. • Knee varus alignment • Medial knee pain / medial compartment osteophytes /medial

Citation	Assessment	Control intervention	Knee OA Exercise Intervention			Diagnosis: KL scale	Inclusion criteria
			Type	***Supervision***	***Details***		
				from 2 to 5 & 7 and 9).	6. Bilateral isometric hip adduction against a rolled-up towel in sitting		joint space narrowing.
Foroughi et. al., 2011	0 w 26 w	Sham: Low intensity exercise: Identical as intervention with minimal resistance and no progression *Time*: 2 sets* 8 reps Same supervision, facilities and equipment	Lower limb progressive resistance training at 80%	Facility-based for all sessions supervised by Exercise Physiologist in a ratio of 1:1-3	*Frequency*: 3 sessions*w *Intensity:* 80% of peak 1RM with 3% increment per session as tolerated according to symptoms. Fortnight re-assessments of 1RM to adjust the new 80%. intensity corresponding to 15–18 on the RPE scale *Time*: 3 sets*8 reps (6-9 sec/repetition with 10-15sec rest) & 1-2 min rest between sets *Type*: Six different exercises utilising pneumatic resistance machines (K400 model, Keiser Sports Health, Inc, Fresno, CA, USA) 1. Unilateral knee extension 2 & 3. Standing hip abduction and adduction 4. Bilateral knee flexion 5. Leg press 6. Ankle plantarflexion	Medial knee OA II, III, IV	• Women ≥40, stable health, • Primary OA in at least 1 leg according to ACR criteria
Hunt et al., 2013	0 w 11 w	Usual clinical management	Lower limb strengthening exercises	Home-based + 5 visits to physiotherapist at w:1,2,3,5,8	Frequency: min of 4*w Intensity: 10RM. Safe resistance progression adjusted during physio session. When applicable, additional resistance was provided Time: 3 sets*10 reps Type: Exercises performed with ankle cuffs 1. Standing hip abduction 2. Side lying hip abduction 3. Standing lunges 4. Mini squats	Medial knee OA II, III, IV	• ≥ 50 years. • OA in at least one knee according to ACR classification criteria • Average knee pain >3/10 on most days of the previous month. Varus alignment &

Citation	Assessment	Control intervention	Knee OA Exercise Intervention			Diagnosis: KL scale	Inclusion criteria
			Type	*Supervision*	*Details*		
					5. Seated knee extension 6. Standing knee flexion to 90° while standing balance on contralateral limb		OA predominantly in the medial tibiofemoral compartment
Cho et al., 2015	0w 13w	20 min x hot pack bilaterally 15 min x TENS at 80 Hz to 120 Hz	Proprioceptive training PTG Quadriceps strengthening QSG	Facility-based Both interventions supervised by physical therapist on a ratio of 1:1	*Quadriceps Strengthening Group* -Frequency: 30min* 2times*w *Intensity:* Gradual increments every 4 w *Time*: 3sets*10 reps 3 min rest between sets *Type*: Isometric exercise to improve muscle power in long sitting and supine positions Protocol: Nakayama, 2003. *Proprioceptive Training GroupFrequency*: 2*30 min*w *Intensity:* Gradual progression of difficulty 1-4 w standing in both legs, eyes open and verbal commands 5-8 w alternation of one leg stand 9-12 w no visual/auditory feedback *Time:* 40 times repeatedly each exe *Type:* Balance exercises in different planes with Torsiomed (Haider Ltd, 2000, Germany) to improve proprioception of ankle thus correct the joint's position a) Sagittal plane exercises: forward and backward tilting b) Frontal plane exercises: lateral and medial tilting	Bilateral knee OA II, III	• Women ≥65 years old • Bilateral diagnosis of OA & radiologically stage II &III of K & L scale • Deficits in sensation, circulation, balance, or range of motion according to lower extremity Manual-Muscle Test

Citation	Assessment	Control intervention	Knee OA Exercise Intervention			Diagnosis: KL scale	Inclusion criteria
			Type	***Supervision***	***Details***		
Henriksen et al., 2017	0 w 13 w	No attention	Strength, stability, and coordination (trunk, hips and knees)	Facility group-based sessions with one or more physiotherapists	*Frequency*: 1 hr.* 3times*w *Intensity:* scale from A (easiest) to E (most difficult). Progression personalised. *Time:* 2-3sets*6-8 reps *Type:* Resistance training in a Circuit basis. Warm- up:10min bicycle ergometer at 80-100 rpm or moderate intensity 11-15RPE) Main exercises: 1. Core stability 2. Hip stability supine pelvic lift 3. Hip abductors: side lying/ standing adduction with rubber bands 4. Knee control: from a flexed position of 15°-20° quickly extend to upright position without hyperextension 5. Squat with a Swiss ball between the back and a wall. 6. Steps up/down with rubber bands	Tibiofemoral knee OA	•≥40 years • Clinical diagnosis of tibiofemoral OA confirmed by radiography, •BMI <20 to >35 kg/m²
Bokaeian et al., 2021	0 w 4 w 8 w	20 min of treadmill walking at self-selected speed	Knee muscle strength or Yoga/gait retraining (medial thrust)⏚.	Physiotherapist supervision at all sessions. All groups received thermotherapy with a hot pack for 20 min. Instructed to avoid sitting in a	*Knee strength group*: *Frequency:* 3 times*w *Intensity:* 10RM without pain and progressive increments within the session *Time*: 3 sets x 10 repetitions with 2 min rest *Type:* Knee Muscle strengthening in a pain free range of motion 1. Seated knee flexion/ extension Set 1 at 60-65% of 10RM	Unilateral or bilateral tibiofemoral OA II, III	• Between 45 and 76 years of age • Knee pain ≥30 on the 100-mm visual analogue scale (VAS) • Unilateral or bilateral tibiofemoral joint OA

Citation	Assessment	Control intervention	Knee OA Exercise Intervention			Diagnosis: KL scale	Inclusion criteria
			Type	*Supervision*	*Details*		
				cross-legged position, kneeling, prolonged standing & stair climbing	Set 2 at 70-75% of 10RM Set 3 at 80-85% of 10RM. YogaMT group (Details summarised on Gait retraining table**)		• Hx of pain for more than a month • Ability to walk without assistive devices

KL scale: Kellgren & Lawerence radiographic severity scale for knee Osteoarthritis 0-IV were IV indicates worst pain

RPE: Borg Rating of Perceived Exertion Scale

OA: osteoarthritis, w: weeks, m: months, d: day, min: minutes, sec: seconds, reps: repetitions, BMI: body mass index, kg: kilograms, TKR: total knee replacement, YogaMT: Yoga plus gait retraining (medial thrust), VAS: visual analogue scale, KMS: knee muscle strengthening

Table 2.4 General characteristics of RCT with diet and exercise intervention

Citation	Assessment	Control intervention	Knee OA Diet +Exercise intervention			Diagnosis: KL scale	Inclusion criteria
			Type	Supervision	Details		
Messier et al., 2020	0 w 26 w 72 w	Exercise	Intensive diet to induced body mass loss: Diet group (D) Diet + exercise group (D+E)	D and D+E: identical dietary intervention. Month 1 to 6: 1on1+3group sessions per month Month 7to 18: 1on 1session every 2 months + 1 fortnight group session.	*Weight loss goal*: Group mean of 10%-15% o Partial meal replacements, up to 2 meal replacements shakes*day Energy-intake deficit: 800– 1000 kcals/day Calorie distribution goal: 15%-20% Protein, < 30% Fat, 45%–60% Carbohydrates As progress, fewer meal replacements were consumed.	• Tibiofemoral Or •Tibiofemoral+ patellofemoral I, II	• ≥55 years old • (KL) grade II or III radiographic tibiofemoral OA one or both knees • ≥27.0 kg m² BMI to 41 kg m² •Sedentary lifestyle,
			Exercise intervention: Diet + Exercise Group (D+E) Exercise Control Group (E)	E and D+E groups: identical exercise intervention Month 1to 6: 2*w (facility-based) + 1*w (home-based). Month 7to 18: Facility-based or home-base or combination (decision taken by participant)	Exercise routine: Frequency: 3*w Intensity: 50%-75% HR reserve Time: 60 min sessions Type: Aerobic- Strength-Aerobic 1. Aerobic 15 min: walking or cycling 2. Strengthening 20 min:1-2 sets*10-12 reps: Leg extension, leg press, leg curl, calf raises, compound row vertical chess or incline press (TheraBand used at home-based) 3. Aerobic 15 min: walking or cycling 4. Cool down: 10 min. stretch		

KL scale Kellgren & Lawerence radiographic severity scale for knee Osteoarthritis 0-IV were IV indicates worst pain

RPE: Borg rating of perceived exertion scale, RPE: Borg Rating of Perceived Exertion Scale, OA: osteoarthritis, E: exercise D: diet, E+D: exercise plus diet w: weeks, m:months, d: day, min: minutes, sec: seconds, reps: repetitions, BMI: body mass index, kg: kilograms, TKR: total knee replacement, kcal: kilocalories, HR: heart rate

2.3.4. 3D Gait Analysis

2.3.4.1. 3D Data Collection

Details of experimental 3D gait analysis methods details are shown in Table 2.5 All studies implemented 3D optoelectronic motion capture systems. Sample frequency for 3D kinematic data ranged from 60 Hz to 200 Hz, one study did not report kinematic frequency ranges. Sample frequency for kinetic data ranged from 480Hz to 2000Hz except for two studies which did not report kinetic frequencies.[19,33,34] Assessors were blinded when capturing data except for two studies.[19,32] One study[33] reported a trained physiotherapist placing markers and another trained a physiotherapist always supervising marker placement during data collection sessions.

Marker set ranged from not reported [19,28,30] to 38[18] reflective markers with most studies (n=4) utilising the Plug in Gait marker set (Davis et. al 1991)[46] Three-dimensional biomechanical modelling was documented with large variation in models employed across studies; three of them [33–35] employing the Plug in Gait model (Davis et. al 1991).[46]

Lim et al., 2018[34] reported marker placement test/re-test reliability, with same researcher setting markers in 11 patients over one week apart [interclass correlation coefficient (ICC) 0.96-0.97]. Bennell et al., 2010[35] and Lim et al., 2008[34] ran a test re-test reliability analysis for external peak KAM during stance phase (ICC 0.97 and 0.93 respectively) while Foroughi et al., 2011[18] reported coefficient of variance CV 0.5% for KAM. No further quality assurance test was reported in any other trial.

Table 2.5 Characteristics of 3D motion capture systems

	Intervention	Reference	3D mocap system	Multicomponent force platform	Marker set	Filtering	3D modelling	Reliability test
Gait retraining		**Cheung et al., 2018**	8 cameras at 200 Hz Vicon	Split belt instrumented treadmill at 1,000 Hz	Plug in gait (Davis et. al. 1991)	Fourth-order, phase-corrected, Butterworth, low pass filter at 8 Hz: 50 Hz	Plug-in-gait with knee & ankle join centres defined midway along the respective joint axes. Body segments were modelled according to a previous study (Hall 2017) For analysis purposes body segments were modelled according to Barrios, 2010.	NR
		Hunt et al., 2018	12 cameras at 100 Hz Motion Analysis,	2 force platforms at 2,000 Hz	22 markers	NR	Modified Helen Hayes (Kadaba, 1989) Inverse dynamics (Software Orthotrak, Motion Analysis Corp.) 3d rotation determined by static model	NR
		Wang et al., 2021	10 cameras 100 Hz Vicon	1 force platform at 1,000 Hz	Anatomical system technique (CAST) marker set (Cappozzo 1995)	Fourth-order, phase-corrected, Butterworth, lowpass filter at 8Hz:50Hz	Expressed as external moments, referenced about proximal end of distal segment. Joint angel definition derived capture system x-y-z	NR
	Exercise	**Bokaeian et al., 2021**	12 cameras 200 Hz Vicon	2 force platforms	18 markers	High-pass Butterworth filter with a cutoff frequency of 6Hz:20 Hz	Segment definition: Plug in Gait (Davis et al. 1991). Inertial properties: 3D Joint rotation: Sequence superior–inferior, anterior–posterior, & medial–lateral (Schache &Baker 2007) Inverse Dynamics: Plug in Gait (Davis et. Al., 1991)	NR

Intervention	Reference	3D mocap system	Multicomponent force platform	Marker set	Filtering	3D modelling	Reliability test
	Lim et al., 2008	8 cameras 120 Hz Vicon	2 force platforms	20 markers. Davis et al. (1991)	NR	Segment definition: Plug-in-Gait (Davis et.al., 1991). Inertial properties: Dempster et al. (1959). 3D joint rotations Cardan sequence y-x-z (mediolateral, anteroposterior, longitudinal); Kadaba et al. 1990) Inverse dynamics: Davis et al. (1991).	11 participants 1wk apart (ICC0.96-0.97)
	Bennell et al., 2010	8 cameras at 120 Hz Vicon,	2 force planforms at 1,080 Hz	Plug-In-Gait Additional markers at sternal notch, T2 and T10.	NR	Segment definition: Plug-in-Gait (Davis et.al., 1991). Inertial properties: NR. 3D joint rotations Cardan sequence y-x-z (mediolateral, anteroposterior, longitudinal); Kadaba et al. 1990). Inverse dynamics: Davis et al. (1991).	11 participants KAM Test-retest (ICC 0.92-0.97) 1wk apart
	Foroughi et. al., 2011(A)	10 cameras at 100 Hz Motion Analysis, S	2 force platforms 1,000 Hz	38 markers 20mm	NR	modified Helen Hayes (Kadaba 1990). The midpoint between the medial & lateral femoral condyle was determined as the knee joint centre & the hip joint centre was define using Bell's method (Bell et al., 1990).	NR
	Hunt et al., 2013	8 cameras at 120 Hz Motion Analysis	2 force platforms 1,200 Hz	NR	NR	lower limb anatomical landmarks during walking as well as over the medial femoral epicondyles & medial malleoli during an initial static standing trial used to determine joint centre locations	NR

	Intervention	Reference	3D mocap system	Multicomponent force platform	Marker set	Filtering	3D modelling	Reliability test
		CHO et al., 2015	8 cameras Motion Analysis	2 force platforms 600 mm × 900 mm;	NR	NR	NR	NR
		Henriksen et al., 2017	6 cameras at 100 Hz Vicon	2 force platforms 1,500 Hz	NR	NR	Plug-in-gait 7 body segments (pelvis, thighs, shanks, feet)	NR
	Diet	**Messier et al., 2020**	6 cameras at 60 Hz Motion Analysis	1 force platform 480 Hz	37 markers Cleveland configuration, (Van den Bogert, A. J 2013)	Low-pass, Butterworth, fc= 6 Hz.	DeVita & Hortobagyi, 2001 to calculate forces	NR

3D mocap: 3-dimentional motion capture system; Hz, hertz; mm: millimetres; KAM: knee adduction moment ICC: interclass correlation coefficient
NR: not reported

2.3.4.2. Experimental 3D Gait Task

Most studies (n=8) ran their statistical analysis over the average of five 3D gait trials, except for Henriksen et al. 2017[30] who recorded ten 3D gait trials and Cheung et al. 2018[31] who ran the experimental task over a treadmill and recorded the average of the last 20 steps of 4 minutes of adaptation. All tests were performed at self-selected gait speed. Upper and lower limits were pre-established in few studies (n=5)[29,30,32,33,35] between ± 3.5% to 10 % of averaged self-selected gait speed. In addition, 5 trials were also collected by Lim et al., 2008[34] at a standardised speed of 1 m/s and Foroughi et al. 2011[18] at maximal speed.

Five studies collected their gait trials barefoot.[18,28,33,35,36] Four studies collected trials instructing participants to wear same shod: their own comfortable/low heel shoes [33,42,43,46], whereas two studies with shod trials provided the same sport shoes model[29] or instrumented shoes[32] across timepoints.

Table 2.6 Gait experimental task methods

Intervention		Reference	Experimental gait testing			Statistical adjustment
			Footwear	Gait speed methods	Gait speed system	
Gait retraining		**Cheung et al., 2018**	Own usual shoes. Same pair across all time points	Self -selected & replicated over follow up sessions. Ave. of last 20 steps of the trial after a 4-min adaptation period.	NR	NR
		Hunt et al., 2018	Barefoot	5 self-selected speed trials No specific instructions	NR	Yes
		Wang et al., 2021	Standardised shoes (assessment & training) with embedded internal sensor	5 self-selected speed trials ±5% difference	Photo gates	NR
	Exercise	**Bokaeian et al., 2021**	Barefoot	5 self-selected speed trials 30 sec rest interval 5 min warm-up at stationary bicycle at self-selected speed, 3-5 trials x familiarization, then, 5 test trials	Same as kinematics system 12m. walkway.	NR
		Lim et al., 2008	Own low-heeled shoes	5 self-selected speed trials 5 trials at gait speed of 1 m/s ± 10%.	Photoelectric beams (placed 4m apart in the middle of the 8m walkway.	Yes
		Bennell et al., 2010	Barefoot	5 self-selected speed trials If at follow up self-selected gait speed varies by >5% between test sessions, additional 5 trials were captured at baseline gait speed.	2 photoelectric beams	Yes

Intervention	Reference	Experimental gait testing			Statistical adjustment
		Footwear	Gait speed methods	Gait speed system	
Diet	**Foroughi et. al., 2011(A)**	Barefoot	10 trials: 5 trials at self-selected speed 5 trials at maximal gait speed 2-3 min of rest between trials.	3D motion analysis system 10m walkway	Yes
	Hunt et al., 2013	Barefoot	5 trials at self-selected speed	NR	Yes
	CHO et al., 2015	Own low-heeled shoes	5 trials at self-selected speed	NR	NR
	Henriksen et al., 2017	Own comfortable shoes	10 trials at self-selected speed (±0.1 km/h of target speed) 10m walkway	photocell system	No
	Messier et al., 2020	Identical make & model athletic shoe during testing: Sport shoes (Nike Air Pegasus)	6 successful self-selected trials ± 3.5%	photoelectric control system with photocells positioned 7.3m apart	Yes

NR: not reported; Ave.:averaged; min: minutes; m: meters; m/s: meters per second; km: kilometers.

2.3.5. KAM Outcomes

Specific details of KAM variables during the stance phase are shown in Table 2.7. All studies measured the maximum adduction moment at the knee during the gait cycle which graphically is represented as the first peak of the plotted graph (KAM 1st peak) on the affected limb(s).

Three out of four studies with a gait retraining group intervention reported significant group effects in KAM 1st peak when comparing gait retraining group vs. controls: Cheung et al., 2018[31] -16% (*P*= 0.035); Bokaeian et al., 2021[33] gait retraining vs. knee strengthening -23 N*m/kg (*P*=0.005); gait retraining vs. control: -28 N*m/kg, P=0.001; Wang et al., 2021[32] -39 BW*HT%; *P*=0.005.

Overall, mean reductions in KAM 1st peak across the three gait retraining studies over time measured immediately after intervention were estimated at 24% (±9.5 SD), This positive effect seems to be in accordance with previous laboratory-based studies with a KAM reduction of 20%.[14,44] Those changes were sustained after six months post-intervention in Cheung et al., 2018,[31] and four-weeks post intervention in Bokaeian et al., 2021.[33]

No significant changes were reported in KAM 1st peak in seven out of eight exercise interventions[29,30,33–36,40] and only Cho et al. 2015[19] reported post hoc test significant reduction of 24% on KAM 1st peak at their proprioceptive/balance training group compared to controls $P<0.05$ while also observing changes in foot progression angle (FPA). This finding suggests that the modulation of KAM may have been influenced by adjustments in FPA, potentially as a result of ankle balance training incorporated in the intervention. Ankle balance training, which enhances proprioception and lower limb stability, could indirectly impact FPA by altering gait mechanics, leading to changes in foot alignment during walking.

Wang et al. 2021[32] provide additional support for this concept, noting that changes in FPA, particularly a toe-out position, are associated with reductions in KAM and knee adduction angular impulse. Their meta-analysis highlights that modifying FPA plays a crucial role in reducing medial knee loading in individuals with knee osteoarthritis, which may slow disease progression and alleviate symptoms. Therefore, it is plausible that the exercise intervention in Cho et al., 2015 study facilitated improvements in KAM by influencing FPA through proprioceptive and ankle balance training.

Messier et al 2020[29] implemented an exercise control group, and interventions of diet only and the combination of both diet and exercise and did not document any significant difference between groups in KAM 1st peak. In fact, did not reduce their magnitude over time.

Table 2.7 KAM Outcomes of included studies, pre- and post-intervention

	Intervention	Reference	KAM Nm/BW*HT%	KAM Intervention Group		KAM Control Group		KAM Analysis post intervention
				Baseline *Mean (SD)*	Post-intervention *Mean (SD)*	Baseline *Mean (SD)*	Post-intervention *Mean (SD)*	
Gait retraining		**Cheung et al., 2018**	KAM 1st peak Nm/kg	0.353 (0.05)	NR	0.322 (0.06)	NR	**Significant improvement between group comparison of 16% diff. (95% CI -15, -34%) *P*=0.035** Effects maintained at 6m follow-up 23% dif. (95% CI -1, -46%) *P*= 0.027
		Hunt et al., 2018	KAM 1st peak	2.41 (0.21)	4m: 2.43 (0.06) 5m: 2.41 (0.07)	2.38 (0.14)	4m: 2.57 (0.06) 5m: 2.57 (0.07)	No significant between-group differences observed on KAM 1st peak
		Wang et al., 2021	KAM 1st peak	2.73 (0.51)	NR	2.66 (0.40)	NR	**Significant improvement between group comparison KAM 1st peak 14.6% P = 0.005,**
	Exercise	**Bokaeian et al., 2021**	KAM 1st peak N*m/kg	KMS: 0.70 (0.16) YogaMT: 0.86 (0.25)	KMS 5wk: 0.80 (0.18) KMS 9wk: 0.67 (0.23) YogaMT 5wk: 0.57 (0.17) YogaMT 9wk: 0.61 (0.42)	0.73 (0.29)	5wk: 0.85 (0.29) 9wk: 0.69 (0.27)	**Significant improvement between group comparison YogaMT vs. KMS P=0.005 YogaMT vs. Control P=0.001** Effects maintained at 9-week follow up

Intervention	Reference	KAM Nm/BW*HT%	KAM Intervention Group		KAM Control Group		KAM Analysis post intervention
			Baseline *Mean (SD)*	Post-intervention *Mean (SD)*	Baseline *Mean (SD)*	Post-intervention *Mean (SD)*	
	Lim et al., 2008	KAM. BWxHT%.	Malaligned: 4.28 (0.63) Neutral: 3.58 (0.94)	Malaligned: 4.40 (0.76) Neutral 3.63 (1.11)	Malaligned: 3.97 (0.57) Neutral: 3.91 (1.01)	Malaligned: 3.91 (0.71) Neutral: 3.79 (1.11)	No significant between-group differences observed. P= 0.431
	Bennell et al., 2010	KAM 1st peak BWxHT%.	3.2 (1.0)	3.3 (0.9)	2.9 (0.9)	2.9 (0.9)	No significant within- or between-group differences observed. P= 0.193
	Foroughi et. al., 2011	KAM1st peak BWxHT%	−2.54 (1.41)	−2.69 (1.30)	−2.72 (0.96)	−2.75 (0.90)	No significant between-group differences observed. P=0.537
	Hunt et al., 2013	KAM 1st peak BWxHT%	3.75 (0.91)	3.70 (0.91)	3.38 (0.78)	3.21 (0.95)	No significant between-group differences observed KAM P= 0.91
	Cho et al., 2015	KAM: 1st peak Nm/kg	*PTG:* 0.57 (0.20) *QSG:*0.54 (0.15)	*PTG*:0.44 (0.22) *QSG:*0.50 (0.12)	0.53 (0.03)	0.53 (0.12)	**Significant improvement between group comparison: PTG vs. Control: -24% KAM 1st peak P< 0.05**
	Henriksen et al., 2017	KAM: 1st peak	0.65 (0.22)	NR	0.67(0.25)	NR	No significant between-group differences observed. KAM 1st peak: P=0.84

Intervention		Reference	KAM Nm/BW*HT%	KAM Intervention Group		KAM Control Group		KAM Analysis post intervention
				Baseline *Mean (SD)*	Post-intervention *Mean (SD)*	Baseline *Mean (SD)*	Post-intervention *Mean (SD)*	
	Diet	**Messier et al., 2020**	KAM Not normalised to BW due to the nature of intervention Nm	KAM Overall participants 28.1 (95%CI 26.8,29.5)	Diet 6m: 29.7Nm (95%CI 27.9, 31.6) Diet 18m: 28.6Nm (95%CI 26.8, 30.5) D+E6m:30.8Nm (95%CI 29.0, 32.6) D+E18m:29.3Nm (95%CI 27.5,31.1)		6m: 29.0Nm (95%CI 27.2,30.8) 18m: 29.0Nm (95%CI 27.1,30.8)	No significant between-group differences observed.

*KAM unites expressed as Newtons/ Body Weight*height% unless is noted in different units*

Results express as mean (±SD Standard deviation) or mean (95% CI Coefficient Intervals)

NR: not reported, KAM: knee adduction moment; N: newtons; kg: kilograms; SD: standard deviation; 95% CI: coefficient of intervals, D+E: diet plus exercise intervention group

2.3.6. Clinical Outcomes

2.3.6.1. Pain

Self-reported clinical outcome "pain" is shown in Table 2.8. The most common pain assessment tool utilised was the Western Ontario and McMaster Universities Arthritis Index (WOMAC)[27] (n=7),[18,28,29,31,33–35] one study[32] utilised the Knee injury and Osteoarthritis Outcome Score (KOOS) [47] and three other studies (exercise intervention) did not report clinical outcomes (self-reported pain and physical function).[19,30,36]

Among the gait retraining studies that reported pain, only 2 out of 4[31,32] showed a significant group x time interaction in knee pain compared to controls, (Cheung et al. 2018[31] -35% difference between groups [*P*=0.028], and Wang et al 2021,[32] −1.43 units on a 0-10 scale (95% CI: −2.55, −0.30) [P=0.014]). Only four RCTs with exercise intervention measured pain; two[34,35] of them reported that the pain reduction was statistically significant when comparing intervention vs. control groups [Lim et al., 2008,[34] -1.3 (0.3SD)] units on a 0-10 scale (*P*=0.00) and Bennell et al., 2010,[35] -2.12 (95% CI -3.24, -1.00) units *P*=0.0003)]. Messier et. al., 2020[29] (diet and exercise trial) presented significant benefits for pain in the D+E vs. Control (exercise alone) of 1.02 units and D+E vs. Diet: 1.13 (*P*<0.002).

Table 2.8 Self-Reported Pain Outcomes

Intervention		Reference	Intervention		Control		Analysis post intervention
			Baseline *Mean (SD)*	**Post-intervention** *Mean (SD)*	**Baseline** *Mean (SD)*	**Post-intervention** *Mean (SD)*	
Gait retraining		**Cheung et al., 2018 WOMAC %**	30% (12.5)	NR	22.5% (12.3)	NR	**Significant mean diff. between groups**: **35% diff (4-66% (95%CI) P=0.028**
		Hunt et al., 2018 WOMAC 0-20	7.6 (0.5)	*4m:* 4.2 (0.5) *5m*: 4.2 (0.5)	6.4 (0.4)	*4m:5.4* (0.25) *5m:*5.3 (0.25)	No significant between-group difference. BL to 4m: P=0.117 BL to 5m: P=0.133
		Wang et al., 2021 VAS 0-10 scale	4.3 (2.2)	NR	4.5(2.0)	NR	**Significant mean diff. between groups: -1.43 (95% CI -2.55, -0.30) P= 0.005**
	Exercise	**Bokaeian et al., 2021 VAS 0-10 scale**	Yoga/MT: 7.8 (1.8) KMS: 6.93 (1.4)	Yoga/MT: 3.5 (2.8) KMS:4.12 (2.99)	7.9 (1.70)	4.4 (1.70)	No significant between-group difference.
		Lim et al., 2008 WOMAC 0-10	Malaligned: 3.3 (1.5) Aligned: 3.6 (1.5)	Malaligned: 2.9 (1.7) Aligned: 2.3 (1.7)	Malaligned: 4.0 (1.40) Aligned: 3.5 (1.60)	Malaligned: 3.6 (1.60) Aligned: 3.4 (1.50)	**Significant mean diff. between groups P=0.007**
		Bennell et al., 2010 WOMAC 0-20	7.7(3.0)	4.9 (4.30)	6.9 (3.30)	6.5 (3.30)	**Significant mean diff. between groups -2.12(95% CI -3.24, -1.00) P<0.0003**

Intervention		Reference	Intervention		Control		Analysis post intervention
			Baseline *Mean (SD)*	**Post-intervention** *Mean (SD)*	**Baseline** *Mean (SD)*	**Post-intervention** *Mean (SD)*	
		Foroughi et. al., 2011 WOMAC 0-20 scale	5.7 (3.30)	3.83 (2.70)	6.70 (3.50)	5.5 (3.60)	No significant between-group difference: P(time*group) = 0.248
		Hunt et al., 2013	NR	NR	NR	NR	NR
		CHO et al., 2015	NR	NR	NR	NR	NR
		Henriksen al., 2017 0-10	5.7 (1.5SD)	NR	6.3 (1.2SD)	NR	NR
	Diet	**Messier et al., 2020 WOMAC 0-20**	D: 6.6 (95%CI 6.1, 7.1) D+E: 6.7 (95%CI 6.1-7.2)	D 6m: 4.9 (95%CI 4.4, 5.3) D 18m: 4.8 (95%CI 4.2, 5.3) D+E 6m: 4.6 (95%CI 4.1-5.1) D+E18m: 3.7 (95%CI 3.1,4.2)	6.1 (95%CI 5.6-6.6)	6m: 4.5 (95%CI 4.0, 5.1) 18m: 4.4 (95%CI 3.9, 4.9)	**Significant mean diff. between groups** **E vs. D+E: 1.02 (0.33, 1.71) P= 0.004** **D vs. D+E: 1.13 (0.44, 1.82) P= 0.001** E vs. D: -0.11 (0.81, 0.59) P=.76

Pain outcomes standardised on a scale 0-10
Results expressed as mean (± Standard deviation) or mean (95% Coefficient Intervals)
NR: not reported; m: month
VAS; Visual analogue 0-10 scale were greater numbers indicates worse pain

2.3.6.2. Physical Function

Self-reported physical function outcomes are shown in Table 2.9. Physical function was evaluated via the WOMAC or KOOS or VAS scales (n=8) in three gait retraining interventions[28,31,32] four exercise studies,[18,34,35] and one diet/exercise intervention.[29]

A significant group x time effect was observed in two gait retraining studies: Cheung et al., 2018[31] [38% (95% CI 11-65%) P= 0.009] and Wang et al., 2021[32] (P<0.04), one exercise trial Bennell et. al., 2010[35] [-6.17 (95% CI -9.41, -2.93) P=0.003], and one diet plus exercise intervention Messier et al., 2020;[29] P<0.003 when compared to controls.

Table 2.9 Self-reported physical function outcomes

Intervention		Reference	Intervention		Control		Analysis post intervention
			Baseline *Mean (SD)*	Post-intervention *Mean (SD)*	Baseline *Mean (SD)*	Post-intervention *Mean (SD)*	
Gait retraining		**Cheung et al., 2018 WOMAC %**	22.5% (1.15)	NR	24.7% (3.1)	NR	**Significant mean diff. between groups: 38% (95% CI 11-65%) P= 0.009**
		Hunt et al., 2018 WOMAC 0-68	28.1 (1.9)	4mo: 13.0 (1.6) 5mo: 14.9 (1.5)	21.4 (1.5)	4mo:16.7 (1.6) 5mo:17.7 (1.6)	No significant between-group difference in KAM 1st peak BL to 4mo: P=0.111 BL to 5mo: P=0.232
		Wang et al., 2021 ADL 0-100	14.6 (2.6)	NR	18.1 (6.7)	NR	**Significant mean diff. between groups: P= 0.046**
	Exercise	**Bokaeian et al., 2021**	NR	NR	NR	NR	NR
		Lim et al., 2008 WOMAC 0-10	Malaligned: 3.14 (1.74) Aligned: 3.32 (1.54)	Malaligned: 2.93 (1.56) Aligned: 2.40 (1.81)	Malaligned: 3.85 (1.45) Aligned: 3.61 (1.57)	Malaligned: 3.65 (1.82) Aligned: 3.24 (1.55)	No significant between-group difference
		Bennell et al., 2010 WOMAC 0-68	24.8(10.9)	16.2 (11.8)	23.7 (11.8)	21.9 (11.0)	**Significant mean diff. between groups -6.17 (95% CI -9.41,-2.93) P=0.0003**
		Foroughi et. al., 2011 WOMAC 0-68 scale	20.6 (11.4)	13.11(10.6)	25.1(11.5)	20.6 (12.9)	No significant between-group difference P= 0.327 (time*group)

Intervention		Reference	Intervention		Control		Analysis post intervention
			Baseline *Mean (SD)*	**Post-intervention** *Mean (SD)*	**Baseline** *Mean (SD)*	**Post-intervention** *Mean (SD)*	
		Hunt et al., 2013	NR	NR	NR	NR	NR
		Cho et al., 2015	NR	NR	NR	NR	NR
		Henriksen al., 2017	NR	NR	NR	NR	NR
	Diet	**Messier et al., 2020 WOMAC 0-68 scale**	D:24.8 (95% CI 23.2, -26.5) D+E:24.6 (95% CI 22.7, 26.5)	D 6m: 18.3 (95% CI 16.6-20.0) D 18m:17.7 (95% CI 15.7-19.8) D+E 6m: 16.5 (95% CI 14.7-18.3) D+E18m: 14.2 (95% CI 12.4, 16.1)	23.1 (95% CI 21.4,24.8)	6m:17.7 (95% CI 15.9,19.5) 18m:17.6 (95% CI 15.8-19.4)	**Significant main effect on** **D+E vs. C: 4.29 (2.07, 6.50) P<0.001** **D+E vs. D: 3.30 (1.09, 5.51) P=0.003** D vs. C: 0.98 (−1.24, 3.20) P=0.38

Physical function outcomes standardised
Results expressed as mean (± Standard Deviation) or mean (95% Coefficient Intervals)
NR: not reported; m: month; D: diet; E: exercise; D+E: diet plus exercise, C: Control
ADL: Activities of daily life scale

2.4. Discussion

2.4.1. KAM results

After searching the published literature to date on the effects of lifestyle interventions on KAM 1st peak, this systematic review only identified 11 RCTs investigating this outcome, with a total of 1,061 participants across all studies. Significant group x time effects on KAM 1st peak when comparing group intervention vs. controls were reported in 3[31–33] out of 4 gait retraining trials (P<0.05) and in one[19] out of seven exercise interventions trials.

An increment of 20% in KAM could increase a six-year risk of radiographic progression sixfold[14] and an 8% increase in peak KAM increases the risk of developing chronic knee pain in four years.[48] The studies presented in this review with positive effects in KAM reported an average of 19% reduction in KAM, and therefore appear to meet the standards for a clinical meaningful effect.

Successful gait retaining strategies were variable, including self-adjustment[31,32] (n=2), and medial thrust.[33] Therefore, no optimum strategy can be identified yet. The optimum duration of interventions is also not known, and 2 out of 3 trials reporting significant effects were relatively short (7 and 5 weeks). However, in those studies which evaluated KAM at follow

up, benefits were not sustainable. Therefore, the challenge lies in the implementation of this technique outside of controlled laboratory environments, with the goal of internalising this as a new motor control pattern which could potentially be maintained during daily activities, The ideal personalised strategy is yet to be identified, in addition to an optimal educational program to implement those patterns.

Only one (Cho et al. 2015)[19] of the 8 exercise interventions improved KAM, with a 24% reduction on KAM 1st peak in the proprioceptive exercise intervention compared to controls. None of the resistance training interventions improved KAM, despite the theoretical basis of an intervention designed to improve muscle strength and thereby improve joint stability and minimise the overloading of the medial joint. Strength improved over time in all exercise studies which evaluated it, although group x time interaction was observed except for Bennell et al., 2010,[35] Exercise routines varied in modalities (machine-based progressive resistance training, elastic bands, ankle cuff weights, isometric exercise, proprioceptive/balance training), intensities and timeframe, making it difficult to compare their outcomes.

It appears to be possible to improve KAM without clinical symptom improvement, (as shown in Hunt 2018 et al.,[28] and Bokaeian 2021 et al.,;[33] and conversely to see clinical improvements when KAM does not improve (as shown in Foroughi et al., 2011[39] & Messiet et al.2020.[29]) These findings likely reflect the fact that the pathway to pain and function in

knee OA is multifactorial and complex, with KAM being only one of many factors aetiological in clinical symptomatology. Additional work is required to define combinations of participant and intervention characteristics which are most likely improve both biomechanical and clinical outcomes, and most importantly, attenuate disease progression to prevent the need for joint replacement and/or mobility disability.

The lack of benefits to KAM in the diet/exercise or diet interventions (Messier et. al.,2020)[29] is consistent with previous studies from the same research team, despite the large weight loss documented. They have suggested that bone-to-bone tibiofemoral compressive forces are more sensitive to changes in BMI than KAM,[15,46,47] weight reduction significantly lowers the loads over the whole lower limb rather than modifying the imbalance in loading specifically over the medial-lateral plateau of the tibiofemoral joint. This research team emphasised the fact that biomechanically there is a slight advantage of dietary weight loss alone, however, the best clinical outcomes are shown in combinations of exercise and diet interventions[15,46] The specific selection of dietary intervention requires additional consideration. This RCT (Messier et. al., 2020)[29] implemented meal replacements once or twice a day, which over the long term may not be sustainable, as the financial, health and phycological impact of such an approach must be taken in consideration. Instead, a holistic, patient-centred nutritional approach should be explored, as there is evidence that changes in dietary patterns can be implemented with positive impact on inflammation as well as additional comorbidities.[50–53]

2.4.2. Clinical Outcomes

Improvements in clinical symptoms were observed in 2 out of 4[31,32] gait retraining and 2/4[34,35] exercise interventions (three exercise interventions did not report pain), and the one diet + exercise intervention[15] (reported in the diet + exercise group when comparing to diet alone or exercise [controls]). Several other studies reported pain improvements in both intervention and control groups over time, without between-group differences. Specifically, Hunt et al., 2018 (gait retraining)[28] and Bokaeian et al., 2021 (exercise and yoga and gait retraining)[33] reported significant pain reduction in all groups including controls; similar to Foroughi et al., 2011[39] who reported pain reduction in intervention and "sham" exercise groups as well as well. It is possible that some of the "control" interventions were effective for pain reduction, as they involved both considerable attention from the research staff as well as low intensity forms of exercise. Future studies may need to include both non-exercise controls as well as various intensities of active interventions to better understand the pathways to pain reduction in knee OA.

2.4.3. Methodological Considerations in Study Designs within this Review

Our ability to synthesise the results of this review into specific clinical recommendations was precluded by the nature of the included studies and methodological limitations, as discussed in the paragraphs below.

First, the large heterogeneity of interventions and assessment paradigms and eligible criteria utilised in the studies in this review precluded meta-analysis being undertaken. There was a substantial variation (Figure 23.2) in sample size (17 to 454 participants), study intervention length (4 to 16 weeks in the gait retraining interventions; 4 to 26 weeks in exercise interventions and 72 weeks in the diet + exercise trial), participant characteristics profile (Tables 2.2 to 2.4): severity of knee OA (from I to IV Kellgren & Lawrence scale of disease severity),[42] knee OA specific location (only medial /medial and patellofemoral / medial and lateral/ no restrictions) and body composition threshold criteria (inclusion/exclusion of obese patients).

Notably, participants' profiles were also quite variable across interventions with regards to the severity of knee OA and BMI inclusion/ exclusion criteria. This is very relevant, as OA, including knee OA, is strongly associated with obesity[50–52,54] and this is one of the modifiable risk factors that exercise, and diet interventions could address as a mechanism to reduce load over the knee. This review identified six RCTs precluding participation for patients with a BMI of ≥34 kg/m^2,[28,30–32,35,36] and only one study was specifically designed for an overweight/obese cohort.[29] Acknowledging the prevalence of OA and obesity in OA, studies implementing such BMI restrictions might result in results that are less generalisable than would be ideal, or potentially exclude the very participants who would be most likely to benefit from the intervention.

The rationale for excluding participants with high BMI may be related to the process of measuring the biomechanical outcomes of interest. Specifically, large volumes of subcutaneous adipose tissue make 3D biomechanical motion data collection challenging. Precise palpation of bony landmarks is difficult in participants with high BMI (≥27.0 kg/m^2 to ≤41 kg/m^2), making it difficult to properly and accurate place passive reflective markers in the same anatomical location across timepoints. Obesity-specific marker sets to estimate muscle and knee joint forces should ideally be implemented to improve reliability of assessments in this cohort. Out of the eleven, only two studies[34,35] reported reliability testing. Both trials performed interclass correlation coefficient tests with excellent results (ICC: 0.96-0.97, and 0.92-0.97, respectively); therefore, any imprecision in data collection in the other studies could have minimised group differences and resulted in a type II error, and thus caution in conclusions drawn is warranted. As a good practice, any trial with motion capture systems should report reliability analysis, especially when assessments are performed more than one week apart.[55]

Five studies[19,29,31–33] specified severity restrictions including only participants with mild to moderate knee OA (only II and III levels of Kellgren & Lawrence scale);[42] in contrast, some others did not set any restriction in this regard,[28,30,34–36,39] (including participants from I to IV levels of Kellgren & Lawrence scale where IV indicates severe radiographic presence of OA.) Interestingly significant benefits in KAM 1st peak were observed only in those studies where radiographic severity were limited to mild and moderate (II and III). If the main

objective is to find interventions to slow the disease progression, it is important to act at the most optimal timeframe of the disease, and it may be that this is at the earlier stages. More studies are needed to confirm this observation.

Laboratory protocols for 3D gait analysis varied across trials, which may have affected the ability to detect significant differences between groups over time. Marker sets ranged from not being reported to up to 38 reflective markers, and although most trials blinded their assessors, no further information referent to staff skills or expertise was reported. Filtering sample rates can determine the quality of kinetics and kinematic data collection, yet this information was only reported in 4/11 trials. Three-dimension modelling varied across studies, and reliability of KAM testing was reported only in 2 out of 11 trials.

2.5. Conclusions

In conclusion, there was some ability to reduce KAM by gait retraining interventions reviewed, with inconsistent improvements in clinical outcomes (2/4 reported improved pain and physical function) By contrast, exercise interventions changed KAM only in one out of eight interventions, although pain and physical function improved significantly in 2 of the 4 exercise studies reporting these outcomes. The only diet+ exercise intervention[29] showed a

positive reduction in knee contact forces but not in KAM 1st peak. In the future, a patient-centred approach with meal-based nutritional intervention and educational programs sustainable in long term should be explored.

Given the heterogeneity of clinical characteristics, (knee OA location and severity, obese/overweight, comorbidities) as well as the variety of interventions reported, it is impossible to define a single evidence-based approach to KAM reduction based on the literature published to date. The intervention with the most positive results appears to be some form of gait retraining. However, the optimum lifestyle intervention has not yet been identified, and it may be that combinations of gait training, exercise, and dietary modification are needed. Longer-term interventions are also needed to determine the sustainability of any lifestyle changes implemented, adverse effects, adherence rates, and evidence of disease progression or need for knee replacement as critical clinical outcomes. Finally, improved standardisation and precision of methodology used to capture and analyse KAM and other biomechanical outcomes in OA trials is vital to advance knowledge in this field.

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CHAPTER 3.

Train High Eat Low for Osteoarthritis Study (THE LO Study): Protocol for a Randomised controlled trial

Chapter Three has been published as:

Guerrero, Yareni, Najeebullah Soomro, Guy Wilson, Yian Dam, Jacinda Meiklejohn, Kylie Simpson, Richard Smith, et al. "Train High Eat Low for Osteoarthritis Study (THE LO Study): Protocol for a Randomized Controlled Trial." *Journal of Physiotherapy* 61, no. 4 (October 2015): 217. https://doi.org/10.1016/j.jphys.2015.05.020.

We have updated the text slightly for inclusion in the thesis.

AUTHORSHIP STATEMENT

This chapter was published in The Journal of the Australian Physiotherapy Association Volume 61 Issue 4 in October 2015. https://doi.org/10.1016/j.jphys.2015.05.020

The co-authors of the paper "Train High Eat Low for Osteoarthritis Study (THE LO Study): Protocol for a Randomised controlled trial" confirm that Yareni Guerrero Ayala has made the following contributions:

- Conception and design of the research
- Conduct and management of study
- Writing of the paper and critical appraisal of the content

As the primary supervisor for the candidate upon which this thesis is based, I can confirm that the authorship attribution statements above are correct.

Professor Maria Fiatarone Singh June 2024

Human research ethics approval committee:

Sydney Local Health District Human Research Ethics Committee

Human research ethics approval number:

(CH62/06/2011-030 HREC/11/CRGH/47) by 31st March 2012

3.1. Background

Osteoarthritis (OA) is one of the most prevalent chronic conditions among older adults,[1] with 1.9 million Australians living with this condition.[2] Among the weight-bearing joints, the medial tibiofemoral joint is the most frequently affected.[3] Increased join loading in people with knee OA may be due to associated pain, impaired gait, balance, lower-extremity muscle weakness, obesity and/or depression.[1] Osteoarthritis is the most common cause of disability in older adults, which imposes great personal and societal burden.[1,3,4] There is no cure for OA currently. Treatment options are often aimed at alleviating symptoms, and in some advanced cases knee replacement surgery maybe the only option.[5] Recent emphasis has been placed on the development of interventions capable of slowing down the progression of disease to reduce the burden of OA.

It is well known that a combination of genetic, lifestyle and mechanical factors contribute to the development, clinical expression, and progression of OA[1,6]. Many

potentially modifiable factors have been confirmed to hasten the progression of knee OA, including abnormal dynamic knee joint load during walking,[3,6] obesity[7] and muscle weakness[8]. Lifestyle programs have great potential to target these risk factors, thus acting as disease-modifying interventions rather than simply providing pain relief. [3,9,10] This distinguishes lifestyle therapy from pharmacologic/analgesic therapy for OA, justifying its role as central to the treatment of OA. Notably, the standard "public health" lifestyle prescription of a healthy diet and increased physical activity[11] (usually walking) are both insufficient to address the above deficits in OA, as well as potentially unrealistic in individuals who may be morbidly obese and markedly restricted in mobility due to pain. This may explain why lifestyle modification is often ignored in favour of pharmacologic management. Therefore, a theoretically grounded lifestyle modification program that better addresses the aetiology and progression of the disease is needed to successfully alter the underlying pathophysiology of knee OA.

Biomechanical assessment of abnormal joint loading has emerged as one of the key intervention targets is recent years. Medial compartment knee load during walking is commonly measured non-invasively using three-dimensional (3D) motion analysis. The primary variable resulting from this analysis is the external Knee Adduction Moment (KAM), which is an indicator of medio-lateral load distribution.[12] The KAM is a torque, which acts to pull the tibia in a more varus position during the stance phase of gait, thereby increasing medial tibiofemoral joint load. Recent interventions, which aim to reduce the progression of OA, commonly target this variable with the aim of reducing disease progression risk.[6]

There are several potential ways to reduce the KAM in people with knee OA, but the optimal approach remains to be defined. One approach is gait modification (gait retraining), which has demonstrated significant reductions in the KAM in some acute exposure as well as longitudinal studies. Various gait modification strategies can yield a variety of effects. Most of the studies have investigated these effects only acutely.[9,13–18] However, the beneficial biomechanical effects seem to also be translated into short-term benefits, including reductions in pain as identified in recent studies.[19,20] Another approach to targeting reductions in the KAM is muscle strengthening, as strength has been inversely associated with the magnitude of the KAM peak,[21] and quadriceps muscle weakness is a predictor of knee OA progression.[21] Since 40% of the gait cycle is unipedal, muscle strength (especially hip abductors) and balance are essential for lower body alignment. Progressive resistance training (PRT), the only specific exercise modality targeting muscle weakness, has been shown to reduce the KAM by 5-10% in healthy subjects.[22] It also encourages the preservation of lean tissue in the face of a weight-loss program, and can improve balance and reduce pain in individuals with OA.[23] Finally, weight loss has been highly correlated to reductions in joint loading [24] with each kilogram (kg) lost associated with a 1.4% reduction in KAM. It is important to highlight that hypo-caloric diets with or without aerobic exercise tend to decrease lean tissue as well, thus supporting the additional role for PRT noted above. A high protein (HP)/low glycaemic index (GI), energy-restricted diet has been shown to be more effective at reducing weight and maintaining weight loss, lean mass and lowering systemic inflammation/insulin resistance than standard energy and fat restriction[25–28] but has never been tested for efficacy in OA specifically.

Thus, we have designed a novel, evidence-based lifestyle intervention, which targets for the first time all the above treatable aetiological factors in knee OA, by including gait retraining, high intensity PRT, and a HP/ low GI, energy restricted diet, in a randomised controlled trial (RCT) known as THE LO STUDY (Train High, Eat Low for Osteoarthritis). The present study will be the first RCT of gait retraining in individuals with medial knee OA over 12 months. It will also be the first trial to directly compare the isolated effects of PRT, HP/low GI diet, and gait retraining in this cohort, as well as the first test of a novel intervention combining all three treatments, in comparison to a lifestyle advice control group.

3.2. Design

We are currently conducting a single-blinded RCT, **THE LO Study,** over one year to investigate the effects of a unique, targeted lifestyle intervention in overweight/ obese adults with symptomatic medial knee OA. This study is an RCT adhering to CONSORT guidelines for conduct and reporting of clinical trials. Ethical approval was obtained from the Sydney Local Health District Human Research Ethics Committee on the 31st of March 2012 (CH62/06/2011-030 HREC/11/CRGH/47) and eligible participants who agree to participate in the study are provided a participant information statement and asked to sign the consent form in person. This study has been lodged with the Australian and New Zealand Clinical Trails Registry (ANZCTR Ref. No. 12612000501842).

3.3. Hypotheses

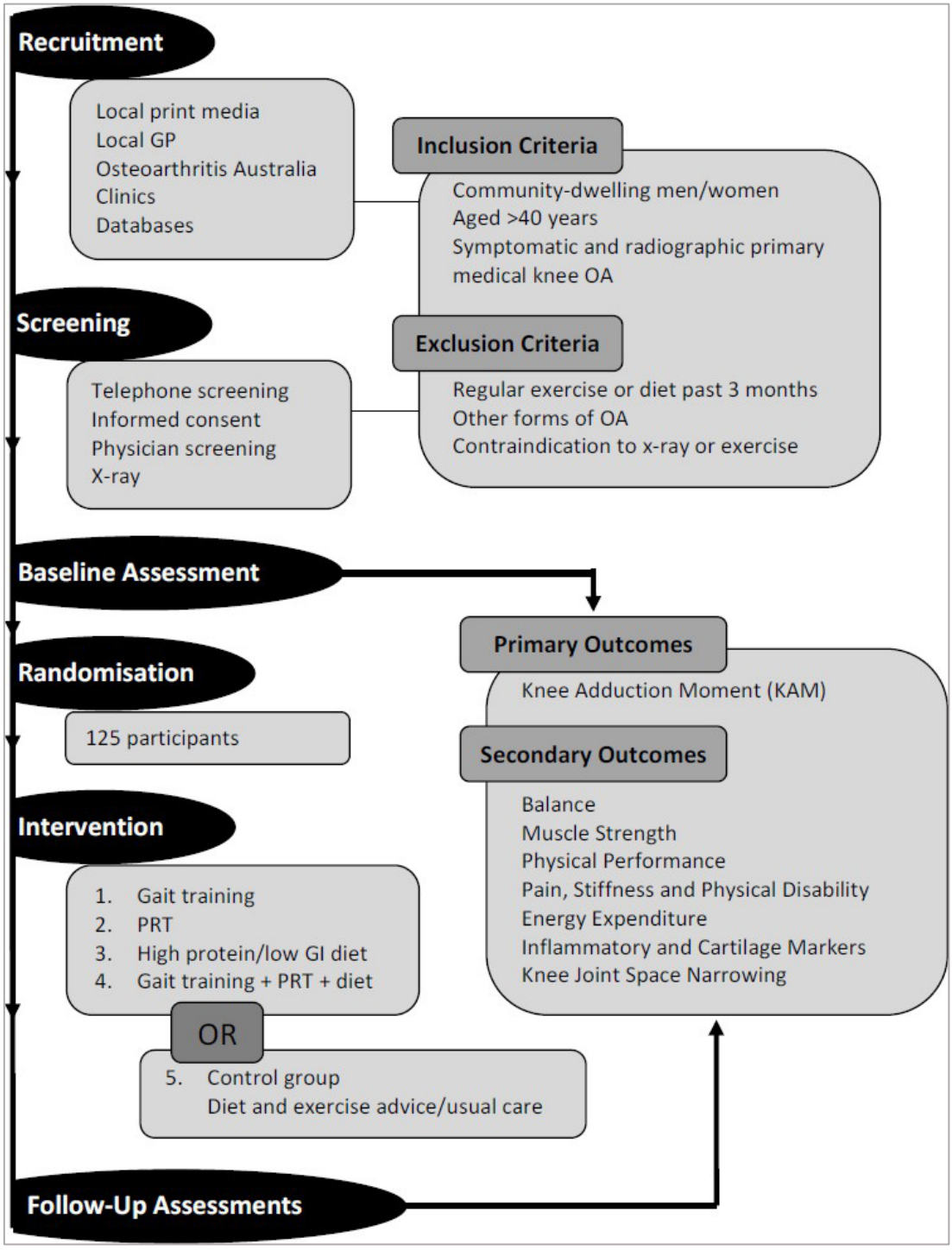
We hypothesise that the effects of the two novel intervention groups: 1) gait retraining, and 2) Combined (HP/low GI energy-restricted diet, high intensity PRT, and gait retraining) will result in significant reductions in KAM compared to the lifestyle advice only Control group. We also hypothesise that the Combined group will be superior to the isolated interventions of the 1) HP/low GI, energy-restricted diet and 2) PRT groups. Finally, we hypothesise that the Combined group will result in a greater range of improvements in secondary outcomes, including muscle strength, functional status, body composition, metabolic profile, and psychological well-being, compared to any of the isolated interventions or Control group.

3.4. Methods

3.4.1. Settings

The study is being conducted at the Faculty of Health Sciences, Cumberland Campus of The University of Sydney, NSW, Australia. Training sessions and measurements are conducted on-site, while X-ray films are acquired at the Radiology Department of Concord Repatriation Hospital, Concord, NSW, Australia. Figure 3.1 shows the flowchart of the study design.

Figure 3.1Flowchart for THE LO Study design



GP: general practitioner; OA: osteoarthritis; KAM: knee adduction moment; PRT: progressive resistance training; GI: glycaemic Index.

3.4.2. Sample Size Estimation

Sample size estimates have been calculated to test the hypothesised differences between the experimental and control conditions for the primary outcome (KAM). A weight loss of about 1 kg has been shown to decrease the peak knee adduction moment (KAM) by 0.496Nm.[24] Therefore, the control group change is based on the lifestyle advice-only control group weight loss of 1.1 kg (=KAM reduction of 0.55 Nm) in the ADAPT trial.[10] Gait retraining benefit is estimated as the average of effects achieved in the literature: Mundermann, et al., 2007[17] (-65%), Fregly et al., 2007[29] (-39%) and in our pilot 4-week trial (The GO study; -48%)We acknowledge potential imprecision since these published trials included only healthy participants, and our pilot data in 10 participants with OA (the GO Study) was limited to 8 sessions over 4 weeks. However, as THE LO study is 12 months rather than 4 weeks in duration, we believe our estimate is conservative. PRT benefit is conservatively estimated as a 10% reduction, similar to the result seen in healthy subjects over 12 weeks.[22] It is expected that the Diet group will reduce their weight by at least 8.9 kg as seen in the IDEA study.[30] Again, this is a conservative estimate, as the novel High Protein/Low GI, energy-restricted diet we are prescribing has been shown to be more effective than typical low fat, energy-restricted diets such as that used in the IDEA study.[25,30,31] The values used for the KAM at baseline and the Standard Deviation (SD) for the effect size (ES) estimates are taken from the baseline of our pilot study of gait retraining (The GO Study).

We have conservatively assumed a less than additive benefit when all three treatments are combined, as shown in Table 3.1, as they may be working through overlapping pathways to some degree. As there is no similar study in the literature, we have estimated the hypothesised change for the combined group as equal to Diet plus Gait Effect Size (ES 1.63). The sample sizes (n) required with alpha 0.05 and beta at 0.2 for each of the treatment arms is shown in Table 3.1.

Thus, if we power the study for the smallest of the ESs for the individual treatment arms vs. control (1.07), we require 15 per group x 5 groups= 75. We have conservatively inflated sample size needs by 40% (to 125) to accommodate anticipated dropout rate, increased heterogeneity in responsiveness to the intervention arms, as well as less than anticipated benefits from the additive intervention over 12 months

Table 3.1 Sample size estimation

Treatment Group	Absolute change in KAM (Nm) or absolute change in body mass (kg)	SD	ES	n/group
Control	-0.55 (1.1 kg weight loss)	14.3	-	-
Gait vs. Control	-16.09 (48% reduction)	14.3	1.07	15
Diet vs. Control	-20.05 (4.6 kg weight loss)	14.3	1.36	10
PRT vs. Control	-7.9 (10% reduction)	14.3	1.20	12
Gait + PRT + Diet vs. Control	-20.05 (4.6 kg weight loss) and -16.09	14.3	2.47	4
Combined vs. Gait	(-36.14) – (-16.09) = -20.05%	14.3	1.39	10
Combined vs. Diet	(-36.14) – (-20.05) = -16.09%	14.3	1.12	14
Combined vs. PRT	(-36.14)- (-7.9) = -28.24%	14.3	1.28	11

Absolute changes in KAM expressed in % (newtons meters) or body mass (kilograms) PRT= progressive resistance training, KAM= knee adduction moment, Nm=Newtons, SD=Standard deviation, ES= effect size, n/group= number of participants per group,*

Therefore, 15 people per group would be required for Gat vs. Control hypothesis testing with allocation of 1:1:1:1:1 for the 5 groups = n of 60 with a 40% dropout we need to recruit 100 participants. However, we will recruit an additional 25 people if there is greater heterogeneity in our cohort than anticipated, due to the inclusion of men and women as well as a broad age range from middle aged to older adults compared to the literature on which the sample size estimates were derived. We have powered the study to look at the effects of the 2 most novel interventions in THE LO study compared to control group (the two which have never been tested in this cohort): Gait vs. Control (ES= 1.07) and Combined vs. Control (ES= 2.47) as well as Combined vs. Diet (ES= 1.12) and Combined vs. PRT (ES=1.28).

3.4.3. Eligibility and Recruitment

Participants are community- dwelling persons aged 40 or above, with medial knee OA in at least one knee according to the American College of Rheumatology (ACR) clinical and radiographic criteria[34]; and have a body mass index (BMI) ≥ 25 kg/m^2. Complete inclusion and exclusion criteria are listed in Table 3.2.

Table 3.2 Inclusion & Exclusion Criteria

Inclusion criteria	Exclusion criteria
• Age ≥ 40 • Competency in English sufficient for assessment and training • Presence of medial Knee OA according to the ACR# • BMI ≥ 25 kg/m^2 • Willing to be randomized and able to commit to study • Not planning to have knee replacement during the study • Able to see and hear sufficiently to participate in planned exercise	• Unstable medical conditions.ǂ • Participation in regular structured exercise > 1/week of moderate to high intensity. • Rapidly progressive or terminal illness. • Secondary osteoarthritis (traumatic or post-surgical), rheumatic disease, gouty or septic arthritis, Paget's disease, pseudo-gout, major congenital abnormalities, hemochromatosis, Wilson's disease, and other rare forms of arthritis). • Amputation above 2nd toe. • Fractured lower limb or any type of lower limb surgery on index knee over the past 6 months. § • Diagnosis of severe recurrent depression/suicidality. ¥ • Severe visual impairment. • Unrepaired abdominal or another known aneurysm. • Myocardial infarction or cardiac surgery within past 6 months. β • Unstable angina or uncontrolled malignant arrhythmias at rest or on exercise stress testing. • Recent retinal haemorrhage or detachment/proliferative retinopathy. • Participating in another research study which would interfere with this study. • Valgus knee deformity (defined as mechanical knee joint alignment of greater than 5° valgus on radiograph). • Inability to comply with study requirements over the course of one year.

ǂ Examples of unstable conditions include uncontrolled arrhythmias, hypertension, hyperglycaemia, symptomatic enlarging hernia, acute pulmonary embolism, deep venous thrombosis, recent or unstable fracture, inflammatory or traumatic joint injuries, etc. Such individuals may become eligible if medical or surgical treatment stabilizes their condition.

 # American College of Rheumatology clinical and radiographic criteria used to make OA diagnosis:[34]
a) Clinical diagnosis:
Knee pain plus at least 3 of the following criteria: Age > 40 years, Stiffness >= 30 minutes, Crepitus, bony enlargement, tenderness at the joint line, no palpable warmth
b) Radiographic criteria:
X-ray diagnosis:
Knee pain plus at least one of the following criteria joint space narrowing, osteophyte formation, subchondral sclerosis
These radiographic features are graded using Kellgren-Lawrence (KL) grading -scale for assessing severity of osteoarthritis based on X-ray findings.

§ Identified by the study physician as the more affected knee with medical knee OA after reviewing radiographs and doing physical examination.

¥ Diagnosis of current or recurrent severe depression: (semi-structured interview conducted by study physician to elicit Diagnostic and Statistical Manual IV (DSM-IV) criteria for current major depressive episode, or current treatment with antidepressant medications, greater than 3 episodes of depression in the last 5 years ("episode": requiring treatment), > 10 episodes requiring treatment over lifetime, past suicide attempts, current bipolar diagnosis, current suicidality or suicidal ideation or psychosis.

β Participants were categorised to be on hold mainly due to potential randomisation into PRT intervention. GP clearance required once they were stable to exercise.

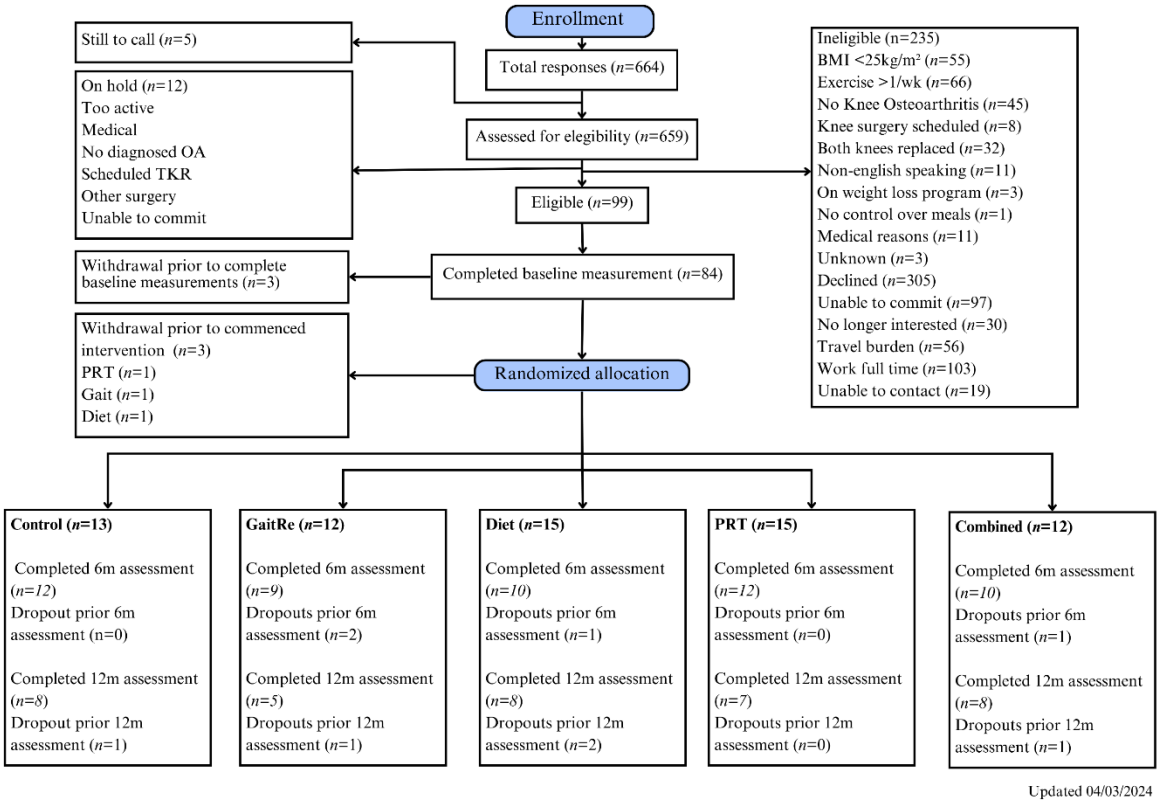
Participants are currently being recruited via Hospital and University intranet advertisements, targeted mail-outs (Arthritis NSW, Concord Hospital) SSWAHS Intranet Arthritis NSW Website, Specialist / GP referral, advertisements in local newspapers and seniors' magazines, brochures distributed to local medical practitioners and pharmacies, as well as social media. We predict that we will need to screen approximately 2000 people to enroll 125 participants. Note: The final CONSORT flow chart at the end of recruitment is presented in Chapter 5.

3.4.4. Screening Procedure

3.4.4.1. Telephone Screen:

Participation flow in the study up to the day of this protocol publication (October 2015) is shown in Figure 3.2. Potential participants initially contact the research assistant by telephone. To assess participant eligibility for THE LO Study, a 30-minute telephone screening form is utilised. The questions on the form are designed to address inclusion and exclusion criteria as well as the participant's basic demographic and contact information, current medical history, medication and physical activity/exercise levels.

Figure 3.2 CONSORT flow chart table



n: total number of participants, OA: osteoarthritis; TKR: total knee replacement; PRT: high intensity progressive resistance training intervention group; GaitRe: gait retraining intervention group; Diet: High protein, low glycaemic index restrictive calorie diet intervention group, BMI: body mass index;

3.4.4.2. Investigator Review:

The study's chief investigator reviews telephone-screening questionnaires upon completion. Participants are informed about their eligibility or placed on hold for further medical information and/or investigation(s). An information package is sent to the eligible participants including an appointment with the study physician, brief outline of the assessment procedures, and information regarding the screening and testing venue. If not eligible, the research team asks the participants for permission to retain their contact details, in case their situation changes over time, and they become eligible later. To obtain medical clarification for participants, letters are sent to their respective doctors along with a signed permission slip from the participant indicating that the physician may release relevant medical information.

3.4.4.3. Radiographs:

To determine the presence of radiographic medial knee OA, potential participants undergo bilateral weight-bearing posterior-anterior knee radiography using a SynaFlexerTM Positioning Frame and Phantom[32] in a standing, semi-flexed position. The severity of radiographic disease will be rated at baseline and follow- up using two clinical scoring systems: the Kellgren and Lawrence OA score[33] and the Osteoarthritis Research Society International (OARSI) atlas of radiographic features.[34] The index knee is the knee that participant identifies as his/her most painful knee; usually but not always,

this is the knee that is worse on x-ray findings and worse on physical exam findings by team leader.[35] If pain and x-ray findings are equal, the study physician makes a clinical judgment based on all data.

3.4.4.4. Physician Screening:

To determine final eligibility, a structured clinical interview including physician screening, radiographs' review, clinical history, and medication record list is performed by the study physician prior to remainder of baseline testing.

3.5. Randomisation

An independent researcher not involved in testing, or training prepares concealed randomisation in variable blocks (block size = 4-8), utilising a computer-generated random number sequence (http://www.randomization.com), created by Dr. Gerard E. Dallal, Tufts University) for the participants who complete the baseline assessments.

Stratification by sex and BMI (≤25-30 kg/m^2 vs. ≥30 kg/m^2) is being carried out. Study identification and sequential treatment allocations are enclosed in numbered, opaque sealed envelopes, and distributed to each participant after baseline assessment. Participants are then designated to one of the five study arms for one year in a balanced ratio according to the above stratification. Trainers in each study arm are informed and the outcome, while all assessors are blinded to the allocation. Participants are reminded

before each assessment visit not to disclose any details of their randomisation allocation to the assessors. Table 3.3 provides detailed information of visits required for each intervention.

Table 3.3 Details of Visits for Testing and Training Sessions

	Control group	Diet group	GaitRe group	PRT group	Combined group
Assessment sessions (Number of time points)	3: Baseline, 6-month 12-month	3: Baseline, 6-month 12-month	3: Baseline, 6-month 12-month	3: Baseline, 6-month 12-month	3: Baseline, 6-month 12-month
Training sessions (over 12 months)	1 visit: At the beginning of the study	17visits: 1st month: once weekly 2nd & 3rd month: once fortnightly 4th to 12th month: once monthly	26 visits: One fortnightly session	104 visits: Two weekly sessions	104 visits: 51 PRT sessions only 17 PRT + diet sessions 26 PRT + Gait sessions
Health Status Check	Weekly: All by telephone call, emailed or posted.	Weekly: During the training period, these will be done in person.	Weekly: During the training period, these will be done in person.	Weekly: During the training period, these will be done in person.	Weekly: During the training period these will be done in person.

PRT: high intensity progressive resistance training intervention group; GaitRe: gait retraining intervention group; Diet: High protein, low glycaemic index energy-restricted diet intervention group.

3.6. Interventions

3.6.1. Gait Retraining

Several gait modification strategies have been shown to reduce the KAM.[15,20,29,36] According to a systematic literature review,[18] the following gait modification strategies have demonstrated immediate reductions in the KAM at varying stages of the gait cycle: increased medio-lateral trunk lean, toe-in gait (walking with feet internally rotated), toe-out gait (walking with feet externally rotated) and medial knee thrust gait (a dynamic medialisation of the knee joint during stance). More recent cohort studies also demonstrated effective reductions in the KAM over time, which has been demonstrated with a toe-out gait modification over 10 weeks[19] and toe-in gait modification over 6 weeks in people with medial knee OA..[20] Whilst there is evidence that immediate load-modifying effects of toe-in and toe-out gait may differ throughout the stance,[37] both studies reduced the early stance peak KAM over the time and achieved symptomatic relief. Furthermore, there is no consensus on the optimal gait modification to implement or the magnitude of modification required, and a single gait modification might not suit all participants or may produce minimal effects. Accordingly, the combined effect of more than one gait modification may yield superior biomechanical effects with more subtle gait changes.[13]

The potential effectiveness of those gait modification strategies for our proposed intervention is supported by Wishart and Lee,[38] who reported that older adults in particular benefit from concurrent augmented visual feedback when learning a bimanual task. Similarly, we have shown that concurrent augmented visual feedback significantly improved patterns of work during an exercise task, compared to no augmented feedback.[39]

In this study, gait retraining will be conducted in a motion analysis laboratory under the supervision of an exercise physiologist trained in biomechanics. We aim to reduce the peak KAM by at least 20% over time. For the supervised portion of the gait retraining intervention, participants will attend a one-hour gait retraining session every fortnight for one year. At the first session, they will be educated on the significance of joint loading, the KAM and the main objective of this study arm. A larger peak observed indicates greater loading placed through the medial "inner" compartment of the knee joint. The participants' natural gait pattern and joint kinetics will be assessed at the initial session for target level of 20% load reduction to be set. Participants will undergo 3D gait analysis using a force platform (model 9281, Kistler Group, Winterthur, Switzerland) and 14-camera motion capture system (Eagle Cameras, Cortex 5 software, Motion Analysis Corporation, USA Rohnert Park, CA, USA). The motion of the affected lower limb will be tracked using 16 passive-reflective markers during habitual gait to evaluate the baseline early stance KAM 1st peak, mid-stance KAM, gait velocity and measure of pain. The KAM will be available graphically in real time using Kintools (Motion Analysis Corporation, Rohnert Park, CA, USA). Participants will be asked to "just walk" along the

laboratory walkway with no instructions provided regarding a modified gait. Three trials will be captured. These variables will be used to monitor biomechanical progress throughout the year by the trainer.

As part of the second session, participants will be made aware of the range of gait modification strategies via a PowerPoint presentation and will be able to choose the modification to attempt first. Participants will then attempt to practice all gait modification strategies while walking in the laboratory. The trainer will aid skill acquisition by the provision of regular verbal feedback or visual feedback using a mirror. Standardised instructions will be provided to them, and each strategy will be systematically tested. Their trials will be recorded, and their knee kinematics will be monitored until an optimal benefit is reached based this on peak KAM reduction measured from the real time graphs.

For subsequent sessions, participants will return to the biomechanics laboratory and will be instructed to perform strategies that led to the greatest reduction in their peak KAM from the previous session. Once an optimal gait modification (or combination) is identified and personalised, the participant will be instructed to perform this on a regular basis. This strategy of personalised gait modifications has been previously supported by Uhlrich et al. 2018[60] with successful results. Each session will provide further feedback about their progress in mastering the gait strategy. Participants will be instructed to perform their modified gait strategy(ies) at home using a mirror each day for a minimum of 10 minutes and to use the modified gait strategy(ies) during all daily walking.

Adherence and pain will be monitored via a daily logbook for the entire 12 months and reviewed by the trainer fortnightly.

3.6.2. Progressive Resistance Training (PRT)

Participants assigned to this group will undergo high intensity PRT twice a week over 12 months. Training sessions will average 60 minutes and include the following exercises: bilateral leg press, unilateral knee extension, bilateral knee flexion, unilateral standing hip adduction and abduction, bilateral chest press, triceps extension and seated row. Keiser (Keiser Sports Health Ltd., Fresno, CA USA) pneumatic strength training equipment, which allows for low impact and smooth, continuous progressive loading will be used. The specific protocol for the strength training has been successfully used in the Resistive Exercise for Articular Cartilage Health (REACH) study by our team and is supported by a large RCT evidence base for the use of PRT in knee OA[40] Knee extensors will be trained unilaterally (3 sets of 8 repetitions) to maximise isolation of the muscle groups and training adaptations, as well as to customise loads for asymmetry in strength due to underlying OA.

Initial resistance will be set at 50% of the baseline one repetition maximum (1RM) and will be increased to 80% of the participant's initial 1RM over the first month of training. The 1RM will be reassessed every 3 weeks and the resistance will be increased progressively at each session by approximately 3% of the new 1RM. The load will be

further titrated to maintain a training intensity between 15 and 18 on the Borg Rating of Perceived Exertion Scale,[41] while still allowing participants to achieve their full unweighted range of motion in good form (modified as needed for joint pain) for all exercises. To maximise the potential of full body strength and individualise rehabilitation of pre-existing musculoskeletal concerns, novel free weight or machine-based exercises will be introduced after every 12 sessions or progressed throughout the training. These exercises may include shoulder lateral raise, shoulder external and internal rotation, shoulder/scapula retraction, ankle cuff exercises, back extension, unilateral leg press, bilateral knee extension, hip extension and hip flexion, ankle dorsiflexion, calf raise, bicep curl. Isometric exercises and ankle cuff exercises for lower extremities will be used to help increase strength if a participant is unable to use the machines correctly.

With each strength training equipment item, the following protocol will be used:

- The participant 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 participants why emphasis is placed on proper breathing technique (exhaling on exertion, avoidance of Valsalva manoeuvre).
- The participant will be assisted to mount the piece of equipment and the settings recorded to ensure proper biomechanics so that they can be replicated for all

training sessions and follow-up assessments.

- The participant will perform 3 sets of 8 repetitions on each machine. Each repetition will be slow for both the concentric and eccentric phase (3-4 seconds), with a 2-3 second rest between repetitions and 60-90 seconds rest between sets.

The participants will be encouraged to discuss with the trainer any problems that arose before, during and after each training session regarding muscle soreness, dizziness, light-headedness, or any discomfort of any kind. Alternating between upper and lower body exercises will be implemented to limit fatigue in particular muscle groups that may impair performance of subsequent exercise.

A modified version of exercises will be prescribed for patients experiencing pain or discomfort. Table 3.4 lists the exercises most commonly requiring modification.

Table 3.4Progressive Resistance Training (PRT) Exercise Modification

Exercise	Difficulty/Symptom	Modification	Instructions And Feedback
Knee Extension	• Patello-femoral pain	Isometric contraction against static resistance hold for 10 seconds (1 repetition) If unable, hold as long as possible Repeat 23 or 15 repetitions If pain is still present: Do sub-Max isometric contractions	Alternate legs. 10 seconds rest between contraction Observe effort and ask patient to visualize pushing against the bar as hard as they can. Place the participant's hand on their muscle for them to ascertain how the muscle feels when they are performing at a maximum effort.
	• Shin pain	Extra padding on padded bar	No pain or pressure
	• Baker's Cyst (swelling behind the knee joint)	Sit further forward on the seat Minimal contact or pressure behind the knee at the seat Extra pad behind the knee,	
	• Pain (during eccentric phase)	Start at 80 degrees and perform the eccentric phase slowly	
Hip Machine	• Knee pain	Move roll bar higher up thigh to avoid touching the knee	No pain
	• Hip pain	Isometric contraction against static resistance	No pain
	• Vertigo	Hold for 10 seconds (1 repetition) Repeat 15 or 23 repetitions Use ankle cuffs Perform the abduction and/or adduction lying prone on a plinth Can perform hip abduction lying on the side	

3.6.3. High Protein / Low Glycemic Index Energy-Restricted Diet. You keep switching between Title Case and Sentence case for Headings and Sub-headings- you need to choose one and fix this throughout the thesis

Participants in this group will be counselled to adopt a HP/ low GI energy-restricted diet, with the goal to reduce weight by 5-10% over 12 months with a sustainable change in eating patterns, improved food choices and moderate energy restriction. Total daily energy intakes will be prescribed according to participants' energy requirements, as estimated using the Harris-Benedict equation with an appropriate activity factor and 2000kJ (500 calories)/day deficit, to encourage a moderate weight loss amongst participants. Four levels of daily energy will be used in the study (5, 7, 9 or 11MJ/day) and participants will be prescribed a diet energy level closest to their calculated energy intakes. The target macronutrient composition is 45% of energy from carbohydrates, emphasising low glycaemic sources, 25-30% from protein and 30% from fat. This macronutrient distribution is similar to the average Australian diet,[42] but protein is modestly higher (~5% of energy), and the GI index is lower. The diet will aim to be as low in GI as practical and achieved by replacing higher GI carbohydrates (e.g., conventional white or wholemeal bread, breakfast cereals, potatoes) with lower GI carbohydrates (e.g., Burgen® grain breads, oats, pasta, Basmati rice). A GI diet value of <50, and a low glycaemic load (GL) diet with a value of 77 will be the goal for participants and will be calculated using published data for Australian foods.[43] In addition, the diet will emphasise lean sources of protein, monounsaturated/ polyunsaturated fats, and restriction of saturated and trans fats.

Individual counselling sessions will be conducted by the study dietitian to identify current dietary patterns, recommend specific changes, identify barriers to dietary changes and provide appropriate strategies to assist changes in behaviour with the participants. Nutrition counselling will incorporate a combination of behavioural theory, cognitive behaviour, and trans-theoretical model in modifying dietary patterns, weight and health risks.[44–47] This will be accomplished with individual sessions with the dietitian once per week for the first month, then fortnightly for the next 2 months, then monthly for the final 9 months for a total of 17 sessions. Most of the nutrition educational materials will be delivered during the first 12 weeks, with information on energy restriction, high protein and low GI addressed within the first 4 weeks and reiterated during sessions thereafter in combination with addressing behaviour modification. The study dietitian will also be available for telephone counselling and email queries outside of scheduled visits for additional support if required. Participants will be provided with a comprehensive written manual explaining all aspects of the diet, including sample meal plans. To further encourage dietary adherence, key foods will be provided in the form of a hamper (sample bag) and food, to give examples of low GI choices available.[43]

All participants will have their waist circumference taken and will be weighed at each diet visit using the same calibrated scale at the laboratory. In addition, participants will be instructed to record their weight and measure their waist circumference weekly and complete a weekly 24-hour food dairy in a pocket-sized logbook provided at the beginning of the program. Regular self-weighing and monitoring has previously been

shown to encourage and significantly enhance compliance and weight loss efforts.[48,49] Participants' logbooks will be reviewed at each visit or phone calls will be made to ensure compliance and to address any problems or concerns encountered by the participant. Additionally, 24-hour dietary recalls will be conducted during diet appointments in conjunction with completion of 3-day food records at baseline, 6 months and 12 months to assess and monitor dietary compliance.

Participants identified to have renal impairment or proteinuria unrelated to urinary infections requiring limitation to protein intake will not be prescribed the higher protein portion of the diet. However, they will be advised to follow the same low GI, reduced-energy diet prescription, and a referral to a nephrologist will be recommended.

3.6.4. Combined Group

Participants assigned to this group will receive a combination of all the components of gait retraining, high intensity PRT and HP/ low GI energy-restricted diet interventions. The visits to the campus will be offered in combined sessions to minimise the burden in this group; thus, participants will attend 104 visits (2 days per week for 12 months) with 61 visits for PRT only (60 min approximately), 17 sessions for PRT and diet consultation (120 min approximately) and 26 for gait retraining plus PRT (120min approximately). Gait retraining will be conducted prior to PRT when they occur on the

same visit to minimise fatigue. Adequate rest periods will be provided between all intervention components.

3.6.5. Control Group

Participants in the Lifestyle Advice Control group will receive standard healthy eating and physical activity advice accompanied by written pamphlets. General lifestyle advice will be given at one education session by a trainer and participants will have the opportunity to ask any questions through their weekly phone calls. Dietary advice will be based on the Australian Guide to Healthy Eating,[42] including information on recommended serves of food each day (e.g., breads and cereals, fruit, vegetables, dairy, meat and alternatives) as well as serving sizes and healthier choices for certain foods (e.g., low fat dairy products, lean meats). No specific energy or macronutrient distributions will be set for this group, however the Australian Guide to Healthy Eating reflects macronutrient distributions of 15-21% protein, 52-57% carbohydrate and 27% fat.[25] In addition, there will not be a specific weight-loss target set for these participants throughout the study period, although weight loss will not be discouraged. Physical activity advice will be based on the Australian Government's National Physical Activity Guidelines of at least 30 minutes of activity on most days of the week.[11] No structured or supervised exercise will be provided.

3.7. Adverse Events

Adverse events will be monitored by a weekly questionnaire, provided in person or by telephone call, and proxy information obtained whenever necessary to minimise missing data. Additionally, participants will be requested to report all changes in medication, health care professional visits, new diagnoses, acute illness or allergies, changes in daily physical activities or any new symptoms. Any musculoskeletal, cardiovascular event or metabolic abnormality attributed to study protocols will be considered as adverse events.[50] Case conferences will be held weekly to discuss all study participants in terms of adherence, changes in health status, intervention modifications, adverse events and behavioural issues that were deemed relevant to study participation.

3.8. Outcome measures

Participants will be assessed at baseline, six months and 12 months (immediately after completion of the 12-month program) by blinded outcome assessors. Blinding of participants is not possible due to the nature of the interventions.

3.9. Primary outcome

Peak KAM during the early stance phase of gait will be obtained in 3D analysis laboratory. Data will be collected using a 14-camera Motion Analysis system (Eagle cameras, Cortex 5 software, Motion Analysis Corporation, Rohnert, CA. USA) synchronised with three force plates (Model 9281, Kistler Group, Winterthur, Switzerland) embedded in the laboratory floor. Spatiotemporal, kinematic, and kinetic will be computed from inverse dynamics analysis of an eight-segment body model defined by 30 markers over anatomical landmarks on the trunk, pelvis and lower limbs. The maximum KAM between heel contact and 50% of stance will be derived and normalised to body weight times height (Bw*Ht). The early stance peak KAM has been shown to be highly reproducible, with a mean difference between test sessions of 0.1%.[51] This biomechanical analysis will be used to assess secondary gait variables, including the KAM impulse, KAM late stance peak, peak knee flexion moment, cadence, velocity, step length, kinematics of the ankle, knee, and hip.

3.10. Secondary outcomes

Radiographic joint-space width (JSW) has been recommended as primary structural endpoint in clinical trials of knee OA by the 1999 guidance document of the Food and Drug Administration (FDA). The JSW represents both the thickness of articular cartilage as well as meniscus extrusion.[52] Some of the variation associated with serial

JSW measurements in clinical trials is caused by image positioning; minimising this source of variation is therefore the key to effective multi-centre radiography.[53] In our study, reduction in radiographic JSW will be measured and recorded with the SynaFlexer™ Positioning Frame (Synarc, Inc.; San Francisco, CA). and Phantom during fixed flexion standing posterior-anterior (PA) knee radiography[32] to determine the change in medial minimum JSW between baseline and 12-months follow-up. The JSW (in millimetres) will be measured using digitised image analysis with Holy's software -ß13™ (Actibase, Lyon, France).[54] In addition, the severity of radiographic disease will be rated at baseline and follow-up using two clinical scoring systems, the Kellgren and Lawrence OA score[33] and the Osteoarthritis Research Society International (OARSI) atlas of radiographic features.[34]

Additionally, several targeted outcomes will be measured as shown in Table 3.4

Table 3.5 Secondary Outcomes Measured

Outcome Measured	Explanation	Description
Health Status	Medical history	Physician completes medical history record and physical examination.
	Habitual physical activity level	Sedentary behaviour, physical activity and sleep quality are measured with two Actigraph® accelerometers worn for eight days. Physical activity is measured with the Actigraph worn on the waist and sleep time with the Actigraph allocated on the wrist. The software program ActiLife (Version 6.11.4) ® is used to initialize (set the start times), download, and analyse data from both monitors.
	Dietary status	Three-day food record is completed by the participants to calculate the energy intake and food variety.
Biochemical status	Serum samples for nutritional, biochemical, and hormonal factors	After 12-hr fasting, a blood draw is taken to measure adipokines and inflammatory markers (serun leptin, serum adiponectin and serum interleuquin-6, high-sensitivity) creatinine clearance, total protein, and 25- OH vitamin D level; Genotyping is used to identify genetic OA risk factors
Cardiovascular health	Blood Pressure	Blood pressure measurement is taken in triplicate and fasted state after lying down on a flat surface for ten minutes in supine position.
	24-hr Blood Pressure	Twenty-four-hour ambulatory blood pressure monitoring awake (every half hour from 5:00AM to 10:00PM) and nocturnal means (every one hour from 10:00 PM to 5:00 AM) circadian rhythm is also obtained utilising the ambulatory blood pressure monitor model: TM-2430 (A&D Co., LTD, Abingdon, Oxon, U.K.).
Body composition	Anthropometry	*Standing height*: Stretch stature is measured only during baseline with a measuring tape and wall mounted Holtain stadiometer (Holtain Limited, Crymmych Pembs. UK)

Outcome Measured	Explanation	Description
		Body mass (weight): Naked weight (weight in gown – weight of gown) is measured utilizing electronic scales (AND HW (<100kg) & SECA Wedderburn (>100 kg)
		Waist circumference: the distance between the iliac crest and lower costal border is palpated and both sites marked to determine the waist mid-way. A flexible tape measure (Graf co®, GRAHAM FIELD, Model # 17-1340-2) is placed around this point
		All of them are being obtained in triplicate after 12-hr fasting and body mass index (BMI) is calculated as fasting body weight (kg/height m^2).
	Dual-energy X-Ray absorptiometry (DXA scan)	Dual-energy X-ray Absorptiometry (DXA) is obtained in fasting condition to determine whole body and regional muscle, fat and bone mass as well as bone mineral density using the Lunar Prodigy DXA Scanner and the enCORE software. (GE Medical Systems Lunar, Madison, Wisconsin).
Exercise Capacity	Muscle strength and endurance	Maximal strength and endurance muscle measurements are obtained using the digital K400 Keiser pneumatic resistance machines (Keiser Sports Health Equipment, Inc. Fresno, CA).
		Exercises performed includes seated leg press, unilateral knee extension, bilateral knee flexion, standing unilateral hip adduction and abduction, chest press, triceps push down and seated row

Outcome Measured	Explanation	Description
	6-minute walk test (6MWT)	Six-minute walk test is a proxy for overall cardiovascular endurance capacity (aerobic capacity). In addition to cardiovascular efficiency, however, in older adults it may be associated with muscle strength and endurance, balance, orthopaedic or neuralgic abnormalities, obesity, self-efficacy, and other contributants. 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 older volunteers as well as healthy older adults.[43]
Physical performance[55]	Habitual and maximal gait speed Conduction Velocity (CV)	Habitual and maximal conduction velocities are assessed over 2 m (Ultra-timer: Raymar, Oxfordshire, UK) with the average of two times taken as Habitual (CV = 8.7%) and Maximal (CV = 7.6%) gait velocity respectively.
	Chair stand	Chair stand test is used as an indicator of lower extremity power, or the ability to generate high forces rapidly, with participants primarily utilizing the hip extensor and knee extensor muscle groups
	Static balance	Static balance is assessed up to 15 seconds in five different positions (feet apart in parallel stance, feet together in parallel stance, half tandem stance, tandem stance, one legged stance and one-legged stance with eyes closed), without the use of assistive. Total static balance is calculated by summing the time recorded for each of the six stances
	Tandem walk	Participants complete a 3-meter forward tandem walk along a marked course with and without a cognitive distracter task (verbal fluency) to assess dynamic balance.
	Stair climb	The purpose of this test is to climb stairs as rapidly as possible to enable the calculation of leg power (Watts)⊥

Outcome Measured	Explanation	Description
Demographic survey	Demographics	The Demographic survey will provide specific information of the study population including, sex, education level, and economic situation.
Depression and self-efficacy	Geriatric Depression Scale (GDS)	The (GDS) is a 30-item self-report assessment designed specifically to identify depression in the elderly. It has been validated against therapist ratings of depressive symptoms[56]
	Ewart Self- Efficiency Scale (EWART)	Participants are asked to rate on a scale of 0 to 100% (from not confident at all to very confident) how confident they are that they could perform the task mentioned, right now. Tasks include lifting objects, climbing flights of stairs, walking, jogging & performing push-ups.[57]
Quality of life, pain, and physical activity assessment	Western Ontario and McMaster University Osteoarthritis Index (WOMAC)	The extensively validated WOMAC questionnaire will be used to assess pain, stiffness, and physical function in patients with hip and / or knee osteoarthritis (OA) WOMAC consists of 24 items divided into three subscales: pain, stiffness, physical function based in the past 7 days.[58]
	Physical Activity Scale for the Elderly (PASE)	PASE is a brief, easy tool for assessment of short-term physical activity in epidemiological studies of the elderly for the past 7 days. It is designed for community-dwelling older adults ages >65 years. This questionnaire addresses the activities commonly engaged in by elderly in addition to sport and recreational activities.
	Physical and mental health summary scales (SF36) ®	The SF-36, Version 2 (norm-based) is a multi-purpose, short-form health survey and includes eight generic health concepts and 2 summary scales. The SF-36 has proven useful in surveys of general and specific populations, comparing the relative burden of diseases, and in differentiating the health benefits produced by a wide range of different treatments.[59]

ǂ Power is calculated from the formula: Power (watts) = $\underline{(M \times D) \times 9.8/t}$ where: M = Body Mass (NN), D = Vertical Distance (m), t = Time (s) and, D = vertical height of the staircase = height of 1 step in meters × number of steps.hr: hour(s); kg: kilograms; BMI: body mass index, m: meter(s); OA: osteoarthritis

3.11. Discussion and Conclusions:

At the time of protocol publication (October 2015), recruitment is 80% complete and it is anticipated to conclude at the end of 2015. The most common reasons for ineligibility have been difficulty to commit time, or being too physically active, rather than medical exclusions, attesting to the potential generalisability of this volunteer sample to typical ageing sedentary adults with multiple stable chronic illnesses. Dropout rate has been lower than expected at 9.7%, which is considered excellent for a long-term intensive intervention trial in an overweight/obese cohort.

Our primary outcomes are anticipated to be available in early 2017. This information will provide novel and robust evidence for the efficacy of strength training, HP/low GI energy-restricted diet and gait retraining for people with knee OA. This study conforms to all CONSORT criteria for the conduct and reporting of RCTs, making it relatively unique in the field to date. Our secondary outcomes will enable the first comprehensive investigation of the relative and combined benefits of strength training, gait training and HP/low GI energy-restricted diet on inflammatory markers for disease progression, depressive symptoms, self-efficacy, quality of life, body composition, musculoskeletal strength, pain due to OA and metabolic health. These outcomes will not only provide evidence of the potentially broad benefits of THE LO Study interventions in this cohort, but also clarify the hypothesised mechanisms contributing to any observed physical outcomes. If successful, we will have initiated a paradigm shift in the clinical approach

to OA: from simply analgesia and palliative treatment to an ability to offer those who suffer from this condition a potent *disease- modifying treatment*.

In summary, THE LO Study will test a novel three component non-pharmacological intervention that targets middle aged and older adults with medial knee OA and is compared to isolated interventions or a usual advice control. By implementing a regime of physical exercise, diet and gait modification we aim to empower the individual, contribute to their physical and psychological health and fitness, slow the progression of the disease and associated co-morbidities, and ultimately improve quality of life and reduce suffering in this growing population.

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CHAPTER 4.

Retest Reliability Study of Three-Dimensional Kinematic Gait Modelling Parameters and Anthropometric Measurements in Overweight /Obese Adults with Knee Osteoarthritis in a Subset of Participants in the Train High Eat Low for Osteoarthritis Study THE LO Study

4.1. Introduction

Three-dimensional (3D) motion optoelectronic systems are identified as a gold standard of practice in research and clinical settings to allow objective and quantifiable 3D biomechanical gait analysis. The system cost and complexity require high levels of expertise, and time to collect and analyse the 3D biomechanical data. Data recorded by a 3D optoelectronic motion capture system is the 3D positional data of the retroreflective markers placed on anatomical landmarks that is then used to model 3D body segments during the motion. This 3D biomechanical modelling relies on precise marker placement on the specific anatomical points on the human body (bony landmarks).[1] and marker placement is therefore one of the most common sources of error that influences the kinematics of knee joint.[2]

Marker placement on the specific anatomical points on the human body has been identified as the largest source of variability.[1,3–6] An analysis conducted by Gorton et al. (2009)[5] across twelve 3D motion analysis laboratories including 24 different examiners reported a 20% decrease in variability in kinematic measurements after implementation of a standardised protocol at each laboratory.[5] This same study reported that more than 75% of the overall variance in kinematic parameters when there is an absence of a standardised protocol is most likely due to variability amongst examiners defining where markers are placed on specific anatomical points on the human body. Furthermore, this issue may be exacerbated in cohorts where bony landmarks are more difficult to palpate

due to overlying adipose tissue (e.g., overweight or obese populations) or inflammation (e.g., joint effusions or oedema).

Traditionally, reliability is defined as the consistency of measurements on a test or the absence of measurement error.[7] In reality, some amount of error will always be present from various sources whether it is human and/or measurement tool precision when collecting repeated measurements. Therefore, reliability may be considered as the amount of measurement error that is acceptable for the effective practical use of a measurement tool.[8–10] In good practice, reliability analysis should be undertaken in all investigations for any sources of error including the validation of new measurement tools and/or equipment, new techniques, unique or novel cohorts, as well as to establish inter-rater reliability when more than one assessor is used.[7]

These reliability procedures have been used in the 3D motion analysis field, more specifically, in gait biomechanics to test reliability among multiple laboratories and independent raters[11] to document within- and between-day reliability of 3D data.[12] A recent systematic review has identified and evaluated the current evidence regarding reliability studies in 3D kinematic gait analysis data.[13] The authors concluded that although most errors in gait analysis are probably 'acceptable', they are not small enough to be ignored during data interpretation. Thus, reliability analysis should be always conducted prior to any further analysis and precented in peer-reviewed manuscripts in this field. Acknowledgement of the critical importance of the quality of marker placement for the accuracy of the 3D kinetics and kinematics measurement derivates is

why this is a key part of the Australian and New Zealand Clinical Motion Analysis Group (ANZ-CMAG) Clinical Practice Recommendations.[1]

To ensure that the protocol of the 3D gait analysis study that was designed as the primary outcome of THE LO Study (as outlined in the Protocol in Chapter 3) was in accordance with the new 2023 ANZ-CMAG Clinical Practice Recommendations[1] (acknowledging that these recommendations were published after THE LO protocol was designed and subsequent data collection completed), this study's reliability needed to be established. This is important, as the primary outcome of THE LO Study was the net knee joint adduction moment (KAM) during habitual gait. This variable is calculated using inverse dynamics and defined as the resultant component when the ground reaction force vector passes through the medial side of the knee and the perpendicular distance from the load vector to the centre of the joint.[14,15]

The KAM is a surrogate measure, well-suited to estimate the medial-lateral force distribution throughout the whole stance phase of gait.[16] Epidemiological studies of patients with medial knee OA demonstrate that a greater KAM at baseline can predict radiographic OA progression at 6 years of follow-up, where the risk of progression of knee OA increased 6.46 times with only a 1% increment in KAM.[15] In fact, a recent systematic review and meta-analysis in similar cohorts demonstrated increased odds ratio of medial knee OA progression with greater baseline peak KAM (OR: 1.88 [95%CI: 1.08, 3.29]).[17] Therefore the analysis of KAM while walking via 3D motion capture system is ideal to study the risk of progression of knee OA during intervention studies. However,

due to the prevalence and great impact of obesity in people with knee OA,[18] accurate measurement in this cohort is hampered by the difficulty in identification of anatomical landmarks on the body, especially in patients with higher amounts of subcutaneous adipose tissue.[19] Thus, the aim of the analyses presented in this chapter is to evaluate whether: 1) the published THE LO Study protocol aligned (Chapter 3) with the new ANZ-CMAG clinical practice recommendations; and 2) the test-retest reliability of marker placement was reliable by comparing 3D kinematic gait modelling parameters and anthropometric measurements in a subset of the overweight or obese adults enrolled in THE LO Study who had minimal or nil body weight changes across the three timepoints in this 12-month study.

Our hypothesis was that: 1) the published protocol would adhere to the new ANZ-CMAG clinical practice guidelines; and 2) the reliability of marker placement in nine overweight or obese adults with minimal (≤ 3% baseline bodyweight) or nil body weight changes over the study duration would demonstrate good or excellent reliability. Test-retest reliability was evaluated via interclass correlation coefficient (ICC) analysis where values above >0.9 are consider excellent, >0.7 moderate and values below <0.7 are consider poor.[11,13,20] Thus, if reliability was established, we would then. be confident to proceed to analyse the KAM changes over time of the entire THE LO Study cohort, as well as investigate differences among intervention groups.

4.2. Methods

The Train High Eat Low for Osteoarthritis Study(THE LO Study) was a randomised controlled trial (RCT) to evaluate the effects of a 12-month intervention of high intensity progressive resistance training (PRT), individualised gait retraining (GaitRe), high protein/low glycaemic index, energy-restricted diet (Diet), and the combined effect of all three interventions in overweight/ obese individuals with medial knee OA, as compared to a lifestyle advice-only control. The primary outcome of this trial was KAM. The complete list of outcomes captured measurements are presented in Chapter 3 and in a previously published protocol.[21]

Ethical approval was granted by the Sydney Local Health District Human and the University of Sydney Human Research Ethics Committees (CH62/06/2011-030 HREC/11/CRGH/47) and written informed consent was obtained from all participants prior to commencing the study.

A sub-sample of twelve participants from THE LO Study was selected to perform the test-retest reliability analysis presented in this chapter. These participants were selected without knowledge of their biomechanical data and had minimal (3%) or nil body weight changes over the study duration of 12 months. This sub-sample set was defined as the reliability sample because they represented the error likely when changes in subcutaneous tissue would have the least impact on the precision of marker placement and subsequent 3D motion analysis variable derivation. Thus, they intentionally represent

the ‘best-case scenario’ for the reliability of data collection methods utilised in this trial of overweight/obese adults with KOA. We recognise that changes in body weight would likely introduce additional imprecision to the biomechanical measurements obtained, but analysis of that complicating condition needed to be performed separately, as a secondary investigation of precision of our 3D motion analysis protocol in the setting of weight change.

4.2.1. Experimental Protocol

Clinical gait analysis was conducted from September 2012 to November 2018 over the 7-year period of the study as part of a full health and performance evaluation of all participants by two different blinded assessors employed to collect all data. Both assessors were experienced exercise physiologists. Three dimensional kinematic and kinetic data were captured, respectively, utilising Motion Analysis System with 14 optoelectrical cameras (Eagle cameras, Cortex 5 software, Motion Analysis Corporation, Rohnert, CA, USA) synchronised with three force platforms (Model 9281, Kistler Group Instruments, Winterthur, Switzerland) embedded in the laboratory floor at the Biomechanics Laboratory within the School of Exercise and Sport Science, Faculty of Health Sciences, Cumberland Campus, University of Sydney. This laboratory had been operating for 15 years at the time of this data collection under the supervision of an internationally recognised biomechanics scholar.

The sampling rates for kinematic and kinetic data collection were 100Hz and 500Hz, respectively. After following a protocol for laboratory preparation and calibration, 30

passive reflective markers were placed with double tape, preferably on the bony part of the structure with minimal muscle or tendon movement using the modified Helen Hayes marker set.[22] The first blinder assessor was instructed by THE LO Chief Investigator Prof. Richard Smith and the Lab Manager Ray Patton, and the second assessor was instructed by the first one to identify the specific location of each marker. When a bony landmark was not able to be palpated, "visual decision was suggested" on specific anatomical bony landmarks of each participant, Table 4.1 shows the list for joints and body segments and Figure 4.1 shows a visual representation and marker placement.

Table 4.1 Marker labelling

Marker No.	Marker Label	Location	Joint/ Segment
1	C7	C7 spinous process	Thorax segment
2	Sternum	Suprasternal notch	Thorax segment
3	T10	T10 spinous process	Thorax segment
4	Sacrum	Spinous process of S1	Pelvis segment
5, 18	Rasis, Lasis	Left anterior superior iliac spine	Pelvis segment
6, 19	Rgtroc, Lgtroc	Greater trochanter of femur	Hip joint
7, 20	Rmidth, Lmidth	Mid-thigh	Thigh segment
8, 21	Rlatcond, Llatcond	Lateral femoral condyle	Knee joint
9, 22	Rmedcond, Lmedcond	Medial femoral condyle	Knee joint
10, 23	Ruptib, Luptib	Upper tibia	Leg segment
11, 24	Rlattib, Llattib	Lateral tibia	Leg segment
12, 25	Rlotib, Llotib	Lower tibia	Leg segment
13, 26	Rlatmal, Llatmal	Lateral malleolus	Ankle joint
14, 27	Rmedmal, Lmedmal	Medial malleolus	Ankle joint
15, 28	Rpostcal, Lpostcal	Posterior calcaneus	Foot segment
16, 29	Rnav, Lnav	Dorsal aspect of the foot, in line with navicular tuberosity	Foot segment
17, 30	R2mpj, L2mpj	2nd metatarsal head	Foot segment

Figure 4.1 Marker set location.

A static trial was recorded as a reference prior any gait trial to determine joint centres, removing the medial condyle and medial malleolus markers of each limb and with only 26 markers left, a dynamic reference template was created by asking participants initially to stand on the platform then marching on the spot for a minimum of 3 seconds. Participants were instructed to walk across the platforms at their self-selected normal speed. The distance from the initial standing point to the platform was between 2 to 3 m, ensuring the ability to obtain a clear gait cycle with foot strike on the platform. Five bare-foot trials were obtained, and an additional five trials with the individual's own comfortable footwear were obtained (footwear trials were not analysed for the purpose of this study).

4.2.2. Data Analysis

The current data analysis was undertaken four years after the last participant's final assessment (analysis conducted between January 2022 to March 2024). This gap was due to a combination of university campus re-location from Cumberland to Camperdown, establishment of a new biomechanics' laboratory, retirement of one of the Chief Investigators of THE LO Study grant who was also co-supervisor of PhD candidate and Covid shut-down, all of which precluded accessing any on-campus study materials during a 4-year period. No reliability procedures were specified in the original study protocol (Chapter 3) and no intra- or inter-rater reliability data for marker placement between the blinded assessors had been previously conducted or reported. Thus, the research team agreed it was necessary to conduct a test-retest reliability analysis prior to any analysis of the biomechanical data outcomes of THE LO Study, to ensure the study procedures aligned with part of the new ANZ-CMAG Clinical Practice Recommendations.[1]

A sub-sample of 12 participants was taken from original THE LO Study. To minimise any potential changes on marker placement over time due to weight reduction (i.e., one of the key outcomes anticipated in the 2 diet groups of THE LO Study), the reliability sub-sample selection criterion was minimal or nil weight reduction, defined as no positive or negative changes in body mass index (BMI) of greater than 4% compared to baseline. The initial plan was to select four participants who had undergone pre-post gait analysis by rater 1; another four participants by rater 2; and another sample of four

participants with BL data taken by rater 1 and follow up taken by rater 2. Participants were not exclusively selected from the Control Group (as initially planned) due to data collection and technical errors found through the selection process. Thus, group intervention participation was removed from the selection criteria.

A total of 35 of the 82 participants who had completed all three evaluations [baseline (BL), 6m and 12m] evaluations were initially pre-selected. Despite the initial plan (above) to select twelve participants, out of the thirty-five participants, only nine of them (three per case) were successfully analysed. Unsuccessful trials were identified by the author (YG) and confirmed by coauthor biomechanical expert (SE) due to data collection and quality control errors (multicomponent force platform error, calibration error, marker misplaced, markers occluded over clothes or improperly attached to skin). The 9 participants included were from the Control group (n=7), the Diet group (n=1), and the PRT group (n=1).

Three out of five walking trials were selected in chronological order per participant at each timepoint. If any of those trials presented technical errors a further trial was then chosen. Data analysis was performed using Visual 3D software (v2022.08, C-Motion, Germantown, MD, USA). A cubic spline was used to interpolate any missing data (10 frames) and then a fourth-order zero-phase Butterworth low-pass digital filter (f_c = 8 Hz) was used to filter the raw 3D kinematic data from the 3D motion analysis system. The cartesian local coordinate system sign conventions for the 3D kinematic data from the 3D motion analysis system were defined as anterior-posterior x-axis, medio-lateral y-

axis, and superior-inferior direction z-axis. The Plug-in Gait Model[22,23] was employed to calculate segment and joint angles as well as segment distances at initial foot strike contact during early stance of the gait cycle.

The original the aim of THE LO Study protocol[21] was to calculate the lower limb joint moments, more specifically the KAM during early stance. Therefore, we investigated the key variables that contributed to the inverse dynamics model to calculate the KAM. Specifically, distances between markers, segment lengths as well as joint and segments angles were calculated to perform a test-retest reliability analysis.

4.2.3. Statistical Analysis

According to the guidelines for reporting reliability and agreement studies (GRRAS),[24] and recommendations from McGinley, 2009[13,] we conducted a test-retest reliability study to measure possible differences between sessions (BL-6m, BL-12m, 6m-12m). A total of 45 different kinematic parameters and anthropometric measurements shown in Table 4.2 were analysed to evaluate test-retest reliability and consistency of marker placement with a total of 135 pairs of comparisons.

Table 4.2 Variables

	Plane/Segment	Variable
Joint angles (°)	Sagittal plane (flexion -extension)	Trunk, hip, knee ankle
	Frontal Plane (adduction-abduction)	Trunk, hip, knee ankle
	Coronal Plane (internal-external rotation)	Trunk, hip, knee ankle
	Sagittal plane (flexion -extension)	Trunk, pelvis, thigh, shank foot
Segment angles (m)	Frontal Plane (adduction-abduction)	Trunk, pelvis, thigh, shank foot
	Coronal Plane (internal-external rotation)	Trunk, pelvis, thigh, shank foot
	Pelvis Segment	Right- Left ASIS, pelvis length, pelvis depth, sacrum to ASIS, greater trochanter to ASIS
Segment distances (m)	Leg Segment	Greater trochanter to femoral condyle; leg length
	Thigh segment	Distal radius; proximal radius; thigh length
	Shank segment	Distal radius; proximal radius; shank length; femoral condyle to lateral malleolus,
	Foot Segment	Distal radius; proximal radius; foot length; femoral condyle to lateral malleolus; lateral malleolus to 2nd metatarsal

Segment distances will be express in meters (m)
Segment and joint angles will be express in degrees (°)
ASIS: anterior superior iliac spine

The average of three gait trials was used to calculate mean and standard deviation (SD) across all variables at BL, 6m and 12m. IBM SPSS- Statistics (IBM Corporation, New York, USA) was used to perform pre and post mean significant changes ($P<0.05$) via paired sample T test, as well as interclass correlation coefficient (ICC)[10,24–26] with 95% confidence intervals. All ICC values of 0.9 or above are considered excellent, >0.7 are considered moderate and values below <0.7 are considered as poor values for reliability. Indicators of ICC are in accordance with similar analysis with kinetic and kinematic variables.[11,13,20] Standard Error of Measurement SEM ($SEM= SD/\sqrt{2}$) [25,27,28] Minimal

detectable difference (MDD) (MDD =SEM ×1.96×$\sqrt{2}$), [19,29–31] and coefficient of variation [(CV)= (√mean squared/mean) ×100] [25,27,32] were calculated in Excel 2021, (v16.0 Microsoft Corp, Redmond, WA, USA).

4.3. Results

4.3.1. THE LO Study General Characteristics

After having completed initial assessment, a total of 110 participants initiated their intervention; and data for 82 participants were available at the 12-month timepoint. The mean age of participants was 62.5±8.15 years, they were predominantly female 67.3% (n=74) and had a mean (SD) Body Mass Index (BMI) of 33.79 (6.62) kg/m^2. At baseline, mean radiographic severity on index knee was 2.3 (1.10) measured by Kellgren & Lawrence Scale (0-4); pain score of 6.48 (3.45) and self-reported physical function score was 24.09 (12.79) both measured by the Western Ontario and McMaster Universities Arthritis Index (WOMAC)[33] questionnaire on subscales of 0-20 and 0-68, respectively. There were no clinically meaningful differences between groups at baseline for participant characteristics, pain, nor physical performance.

4.3.2. Descriptive Statistics of Sub-Sample

Baseline characteristics of the sub-sample of nine participants selected for the test-retest reliability analysis are shown in Table 4.3; three of the twelve participants preselected

could not be analysed due to absence of markers (n=1) or makers misplaced (n=2). The final sample consisted of 6 female and 3 male participants [mean (SD) age: 61.78 (4.97) years, height: 1.67 (.079) m]. Mass and BMI at baseline were 91.83 (15.99) kg and 33.37 (7.23) kg/m²; and at 12 months were 91.73 (15.85) kg and 33.29 (6.91) kg/m² respectively. Sub-sample distribution across assessors and group allocation is shown in Table 4.4.

Table 4.3 Baseline characteristics of participants for reliability analysis

Characteristic	Subsample
N	9
Age	61.8 (4.96)
Sex (female) n (%)	6 (66.6%)
Height (m)	1.67 (0.08)
Fasting weight (kg)	85.65 (74.56- 129.20)
Body mass index kg/m²	31.84 (25.74- 50.47)
Waist circumference (cm)	105.37 (95.57-134.63)
Index knee (left: right%)	2/70 (22%/78%)
Radiographic severity KL grade, n (%)	
1	1(14%)
2	4(57%)
3	1(14%)
4	1(14%)
Pain (WOMAC 0-20 scale)	6.45 (3.05)
Physical function (WOMAC 0-68 scale)	20.23 (11.99)
Sit to stand test (sec)	12.44 (7.12-18.50)
Stair climbing test (sec)	4.56 (2.90-11.12)
Six-minute walk test (m)	466.77 ±127.96
Habitual gait speed (m/s)	0.83 (0.67- 1.17)
Maximal gait speed (m/s)	0.55 (0.45-0.91)
Bilateral strength 1RM test (N)	1661.67 (708.95)
Unilateral strength 1RM test (N)	42(10-93)

Normally distributed data presented as mean (standard deviation). Non-normally distributed data presented as median (range) of frequency (%)
KL= Kellgren and Lawrence radiographic numerical rating scale (0-4 higher scores indicating worsening radiographic Osteoarthritis
WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index (pain subscale 0-20, higher score indicating worse pain); (physical function subscale 0-68, higher scores indicate worse function
Bilateral strength 1 Repetition Maximum tested on pneumatic Leg Press machine
Unilateral strength 1 Repetition Maximum tested o pneumatic knee extension machine on index leg

Table 4.4 Participant distribution across assessors over assessment time-points

Participant	Group of intervention	Assessor A			Assessor B		
		BL	6m	12m	BL	6m	12m
1	Control	x	x	X			
2	Control	x	x	X			
3	PRT	x	x	X			
4	Control	x	x				x
5	Control	x	x				x
6	Control	x				x	x
7	Control				x	x	x
8	Diet				x	x	x
9	Control				x	x	x

BL: baseline; 6m: 6 months assessment; 12m: 12 months assessment
Three gait cycle trials at each time-point was individually processed with a total of 81 gait cycle trials and independently cleaned and evaluated.

4.3.3. THE LO Study Adherence to The New 2023 Australia and New Zealand Clinical Motion Analysis Group (ANZ-CMAG) Clinical Practice Recommendations

Adherence to the new ANZ-CMAG clinical practice recommendations is summarised in Table 4.5. Out of 71 items listed, THE LO Study protocol for biomechanical gait analysis did not meet the criteria in 31% (n=22) of them. This included continuous professional training and staff evaluation, records of manuals of procedures in data collection, data analysis, data processing, quality assurance, and reliability in marker placement between assessors.

Table 4.5 Australia and New Zealand Clinical Motion Analysis Group (ANZ-CMAG) clinical practice recommendations[1]

THE LO Study Gait assessment protocol evaluation

Yes= meet criteria No= did not meet criteria N/R= not reported N/A= not applicable

		YES	NO	N/R	N/A
Requiremnets for motion analysis service					
Staffing	Mandatory training	●			
	Minimum prefessional qualification and registration	●			
	Continuing professional development (including gait analysis courses)		●		
	Student placement requirements				●
	Infection control and incident reporting	●			
Facilities and Equipment	**Clinical assessment and examination area**				
	Adequate location, furnishing and room size for examination area	●			
	Laboratory space and considerations				
	Level of Building	●			
	No windows or windows blocked out and completely coverd	●			
	Wall colour/finish	●			
	Floor type	●			
	Room size	●			
	Minimum equipment to oparate clinical motion analysis				
	Stereophotogrammetry system (optoelectrical cameras)	●			
	Force platform/s	●			
	Electromyography (EMG)				●
	2D video system	●			
	Equipment management and maintenance				
	Serial number, company and model	●			
	Software/firmware versions	●			
	Known time delays and synchronisation of data			●	
	Calibration details			●	
	Schematic drawing/fault tree	●			
	Electrical safety testing record	●			
	TGA/Medsafe approved registration number	●			

Australia and New Zealand Clinical Motion Analysis Group (ANZ-CMAG) clinical practice recommendations[1]

Continuation 2/3

		YES	NO	N/R	N/A
Patients and stakeholders					
Pre-appointment	Referal process including elegibility criteria	●			
	Information sheets	●			
	Consent forms	●			
	Identification of risks and risk management plans	●			
	Consumer engagement strategies				●
During assessment	Patient history and physical examination	●			
	Diagnosis and other relevant medical conditions and medications	●			
	Participation in physical activity	●			
	Pain and its impact on movement	●			
	Current client concerns and goals	●			
	Marker placement for each model used in assessments	●			
	EMG surface/finewire				●
	Patient preparation	●			
3-dimentional motion analysis					
Data collection	Considerations of possible effects of fatigue and behaviour of patient	●			
	Skin shift, adipose tissue effects on model, marker placement		●		
	Record any changes to standard protocol		●		
	Collect enough data to produce typical gait output for kinematics and kinetics				●
	Facilities preparation	●			
	System calibration	●			
Data analysis	Clear protocol of processing methods		●		
	Documentation of 3-dimensional gait data interpolation parameters		●		
	Method for identifying gait cycle events		●		
	Identification of the 3-dimensional gait model used and changes		●		
Data interpretation	Kinematic and kinetic graphs				●
	Electromyography reporting				●
	Temporo-spatial parameters	●			
	Combining physical assessment with gait data				●
	Clinical interpretation				●
	Clinical recommendations				●

Australia and New Zealand Clinical Motion Analysis Group (ANZ-CMAG) clinical practice recommendations[1]

Continuation 3/3

		YES	NO	N/R	N/A
Quality assurance					
Patient records	History taking	●			
	Clinical examinations	●			
	List of medications	●			
Records of staff trainig sessions	Evidence of repeatability comparison with at least 1 member of staff before the new staff member works independently		●		
	Protocol to explain how the trainer determines when the trainee has reached the required proficiency to complete the task independently		●		
Marker placement	Repeated data collections should be completed on a single subject		●		
	Marker placement must be performed by team members with specific experience, and applying validated protocols		●		
	Evidence of inter and intra-rater reliability for marker placement		●		
Data procesing	At least one set of data should be processed by all team members responsible for data processing		●		
	Reliability testing should include event detection: events detected from force plate and events when no force plate data is available		●		
	Data processing should include technical or clinical judgement processes (e.g. knee cross plane correction, adjustments to hip joint centre)		●		
Data mangment	All raw data should be stored for future reference or inspection	●			
Biomechanical models	Description of biomechanical model implemented		●		
	Strategies implemented to minimise most common concerns/ errors related to the biomechanical models				
	Implementation of Skin tissue artefacts (STA)		●		
	Imaging and subject specific models		●		
	Hip joint centre (HJC) location		●		
	Identification of the 3-dimensional gait model used and changes		●		
	Pelvic segment - angle sequence	●			
	Knee kinematics cross talk			●	
	Foot /ankle graphs			●	

4.3.4. Test-Retest Reliability Analysis

Segment distances(m), segment angles (º) and joint angles(º), variables with significant differences analysed via paired sample T test, MDD, SEM ICC and CV analysis are shown in Tables 4.5, 4.6 and 4.7, respectively. A complete list of all analyses is presented in Appendix I. Overall, from BL to 6 months, BL to 12 months and 6 months to 12 months, pre-post paired sample *t*-test comparisons showed significant differences (P= <0.05) in 26 out of 135 (19.26%) pairs of comparisons occurring in joint and segment angles across the three different planes as well as over segment distances. The ICC test demonstrated low correlation (ICC= <0.70) in 82 out of 135 (61%) pairs of data.

Table 4.5 Segment distances reliability analysis

	Variable	Timepoint	Paired Samples Test			MDD	SEM	*ICC (95%CI)*	CV%
			Mean Diff. (SD)	*T-value*	P-value				
Pelvis Segment	R- L ASIS (m)	BL to 6m	-0.01 (0.04)	-0.65	0.54	0.07	0.03	**0.21 (-0.537, 0.75) §**	10%
		BL to 12m	0.02 (0.07)	0.72	0.49	0.13	0.05	**-0.43 (-0.94, 0.34) §**	14%
		6m to 12m	0.02 (0.04)	1.66	0.14	0.09	0.03	**0.39 (-0.19, 0.81) §**	10%
	Pelvis Length (m)	BL to 6m	0.01 (0.03)	0.74	0.48	0.07	0.02	**0.28 (-0.46, 0.8) §**	15%
		BL to 12m	0.01 (0.04)	0.24	0.82	0.08	0.03	**0.041 (-0.73, 0.68) §**	14%
		6m to 12m	-0.01 (0.03)	-0.60	0.57	0.05	0.02	**0.54 (-0.15, 0.88) §**	9%
	Sacrum to ASIS (m)	BL to 12m	0.01 (0.03)	2.22	**0.04¥**	0.05	0.02	0.78 (0.47, 0.91)	6%
	GT to ASIS (m)	BL to 12m	-0.02 (0.06)	-1.88	0.08	0.12	0.04	**-0.26 (-0.60, 0.20) §**	24%
		6m to 12m	-0.03 (0.05)	-2.57	**0.02¥**	0.10	0.04	**-0.17 (-0.46, 0.25) §**	21%
Leg Segment	GT to FC (m)	BL to 6m	-0.02 (0.02)	-3.14	**0.006¥**	0.05	0.02	0.79 (0.37, 0.93)	4%
		BL to 12m	0.03 (0.07)	1.92	**0.07¥**	0.13	0.05	**-0.14 (-0.49, 0.3) §**	13%
		6m to 12m	0.05 (0.06)	3.29	**0.004¥**	0.12	0.04	**-0.17 (-0.42, 0.23) §**	12%
Thigh segment	Distal Radius (m)	BL to 12m	0.01 (0.01)	1.44	0.17	0.02	0.006	**0.52 (0.10, 0.78) §**	10%
		6m to 12m	0.01 (0.01)	0.31	0.76	0.02	0.006	**0.47 (0.01, 0.77) §**	10%
	Proximal Radius (m)	BL to 6m	-0.01 (0.09)	-0.64	0.52	0.04	0.01	**0.37 (-0.12, 0.71) §**	11%
		BL to 12m	0.06 (0.03)	0.69	0.49	0.07	0.02	**-0.28 (-0.69, 0.22) §**	21%
		6m to 12m	0.01 (0.02)	1.66	0.11	0.04	0.02	**0.53 (0.12, 0.79) §**	13%
	Thigh Length (m)	BL to 12m	0.02 (0.03)	2.33	**0.03¥**	0.06	0.02	**0.39 (-0.03, 0.71) §**	5%
		6m to 12m	0.02 (0.03)	3.09	**0.007¥**	0.05	0.02	**0.44 (-0.01, 0.75) §**	4%

	Variable	Timepoint	Paired Samples Test			MDD	SEM	*ICC (95%CI)*	CV%
			Mean Diff. (SD)	***T-value***	**P-value**				
Shank segment.	Distal Radius (m)	BL to 12m	0.001 (0.01)	1.08	0.29	0.005	0.002	**0.66 (0.31, 0.86) §**	0%
	Proximal Radius (m)	BL to 12m	0.003 (0.0)	1.44	0.17	0.02	0.01	**0.52 (0.10, 0.78) §**	10%
		6m to 12m	0.001(0.01)	0.305	0.76	0.02	0.01	**0.47 (0.01, 0.77) §**	10%
	Shank Length (m)	BL to 6m	0.01 (0.01)	2.42	**0.03¥**	0.03	0.09	0.77 (0.43, 0.91)	2%
		BL to 12m	-0.01 (0.02)	-1.67	0.11	0.04	0.02	**0.65 (0.29, 0.85) §**	4%
		6m to 12m	-0.02 (0.03)	-2.74	**0.01¥**	0.05	0.02	**0.53 (0.09, 0.80) §**	4%
	FC to LM (m)	BL to 12m	-0.01 (0.02)	-2.71	**0.02¥**	0.04	0.02	**0.63 (0.19, 0.85) §**	4%
		6m to 12m	-0.02 (0.03)	-2.88	**0.01¥**	0.05	0.02	**0.5 (0.06, 0.78) §**	4%
Foot Segment	Distal radius (m)	BL to 12m	0.001(0.01)	1.08	0.30	0.01	0.002	**0.66 (0.31, 0.86) §**	4%
	Foot Length (m)	BL to 6m	-0.01 (0.01)	-2.55	**0.02¥**	0.02	0.01	**0.50 (0.07, 0.78) §**	5%
		BL to 12m	-0.01 (0.01)	-3.34	**0.004¥**	0.02	0.01	**0.48 (0.01, 0.76) §**	4%
	LM to 2nd M (m)	BL to 6m	-0.01 (0.01)	-3.01	**0.008¥**	0.02	0.01	**0.52 (0.06, 0.80) §**	5%
		BL to 12m	-0.01 (0.01)	-3.23	**0.005¥**	0.02	0.01	**0.48 (0.01, 0.77) §**	5%

Paired sample T-test data presented as mean (difference standard deviation). ¥: P<0.05
ICC (95% CI): Interclass Correlation Coefficient (95% Confidence Intervals; CIs), §: ICC < 0.70
MMD: minimal detectable difference; SEM: standard error of measurement; CV%: coefficient of variation expressed in %; BL: baseline assessment; 6m: 6-month assessment; 12m: 12-month assessment; m: meters; R- L: right- left; ASIS: anterior superior iliac spine; GT: greater trochanter; FC: femoral condyle; LM: Lateral malleolus; 2nd M: second metatarsal

Table 4.6 Segment angles reliability analysis

Variable		Timepoint comparison	Paired Samples Test			MDD	SEM	*ICC (95%CI)*	CV%
			Mean Diff. (SD)	*T-value*	P-value				
Sagittal plane (flexion-external)	Trunk (°)	BL to 6m	2.69 (3.82)	2.99	**0.008¥**	7.48	2.70	**0.63 (0.17, 0.85) §**	-85%
		BL to 12m	2.91 (4.78)	2.58	**0.02¥**	9.37	3.38	**0.45 (0.02, 0.75) §**	-103%
		6m to 12m	0.22 (4.11)	0.23	0.82	8.06	2.91	**0.56 (0.13, 0.81) §**	-63%
	Pelvis (°)	BL to 6m	-0.71 (4.06)	-0.75	0.47	7.95	2.7	**0.68 (0.34, 0.87) §**	-73%
		BL to 12m	-1.98 (4.07)	-2.06	**0.06¥**	7.98	2.88	**0.62 (0.23, 0.84) §**	-87%
		6m to 12m	-1.26 (2.60)	-2.07	**0.06¥**	5.09	1.84	0.74 (0.42, 0.90)	-62%
	Thigh (°)	BL to 6m	-1.33 (3.92)	-1.44	0.17	7.68	2.77	**0.43 (0.001, 0.74) §**	21%
		BL to 12m	-1.67 (3.53)	-2.01	0.06	6.92	2.50	**0.44 (0.02, 0.74) §**	18%
	Shank (°)	BL to 6m	-1.32 (2.71)	-2.07	**0.05¥**	5.31	1.92	**0.63 (0.25, 0.85) §**	-19%
		BL to 12m	-0.43 (2.69)	-0.69	0.50	5.26	1.90	**0.68 (0.33, 0.87) §**	-18%
	Foot (°)	BL to 6m	0.31 (2.93)	0.15	-0.40	0.58	0.45	**0.66 (5.74, 2.07) §**	-14%
		BL to 12m	0.67 (2.00)	0.66	0.30	0.86	1.42	**0.17 (3.92, 1.41) §**	-9%
Frontal Plane (adduction-abduction)	Trunk (°)	6m to 12m	0.00 (2.56)	0	1	5.02	1.81	**0.30 (0.18, 0.83) §**	*
	Thigh (°)	BL to 12m	0.57 (3.30)	0.73	0.48	6.48	2.34	**0.59 (0.18, 0.82) §**	*
		6m to 12m	-0.03 (3.25)	-0.04	0.97	6.37	2.30	**0.68 (0.32, 0.87) §**	*
	Shank (°)	BL to 6m	-0.35 (3.21)	-0.46	0.65	6.30	2.27	**0.45 (-0.02, 0.75) §**	*
		BL to 12m	-0.32 (2.78)	-0.49	0.63	5.44	1.96	**0.68 (0.31, 0.87) §**	*
		6m to 12m	0.02 (2.32)	0.05	0.96	4.54	1.64	**0.69 (0.34, 0.87) §**	*
	Foot (°)	BL to 6m	4.41 (9.50)	0.65	0.28	0.85	1.97	**0.07 (18.62, 6.72) §**	*
		BL to 12m	1.50 (6.41)	0.89	0.74	0.96	0.97	**0.35 (12.56, 4.53) §**	*

Variable			Timepoint comparison	Paired Samples Test			MDD	SEM	*ICC (95%CI)*	CV%
				Mean Diff. (SD)	*T-value*	P-value				
			6m to 12m	-2.94 (7.80)	0.72	0.41	0.89	-1.60	**0.13 (15.25, 5.50) §**	*
Coronal (internal-external rotation)	Plane	Trunk (°)	BL to 6m	0.00 (5.72)	0	1	11.21	4.04	**0.32 (-0.18, 0.70) §**	*
			BL to 12m	0.00 (5.26)	0	1	10.31	3.72	**-0.16 (-0.62, 0.34) §**	*
			6m to 12m	0.00 (6.48)	0	1	12.70	4.58	**0.094 (-0.41, 0.54) §**	*
		Pelvis (°)	BL to 12m	0.00 (4.81)	0	1	9.43	3.40	**0.47 (0.01, 0.77) §**	*
		Thigh (°)	BL to 6m	3.19 (8.82)	1.53	0.14	17.29	6.24	**0.48 (0.06, 0.77) §**	*
			BL to 12m	1.17 (11.06)	0.45	0.66	21.69	7.82	**0.25 (-0.25, 0.64) §**	*
		Foot (°)	BL to 6m	0.63 (5.45)	0.84	0.62	0.94	0.49	**0.63 (10.69, 3.85) §**	*
			BL to 12m	0.94 (6.35)	0.76	0.47	0.90	0.63	**0.54 (12.44, 4.49) §**	*

Paired sample T-test data presented as mean difference (standard deviation SD). ¥: P<0.05
ICC (95% CI): Interclass Correlation Coefficient (95% of Confidence of intervals), §: ICC < 0.70
MMD: minimal detectable difference; SEM: standard error of measurement; CV%: coefficient of variation expressed in %; BL: baseline assessment; 6m: 6-month assessment; 12m: 12-month assessment; m: meters.

Table 4.7 Joint angles reliability analysis

Variable		Timepoint comparison	Paired Samples Test			MDD	SEM	ICC (95%CI)	CV%
			Mean diff. (SD)	T-value	P-value				
Sagittal plane (flexion-extension)	Trunk (°)	BL to 6m	0.99 (4.20)	1.004	0.33	8.24	2.97	**0.36 (-0.10, 0.70) §**	-30%
		BL to 12m	-0.47 (4.75)	-0.42	0.68	9.32	3.36	**0.12 (-0.39, 0.55) §**	-37%
		6m to 12m	-1.4 (1.63)	-3.82	**0.001¥**	3.20	1.15	0.85 (0.36, 0.95)	-12%
	Hip (°)	BL to 6m	0.34 (5.98)	0.24	0.81	11.72	4.23	**0.68 (0.31, 0.87) §**	21%
	Knee (°)	BL to 6m	0.26 (5.37)	0.2	0.84	10.53	3.8	**0.55 (0.12, 0.81) §**	16%
		BL to 12m	-0.64 (4.88)	-0.55	0.59	9.57	3.45	**0.67 (0.3, 0.86) §**	15%
	Ankle (°)	BL to 6m	0.65 (3.28)	0.73	0.42	0.89	0.84	**0.41 (6.44, 2.32) §**	-48%
		BL to 12m	0.35 (2.74)	0.80	0.54	0.92	0.54	**0.60 (5.37, 1.94) §**	-42%
		6m to 12m	-0.30 (3.43)	0.67	0.3	0.86	-0.37	0.72 (6.73, 2.43)	-49%
Frontal Plane (adduction-abduction)	Trunk (°)	BL to 6m	0.00 (3.39)	0	1	6.65	2.40	**-0.15 (-0.61, 0.35) §**	*
		BL to 12m	0.00 (1.84)	0	1	3.61	1.30	**0.45 (-0.02, 0.76) §**	*
		6m to 12m	0.00 (1.89)	0	1	3.71	1.34	**0.67 (0.30, 0.86) §**	*
	Hip (°)	BL to 6m	-0.59 (2.91)	-0.87	0.40	5.70	2.05	**0.63 (0.25, 0.84) §**	66%
		BL to 12m	0.26 (3.91)	0.28	0.79	7.70	2.77	**0.15 (-0.36, 0.57) §**	102%
		6m to 12m	0.85 (4.06)	0.89	0.39	7.96	2.872	**0.37 (-0.1, 0.71) §**	95%
	Knee (°)	BL to 6m	0.41 (2.32)	0.74	0.47	4.55	1.64	0.82 (0.58, 0.93)	-31%
		BL to 12m	1.59 (3.47)	1.94	0.07	6.81	2.46	**0.56 (0.17, 0.81) §**	-41%
		6m to 12m	1.18 (2.08)	2.41	**0.03¥**	4.08	1.47	0.82 (0.52, 0.93)	-24%
	Ankle (°)	BL to 6m	-0.75 (10.73)	0.50	**0.04¥**	0.78	-0.30	0.77 (21.03, 7.59)	-202%

Variable		Timepoint comparison	Paired Samples Test			MDD	SEM	ICC (95%CI)	CV%
			Mean diff. (SD)	T-value	P-value				
		BL to 12m	-1.24 (5.36)	0.91	0.78	0.96	-0.98	**0.34 (10.50, 3.79) §**	-108%
		6m to 12m	-0.49 (8.33)	0.641	0.253	0.85	-0.249	0.806 (16.3 5.892)	-188%
Coronal Plane (internal-external rotation)	Trunk (°)	BL to 6m	0.00 (5.47)	0	1	10.72	3.87	**0.16 (-0.36, 0.58) §**	*
		BL to 12m	0.00 (5.01)	0	1	9.82	3.54	**0.47 (-0.01, 0.76) §**	*
		6m to 12m	0.00 (3.52)	0	1	6.90	2.49	**0.60 (0.17, 0.83) §**	*
	Hip (°)	BL to 12m	5.09 (8.95)	2.41	**0.027¥**	17.55	6.33	**0.50 (0.07, 0.77) §**	-251%
	Knee (°)	BL to 6m	2.51 (7.86)	1.35	0.19	15.41	5.56	**0.56 (0.16, 0.81) §**	-40%
		BL to 12m	-2.19 (12.01)	-0.77	0.45	23.53	8.49	**-0.03 (-0.5, 0.44) §**	-73%
		6m to 12m	-4.69 (8.08)	-2.46	**0.02¥**	15.85	5.72	**0.37 (-0.05, 0.69) §**	-44%
	Ankle (°)	BL to 6m	-3.75 (6.43)	0.55	0.123	0.80	-2.48	**0.02 (12.61, 4.55) §**	67%
		BL to 12m	-2.62 (6.96)	0.47	**0.045¥**	0.76	-1.60	**0.13 (13.64, 4.92) §**	79%
		6m to 12m	1.13 (5.88)	0.53	0.12	0.80	0.82	**0.42 (11.53, 4.16) §**	51%

Paired sample T-test data presented as mean difference (standard deviation SD). ¥: P<0.05
ICC (95% CI): Interclass Correlation Coefficient (95% of Confidence of intervals), §: ICC < 0.70
MMD: minimal detectable difference; SEM: standard error of measurement; CV%: coefficient of variation expressed in %; BL: baseline assessment; 6m: 6-month assessment; 12m: 12-month assessment; m: meters.

4.4. Discussion

The original 3D gait analysis protocol implemented as part of THE LO Study to evaluate pre- and post-intervention effects on the KAM (Chapter 2) did not meet 23% of the new 2023 Australia and New Zealand Clinical Motion Analysis Group (ANZ-CMAG) clinical practice recommendations.[1] Five of the key recommendations identified that were not adhered to in the THEO study included:

1) Staffing: appropriate initial training, continuing professional development, and regular quality controls were not implemented.
2) Reliability of marker placement within and between raters was not implemented.
3) Data collection: Records of changes over standard protocol, strategies implemented to overcome skin shift/ adipose tissue/ swollen joints not recorded.
4) Data processing protocols were not defined *a priori:* Absence of protocols of data processing methods. Dynamic hip pelvis model was not documented
5) Constant quality control of systems was not documented.

We acknowledge that data collection of THELO study concluded in 2018, five years prior the ANZ-CMAG guidelines were published. However, the importance of marker placement on the specific anatomical points on the human body[5,6] was published within the literature prior to this study's data collection commencement

Contrary to our hypothesis, test-retest reliability analysis of 3D kinematic gait modelling parameters collected in THE LO Study demonstrated significant differences in pre-post sample *t*-test in 26 out of 135 (19.26%) pairs of comparisons occurring in segment distances and joint and segment angles across the three different planes. Low-to-moderate reliability in more than 60% of variables measured were accompanied by high percentages of variance (CV%) in a subgroup of overweight or obese adults with minimal or nil body weight changes over this study's duration. Given the fact that we intentionally limited this reliability analysis to participants who has a minimal change in body weight during the 12 months of the trial, it likely underestimates the issues with reliability of data collection in the overall study cohort. Thus, despite documentation of the protocol that was published to the best of knowledge the researchers at the time of the study's inception, unintentional errors in data collection can, and did, occur that may affect the study's outcome goals. Based on our results in this chapter, further analysis of the KAM in this RCT study would not afford reliable 3D gait analysis results. The importance of the new ANZ-CMAG clinical practice recommendations[1] enable practitioners to ensure this pitfall is avoided in future studies. High quality 3D gait analysis is required to inform our management of knee OA in our ageing population, given the demonstrated predictive ability of abnormal KAM and related outcomes with regards to disease severity and progression.

Test-retest analysis refers to the consistency of a measured value when it is repeated over time.[25] This identifies reliability by using a variety of statistical measures including paired sample t-test, ICC with 95% CIs, SEM, MDD and CV. We chose this multiple statistical methods approach as the paired sample *t*-test alone may report significant mean

differences that could expose random errors, but systematic errors might not be evident. This is why Atkinson and Nevill, 1998[8] recommended not to employ paired *t*-testing on its own as an assessment for reliability, as this test does not provide indication of random variation between tests. Furthermore, the ICC should be taken into consideration alongside results from paired sample t-test. The ICC test might depend on the sample size; however, in this study, the number of trials tested were sufficient. Another factor to be considered is that the reliability test measured by ICC should be interpreted with caution as not all fields use the same values to reflect standards of reliability, such as high (>0.9), moderate (>0.7) or poor reliability (>0.6). Birmingham et. al, 2007[20] reported an ICC of 0.86 in kinematic parameters in a similar cohort and this was considered excellent reliability. To improve reliability, we need to understand the nature and difficulty of the marker placement process. For example, a 1-cm difference in the measurement from the greater trochanter to the femoral condyle will not reflect a similar magnitude of the error compared to 1-cm difference between the medial and lateral condyles. For that reason, the paired sample *t*-test by itself would not be sufficient, and measures such as the CV% and the MDD are needed as well.

We acknowledge the difficulty to overcome in the identification of marker placement locations in this study's cohort of overweight or obese adult patients. Adipose tissue may likely interfere with the accurate identification of the marker placement location and swollen joints may add complexity when palpating and potentially causing pain that affects accurate marker placement. The effect of marker placement and reliability within young obese cohort has been explored,[19] where 23 out of 28 kinematic parameters reported acceptable ICC (≥0.70). Variables with lower values were observed at the pelvic

region, suggesting that substantial effort are required to position pelvic markers during repeated sessions.

We cannot transfer the reliability data from healthy, normal weight individuals previously reported to clinical cohorts such as THE LO Study participants. Constant quality control evaluation should be implemented during the period of data collection[22,25] (seven years in this case in this longitudinal study). There are methodological procedures that can be implemented and adhered to within overweight or obese individuals which would likely have improved reliability in this study. For example, knee alignment devices (KAD),[26] to determine knee joint centres with interpolation of three reflective markers rather than rely just on medial and lateral femoral condyle palpation to determine the knee joint centre; radiographic imaging methods such as dual-energy x-ray or ultrasound[27] to identify and set pelvis markers; or subject-specific skeletal models[34,35] have demonstrated satisfactory outcomes in gait analysis. Thus, the implementation of similar strategies should be utilised in this population in future research.

In conclusion, this study highlights the fact that despite the highly detailed study RCT published protocol, any 3D gait study should also include a specific gait quality assurance protocol to ensure the accuracy of the biomechanical outcomes obtained. A synthesised version of the ANZ-CMAG Clinical Practice recommendations in a of check-list format (Appendix 4.1) can be implemented in further studies. THE LO Study protocol for 3D gait analysis established in 2012 and data collected between September 2012 to November 2018, did not meet the new 2023 ANZ-CMAG recommendations for clinical

motion analyses. In identifying the effect of marker placement in a subgroup of overweight or obese adults in this study, the test-retest reliability analysis on nine overweight patients with medial knee OA reported moderate to low inter-session reliability on 61% of pre- and post-intervention pairs of kinematic gait modelling parameters variables. This demonstrates that the often-forgotten part of a 3D movement study is the reliability of marker placement and the immense impact it can have on study outcomes. In this large RCT, encompassing the longest period of gait retraining of any study to date (see Chapter 2), unfortunately the primary outcome of the KAM in THE LO biomechanics data set will not be processed due to major concerns in the identification of marker placement location and the reliability of the outcome variables. We highly recommend researcher and biomechanics laboratory adherence to the new ANZ-CMAG clinical practice recommendations[1] to avoid crucial loss of data in future investigations in similar cohorts.

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CHAPTER 5.

High Eat Low for Osteoarthritis (THE LO) STUDY: Secondary Outcomes of a Randomised Controlled Trial of 12 Months of Gait Retraining, Progressive Resistance Training, and/or High Protein/Low Glycaemic Index, Energy-restricted Diet on Pain and Physical Function in Adults with Knee Osteoarthritis

5.1. Introduction

Osteoarthritis (OA) is differentiated from many other chronic disease conditions due to the presence of chronic pain. Overall, pain caused by osteoarthritis ranks as the 12th as leading cause of disability globally.[1] Knee OA may reduce physical activity due to the associated pain, resulting in a vicious cycle of depression, impaired gait and balance and lower-extremity muscle weakness due to disuse from restricted level of mobility.[2] Since no cure for OA has yet been found, treatment is typically driven by a pharmacologic approach to provide analgesia and reduce inflammation, with knee replacement surgery as the only option in advanced cases. Therefore, there is a need to explore and promote other evidence-based alternatives to alleviate symptoms. International and Australian clinical guidelines currently recommend education, regular exercise, and weight reduction (when needed) as the core and initial treatments for non-surgical management of OA.[3–6]

Multiple randomised controlled trials have been conducted to evaluate the efficacy of energy-restricted diets for weight reduction and exercise interventions to reduce pain and improve physical function in knee OA.[7–10] Outcomes have been variable in terms of symptom relief, disability status, and but have not demonstrated attenuation of disease progression. Some have demonstrated reduction in tibiofemoral compressive forces (load reduction).[8,11] The novel design of our long-term intervention: Train High Eat Low for Osteoarthritis (THE LO) Study including a low Glycaemic Index (GI)/high protein, energy-restricted diet (Diet), high intensity progressive resistance training (PRT), individualised gait retraining (GaitRe) or the combination of all 3 interventions

(Combined) had as its primary outcome a reduction in the imbalance of the medial to lateral load during gait. It is the first trial to our knowledge to test the isolated and combined efficacy of these 3 interventions on one of the most important mediators of disease progression in this cohort. As described in Chapter 4, the technical difficulties encountered during the biomechanical data collection precluded analysis of these forces at the knee joint. However, the trial was also designed secondarily to improve vital clinical outcomes including pain and physical disability associated with knee OA, which is the focus of this chapter.

This chapter will present the effects observed over time and between groups during the 12-month intervention (GaitRe, PRT, Diet, or Combined compared to Controls) in pain and self-reported physical function evaluated via the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC).[12] This questionnaire is a valid and reliable tool used to measure clinically important changes in health status due to a treatment intervention developed for people with hip or knee osteoarthritis.[13,14]

The study was powered to show a difference in KAM between GaitRe or Combined and Control groups. We did not power the study to show differences in the secondary outcomes of the WOMAC sub-scales, therefore all analyses in this chapter should be considered secondary and exploratory.

5.2. Methods

The present study follows the Osteoarthritis Research Society International (OARSI) recommendations for design and conduct clinical trials of rehabilitation interventions for OA[15] as well as CONSORT Statement recommendations.[16] The data presented in this report are from the Train High Eat Low for Osteoarthritis (THE LO) RCT, for which the detailed protocol has been published[17] and is presented in Chapter 3 of this thesis. Written informed consent was obtained from all participants, and the protocol was approved by the Sydney Local Health District Human and the University of Sydney Human Research Ethics Committees (CH62/06/2011-030 HREC/11/CRGH/47).

Overview

One hundred and ten participants were screened between September 2012 and November 2018 and then randomised to receive a 12-month intervention of GaitRe, PRT, Diet, Combined or usual care (Controls) to investigate their effects on knee joint load in overweight or obese patients with medial knee OA. Perceived pain and self-reported physical function were included along with other secondary outcomes.

Inclusion criteria included age ≥40, presence of medial knee OA following the American College of Rheumatology (ACR) criteria,[18] body mass index (BMI) ≥ 25 kg/m^2 , willing and able to participate in exercise and/or diet interventions, sedentary (no resistance training; structured exercise ≤1 day/ week; less than 150 min/week low or moderate intensity walking or other unstructured exercise), no unstable diseases precluding

exercise participation in the judgment of the study physician, no planned knee replacement surgery during the duration of the study.

5.2.1. Training Protocol

One clinician expert in each field has been assigned to deliver the intervention of each group (PRT, GaitRe, Diet). Participants allocated into the Combined group were trained by same clinicians. As this was a longitudinal study and, staff went on leave or resigned from their position, a different clinician was assigned to that group. This occurred 1 time in PRT, 0 times in Diet and 4 times in GaitRe. Extensive manuals of procedures for each intervention arm assured fidelity when changes occurred.

5.2.1.1. Individualised Gait Retraining Intervention

Sessions with the trainer were once per week for the first month, then fortnightly for the following five months, and then once per month for the final six months, with a total of 20 individual sessions over the 12-month trial.

Increased medial-lateral sway, and altered foot progression angles can reduce the Knee Adduction Moment (KAM).[19,20] Recognising that a single gait modification might not suit all participants, our strategy was to ask subjects to adjust their gait in whatever way reduced pain and KAM, while receiving visual feedback reinforcement. The potential

effectiveness of this motor learning approach for our proposed gait training intervention is supported by Wishart and Lee[21] who found that older adults in particular benefit from concurrent augmented visual feedback when learning a bimanual task. Furthermore, concurrent augmented visual feedback significantly improved patterns of work during an exercise task, compared with no augmented feedback.[22]

During the initial session, five trials of participants' habitual gait were initially recorded on a 3-dimensional (3D) motion capture system where kinetics and kinematic data were synchronised, and KAM magnitudes calculated to provide immediate feedback. The trainer provided a detailed explanation of the significance of joint load and the meaning of KAM, stating: "the proximity of the vector to the midpoint of the knee joint indicates low KAM and medial deviation from the knee joint indicates high KAM". The trainer also mentioned the potential strategies to be used to alter the gait and thereby reduce KAM and knee pain. The strategies introduced to patients were toe in, toe out, trunk lean, or medial knee thrust. During the second and third sessions, five trials with each strategy were recorded to rank the most beneficial according to KAM reduction magnitude, but also the most comfortable and potentially sustainable over time. This was necessary so that the chosen strategy could be adopted daily to optimise adherence outside of the laboratory. The aim of the following sessions was to acquire and adapt the personalised strategy by providing constant feedback from the motion capture system. During the gait trials, the trainer provided visual feedback of their ground reaction force vector and its position relative to the knee joint, via a visual frontal and sagittal plane video recording and verbal feedback. After each session, participants were asked to rank pain experiences

on a Likert scale and report whether using the modified gait during sessions and/or at home induced any other discomfort.

Once the personalised strategy was selected, participants returned to the biomechanics laboratory at the scheduled sessions to gain further feedback about their progress in mastering the pain-reducing gait technique. They were encouraged to practice the adopted strategy daily, beginning with 10-minute sessions, until they could adopt the strategy routinely during their normal daily activities. Daily home practice was recorded on a pocket-size logbook and reviewed by the trainer every session.

5.2.1.2. Low Glycemic Index (GI)/High Protein, Energy-restricted Diet Intervention

Participants randomised to this group received counseling from an expert dietitian registered and accredited by Dietitians Australia to adopt a low GI and high protein, energy-restricted diet with the goal to reduce bodyweight by 5% to 10% of baseline over 12 months via a sustainable change in eating patterns and moderate energy restriction similar to the Diabetes Prevention Program.[23] The ideal macronutrient composition was 45% of energy from carbohydrates, emphasising low glycaemic sources, 35% from fat, and 20% from protein. This macronutrient distribution is similar to the average Australian diet, but the GI index is lower. The aimed to be as low in GI as practical and achieved by replacing higher GI carbohydrates (e.g., conventional white or wholemeal bread, breakfast cereals, potatoes) with lower GI carbohydrates (e.g., Burgen® grain breads,

oats, pasta, Basmati rice). The target GI of the diet was <50 (glucose = 100) and was calculated using published data for Australian foods.[24] The diet emphasised lean sources of protein and restriction of saturated and trans-fat (but not total fat). Individual dietary counselling was stablished to identify current dietary patterns, recommend specific changes, and identify barriers and target behavioural change strategies to the individual successfully. This was accomplished by having the accredited dietitian meet individually with participants at the beginning or end of their exercise sessions once per week for the first 6 months, then fortnightly for 3 months, and then monthly for the final 3 months (33 sessions over 12 months). Participants were also provided with leaflets that outlined the carbohydrate choices and the food amounts that constituted one serving. The dietitian also provided information on the whole diet to ensure energy and overall nutrient balance; and was available for telephone queries outside of scheduled visits. To further encourage dietary adherence, key foods were provided at the first session in the form of a hamper.[19]

All participants were weighed at each diet visit on the same calibrated scale at the laboratory.[25] Results were recorded in a pocket-sized log that the participant kept for the year, and in which they recorded their self-measured waist circumference and weight weekly. These logs were reviewed at the time of weighing by the dietitian during in person sessions. At 3, 6, 9 and 12 months, unannounced 24-hour food recall interviews were conducted in conjunction with collection of 3-day food diaries to assess dietary compliance.

5.2.1.3. High Intensity Progressive Resistance Training (PRT)

Participants in this training group performed high intensity PRT 2 days per week (approximately one hour per session) for 12 months (a total of 96 sessions due to holidays), including seated leg press, unilateral knee extension, bilateral knee flexion, standing hip adduction and hip abduction, chess press, horizontal back seated row, and bilateral triceps extension using Keiser pneumatic strength training equipment (K400, Keiser Sports Health Ltd., Fresno, CA USA), which allows for low impact, and smooth, continuous progressive loading. The specific protocol for the strength training has been successfully used in the REACH[9,26] study by our team and is supported by a large RCT evidence base for the use of PRT in knee OA which was previously reviewed.[27,28] Participants performed 3 sets of 8 repetitions, with initial resistance set at 50% of the baseline One Repetition Maximum (1RM), and increased to 80% of participant's initial 1RM over the first 2-4 weeks of training. The resistance was increased progressively at each session by approximately 3% or the appropriate load to keep the training intensity between 15 and 18 (HARD to VERY HARD) on the Borg scale of Perceived Exertion,[29] modified as needed for joint pain.

5.2.1.4. Combined Group

The combined group received the three interventions and followed the same protocols in the individual PRT + GaitRe + Diet groups. Participants attended the center twice a week before or after their PRT session (1 hour approx.) to attend either their Diet or GaitRe

session, thus they did not have a session longer than 2 hours. Multi-skilled OA educators with expertise in both the dietary and exercise components of the lifestyle modification program oversaw the intervention and nurtured participant perception that these elements are inextricably linked to successful long-term weight control and OA management.

5.2.1.5. Control Group

Participants in this group received only one initial session where general recommendations were given: Arthritis Australia general recommendations for patients with knee OA.[30] They were advised that one of our assessors would call them once every fortnight to answer a short questionnaire to evaluate their health status. The same questionnaire was answered by all other participants during their own sessions.

5.2.1.6. Adherence

Adherence was measured based on attendance at sessions over the 12-month period, tracked via participant's logbooks (for GaitRe daily and Diet recording of weight and waist circumference once a week) and trainers records for PRT sessions. Participants who had low adherence (<75%) to any component of the intervention (GaitRe, PRT, Diet) received additional individual booster sessions by the OA educators, in person or by telephone if they were not attending sessions. The behavioural change principles utilised

to maximise adherence included the theoretically-grounded principles of decisional balance, social cognitive theory and the stages of change model.

5.2.2. Assessment Protocol

Blinded outcome assessments were conducted at the University of Sydney, Australia at baseline, 6 and 12 months between (November 2012 and December 2018).

Participants were initially screened over a telephone call (1 hr session) to assess eligibility; after this pre-screening session, participants who were potentially eligible attended three in-person sessions. This involved imaging evaluation (at Concord Hospital, Concord, NSW, Australia) to confirm radiographic presence and severity of medial knee OA; a geriatrician 1-2 hr session (Sydney University, Lidcombe, NSW, Australia) to confirm clinical evidence of medial knee OA and evaluate any additional co–morbidities that could preclude participation in the study, followed by questionaries, physical performance tests and health measurements as detailed in Chapter 3: Table 3.5. All measurements and sessions were repeated 6 and 12 months after randomisation with the exception of X-rays (only taken at baseline and 12-month sessions).

Self-reported pain and physical disability was evaluated via the Westen Ontario and McMaster Universities Arthritis Index (WOMAC) questionnaire,[12] which was administrated on paper by a blinded assessor prior any physical performance or exercise

test in the morning to prevent any fatigue. The WOMAC is a valid and reliable 24-item questionnaire tool for patients with OA and evaluates three different dimensions: Pain, (5 items) Stiffness (2 items) and Physical Function (17 items). In this chapter, we will report outcomes of the Pain and Physical Function subscales. The Likert version was implemented, such that each question had five possible responses rated in an ordinal scale from 0 to 4, where lower scores represent better outcomes (less pain and better physical function) for a total of 20 points for pain and 68 for physical function.

5.2.3. Randomisation, Allocation, Concealment and Blinding

An independent researcher not involved in testing or training prepared concealed randomisation in variable blocks (block size = 4-8), utilising a computer-generated random number sequence (http://www.randomization.com), created by Dr. Gerard E. Dallal, Tufts University) for the participants who completed the baseline assessments.

Stratification by sex and BMI (≤25-30 kg/m^2 vs. ≤30 kg/m^2) was carried out. Participants were randomised to one of the five study arms for 12 months in a balanced 1:1:1:1:1 ratio. Study identification and sequential treatment allocations were enclosed in numbered, opaque sealed envelopes, and distributed to each participant after completion of baseline assessment.

Trainers in each study arm were informed of the outcome, as were the participants, while all assessors for all primary and secondary outcomes were blinded to the allocated interventions. Participants were explicitly reminded before the 6- and 12-month assessments not to mention anything about their intervention activities which could potentially unblind the assessors.

5.3. Statistical Analysis

Data were initially assessed for normality and expressed as mean (standard deviation); non-normally distributed data as median (range) of frequencies and percentages as appropriate. For non-normally distributed data, a logarithmic transformation was applied for use with parametric statistics if possible. The main comparisons between groups were performed under the intention-to-treat principle, including all participants' data according to their randomised intervention group, regardless of dropout or follow-up, with missing data imputed by the linear mixed models as long as data from one timepoint was available. All participants were encouraged to attend follow up measurement's sessions, regardless of their level of participation in their intervention program.

Two separate linear mixed model analyses were constructed to determine the effects of the interventions on self-reported pain and physical function (WOMAC questionnaire subsections of pain and physical function). In the first model, group assignment and time were used as factors to determine if there was a Group allocation x Time interaction or an effect of Time. In the second model, randomisation strata elements (gender and BMI) were added as covariates to the model of Time and Group x Time interaction. The AR1

covariance structure was used, which assumes that timepoints which are closer together are more similar to each other. If a significant Time or Group x Time effect was found, then *post hoc* t tests were conducted on all pairwise comparisons to determine which timepoints and/or groups were significantly different from each other. The covariate-adjusted linear mixed model was used in all final analyses reported below.

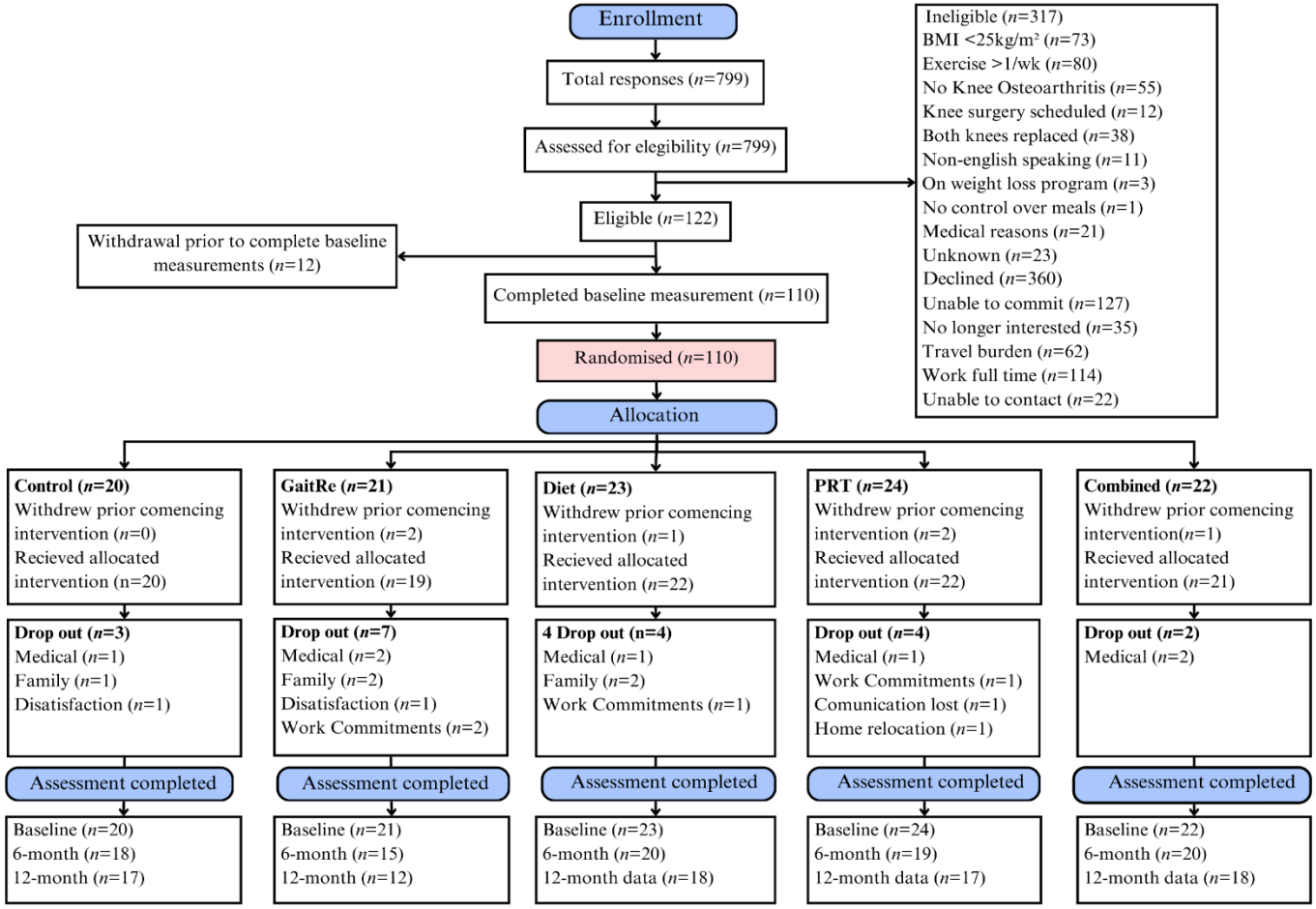
All statistical analysis was performed from February to April 2024 utilising SPSS for Windows, (IBM Corp. Armonk, New York, USA). A significance level for all analyses was set at P value <0.05 without Bonferroni adjustment.[31] as all hypotheses were specified *a priori.*

5.4. Results

5.4.1. Participants' General Characteristics

Participant flow in the study is shown in the CONSORT diagram, Figure 5.1. Trial recruitment was conducted between August 2012 until November 2018. A total of 799 potential participants expressed their initial interest in the study and 122 initiated assessment sessions. Completed baseline measurements were taken for 110 participants who were randomised prior to commencing the intervention to one of the five different groups: Control (n=20), GaitRe (n=21), PRT (n=24), Diet (n=23) or Combined (n=22).

Figure 5.1 CONSORT Flow Chart



Data was analysed based on intention to treat approach therefore randomised number of participants (n=110) are the total amount of participants analysed

Participant baseline characteristics are reported in Tables 5.1 Baseline WOMAC questionnaire and anthropometric data were available for all 110 participants who commenced the intervention and data for 82 participants were available at the 12-month time point. However, all 110 participants were included in the linear mixed models, which allow for those with missing data to be included. The most common reasons for withdrawal were medical complications (n=9), work commitments (n=6) and family or personal issues (n=6). The mean age of participants was 62.5±8.15 years, they were predominantly female 67.3% (n=74) and had a mean (SD) BMI of 33.79 (6.62) kg/m^2. At baseline, mean radiographic severity of index knee was 2.3 (1.10) measured by Kellgren & Lawrence Scale (0-4); Pain score of 6.48 (3.45) and self-reported Physical Function score was 24.09 (12.79), both measured by measured by WOMAC questionnaire on sub-scales of 0-20 and 0-68 respectively. There were no meaningful differences between groups at baseline for participant characteristics, pain, nor physical performance. As per current CONSORT guidelines,[32] no statistical comparisons were made among groups at baseline.

5.4.2. Adverse Events

Eleven adverse events were reported over the course of the study. Ten of them were minor adverse events unrelated to the study, six were upper limb musculoskeletal related;(Combined=3, Diet=2 Control=1) 2 were falls causing musculoskeletal pain (Combined=1, GaitRe=1), and 2 were worsening knee pain; (GaitRe=1, PRT=1), unable to

exercise (not attributed to the study procedures). One serious unrelated adverse event was a new cancer diagnosis (n=1 control group).

Table 5.1 Baseline Participant Characteristics

Characteristics	Total	Control	PRT	GaitRe	Diet	Combined
N	110	20	24	21	23	22
Age (yrs)	62.52 ±8.15	64.30 ± 8.00	62.38 ± 8.22	63.33 ± 8.50	61.26 ± 8.51	61.60 ±7.85
Sex (female) n (%)	74 (67.3)	15 (75)	16 (66.7)	15 (71.4)	15 (65.2)	13 (59.1)
Height (m)	1.63 (0.09)	1.64 (0.08)	1.62 (0.09)	1.62 (0.09)	1.64 (0.10)	1.63 (0.10)
Fasting weight (kg)	86.47 (74.53-86.47)	81.62 (74.73- 81.62)	84.98 (75.29 - 91.61)	81.37 (72.61-81.37)	88.2 (85.65- 112.62)	93.24 (72.83-108.14)
Body mass index (kg/m^2)	32.03 (28.82-37.57)	30.8 (27.32-35.15)	30.9 (28.09-37.35)	32.6 (28.89-39.01)	32.4 (30.25-38.89)	33.2 (30.45-37.66)
Waist circumference (cm)	107.16 (96.73-116.90)	101.64 (94.34-115.79)	104.17 (97.44-113.07)	107.74 (97.27-116.25)	110.3 (95.82-117.75)	109.40 (97.1-123.09)
Index knee (left right%)	44.5: 55.5	55: 45	41.7: 58.3	28.6: 71.4	47.8: 52.2	50: 50
Radiographic severity KL grade, n (%)						
1	29 (29.3)	5 (31.25)	11 (47.83)	3 (15.79)	7 (33.33)	3 (15)
2	34 (34.3)	7 (43.75)	6 (26.09)	8 (42.11)	5 (23.81)	8 (40)
3	16(16.2)	1 (6.25)	3 (13.04)	4 (21.05)	4 (19.05)	4 (20)
4	19(19.2)	3 (18.75)	3 (13.04)	3 (15.79)	5 (23.81)	5 (25)

Normally distributed data presented as mean (standard deviation).
Non-normally distributed data presented as median (range) of frequency (%)
PRT: High intensity progressive resistance training group; Gait: Individualised gait retraining group; Diet: Low glycaemic index/high protein, energy-restricted diet group; Combined: PRT+GaitRe+Diet group; n: total number; m: meters; kg=kilograms; cm; centimeters, yrs.: years;KL: Kellgren and Lawrence radiographic numerical rating scale (0-4 higher scores indicating worsening radiographic osteoarthritis

Characteristic	Total	Control	PRT	GaitRe	Diet	Combined
Pain (WOMAC)	6.5 (3.5)	7 (4.1)	6.5 (3.5)	6 (2.6)	6.1 (3.3)	6.8 (3.8)
Physical function (WOMAC)	24.1 (12.8)	25.8 (13.1)	24.9 (13.7)	21.8 (10.3)	24.2 (12.8)	23.8 (14.4)
Sit to stand test (sec)	12.30 (15.75-33.25)	12.58 (10.81-14.86)	11.69 (9.42-14.2)	11.59 (10.08-16.3)	12.28 (9.98-13.58)	13.21 (10.13-17.63)
Stair climbing test (sec)	5.26 (3.81- 6.72)	4.68 (3.79-7.57)	5.72 (3.16-7.25)	4.99 (3.6-6.33)	5.84 (3.87-8.56)	5.33 (4.06-6.45)
Six minutes walking test (m)	466.19 (109.16)	456.30 (140.70)	476.90 (115.20)	462.91 (121.25)	473.19 (86.047)	459.33 (85.51)
Habitual gait speed (m/s)	0.885 (0.77- 1.01)	0.82 (0.74-1.02)	0.85 (0.76-1.02)	0.95 (0.84-1.1)	0.88 (0.79-1)	0.96 (0.73-1.04)
Maximal gait speed (m/s)	0.5.92 (0.51-0.67)	0.58 (0.5-0.65)	0.58 (0.5-0.69)	0.6 (0.55-0.67)	0.6 (0.53-0.71)	0.63 (0.55-0.69)
Bilateral strength 1RM test (N)	1732.65 ±669.82	1552.4 ±661.04	1780.65 ±595.70	1961.84 ±732.21	1750.68 ±782.25	1625.48 ±552.37
Unilateral strength 1RM test (N-m)	45.0(27.5- 62.5)	41 (31.25-59.25)	42.5 (22-54)	44.5 (29.75-81.5)	48 (26-70)	51 (25.75-70.25)

Normally distributed data presented as mean (standard deviation)
Non-normally distributed data presented as median (range) of frequency (%)
PRT: High intensity progressive resistance training group; Gait: Individualised gait retraining group; Diet: Low Glycaemic index and High Protein energy restricted diet group; Combined: PRT+GaitRe+Diet group; sec: seconds; m: meters; m/s: meters per seconds; N: newtons;
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index (pain subscale 0-20, higher score indicating worse pain); (physical function subscale 0-68, higher scores indicate worse function)
Bilateral strength 1 Repetition Maximum tested on pneumatic leg press machine
Unilateral strength 1 Repetition Maximum tested on pneumatic knee extension machine on index leg

5.4.3. Pain

Contrary to our hypothesis, there was no significant Group x Time interaction effect for pain. However, there was a significant Time effect for pain, *P*=0.027. As shown in Table 5.2, post-hoc, pairwise comparisons demonstrated a significant Time effect for pain from baseline to 6 months [mean difference -0.85 units (95% CI, -1.50, -0.2) P= 0.011]; and from baseline to 12-month assessment point [mean difference 0.95 units, (95%CI, -1.78, -0.11); P= 0.027], indicating less pain at follow-ups. There was no significant difference between 6 and 12 months [mean difference -0.09 units, (95% CI, -0.79, 0.6): P=0.78).

Overall, our reduction in pain score of 14.8 % at 12 months exceeds the Minimum Clinically Important Difference (MCID) for improvement compared to a similar cohort in rehabilitation interventions (non-surgical interventions), which is reported as 12% improvement from baseline score[33] on the WOMAC pain subscale. However, the CIs are wide, ranging from a non-clinically meaningful reduction of 1.7% to a highly meaningful reduction of 28%. Thus, we are not confident that the clinically meaningful reduction in pain would always occur.

5.4.4. Physical Function

Results for self-reported physical function changes (WOMAC subscale questionnaire) are shown in Table 5.2. There was no Group x Time interaction effect observed for physical function. However, as for pain, the Time effect was significant after 12 months of intervention *P*=0.001. *Post hoc*, pairwise comparisons demonstrated a significant time effect across the entire cohort, from baseline to 6 months [mean difference -2.40 units; 95% CI (-4.44, -0.37,); P=0.021], baseline to 12-month evaluation [mean difference -5.2 units; 95% CI (-7.86, -2.48,); P= 0.0001]. and 6 months to 12 months [mean diff -2.8 units; 95% CI (4.94, 0.59,); P=0.013], indicating improvement in self-reported physical function at follow-up.

Overall, our reduction in physical function score of 22% (-5.2 units) at 12 months exceeds the MCID for improvement in comparison with similar cohorts in rehabilitation interventions (non-surgical interventions) which has been reported to be a 12% reduction on the WOMAC physical function scale.[33] However the CIs are wide ranging from not quite clinically meaningful reduction of 10.3% to highly meaningful reduction of 33%. Thus, we are not completely confident that the clinically meaningful reduction in physical function would always occur, although it appears very likely.

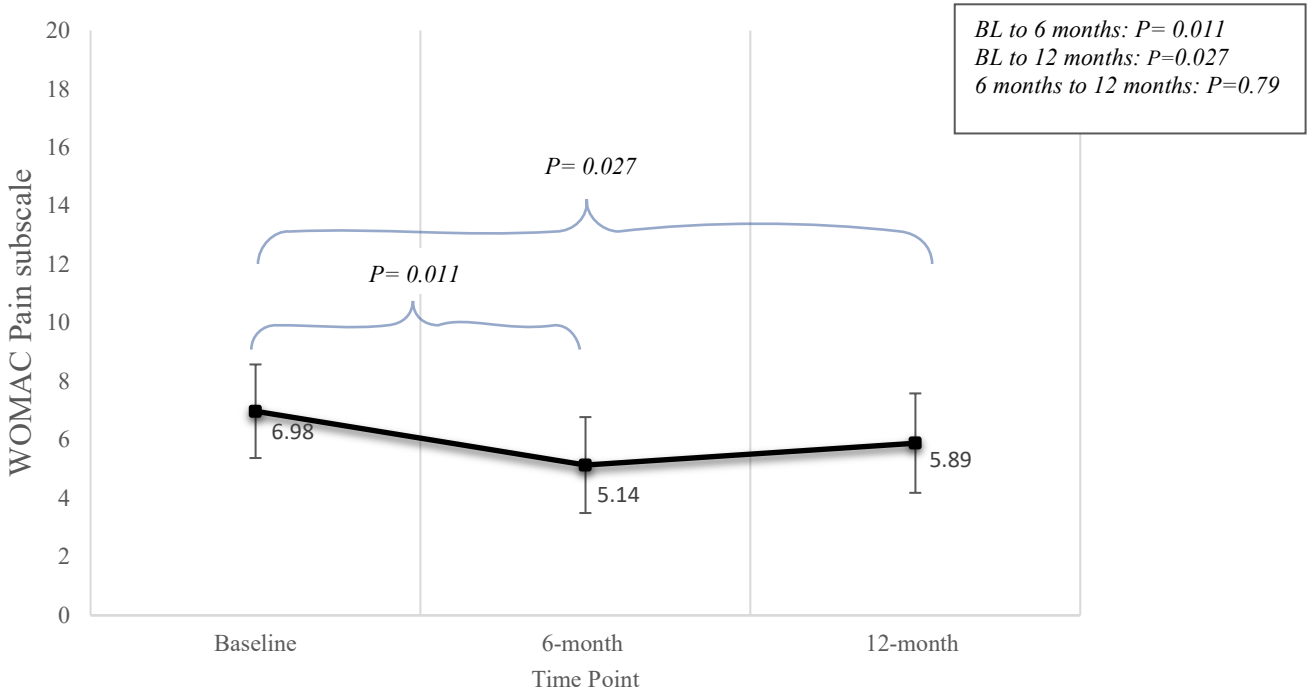
Neither pain nor physical function confidence intervals extended into values indicating worsening of clinical symptoms. Thus, there is no evidence of potential harm across the variety of intervention strategies we investigated.

Table 5.2 Overall Changes Over Time on WOMAC Pain and Physical Function Subscales

	Baseline	6 months	12 months	6 months - BL		12 months -BL		6 months to 12 months	
				Statistical difference		Statistical difference		Statistical difference	
All participants n=110	**Mean (SD)**	**Mean (SD)**	**Mean (SD)**	**Mean difference (95%CI)**	**P-value**	**Mean difference (95%CI)**	**P-value**	**Mean difference (95%CI)**	**P-value**
Pain (WOMAC)	6.4 (3.6)	5.6 (3.8)	5.5 (4.0)	-0.85 (-1.5, - 0.2)	0.01⸸	-0.95 (-1.78, -0.11)	0.03⸸	-0.09 (0.60, -0.79)	0.79
Physical function (WOMAC)	23.9 (12.8)	21.5 (13.4)	18.7 (14.6)	-2.4 (-4.44, -0.37)	0.02⸸	-5.2 (-7.86, -2.48)	<0.0001⸸	-2.8 (-0.59, -4.94)	0.013⸸

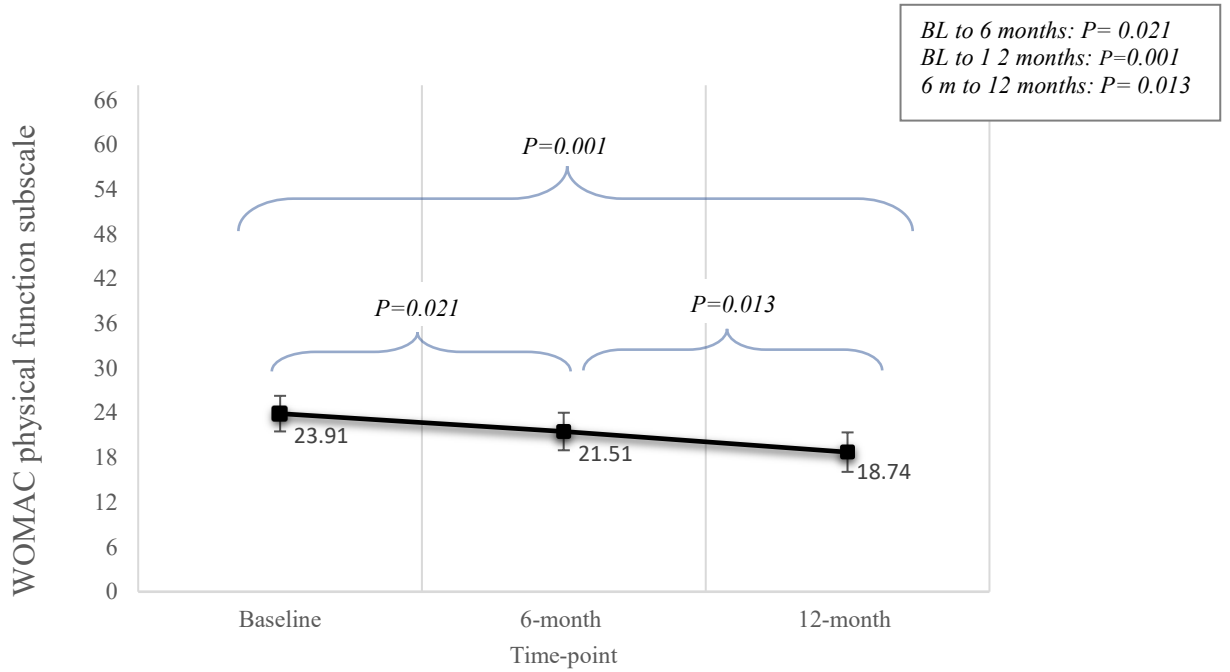
Changes over time were assessed using linear mixed model over three time points including sex, BMI at baseline, and age as covariates.
WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index[12] *(pain subscale 0-20, higher score indicating worse pain); (physical function subscale 0-68, higher scores indicate worse function*
⸸*= P value <0.05*

Figure 5.2 Time effect on WOMAC Pain Subscale in the overall THE LO Study Cohort



Graph shows time effect in WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, Pain Subscale 0-20, where higher score indicates worse pain. Results expressed in mean along with 95% Confidence Intervals (error bars) at each time point.
Post hoc t tests for all pairwise comparisons in the linear mixed model of time effect demonstrated significant pain reduction when comparing baseline to 6 months; Pvalue = 0.011and baseline to 12 months; Pvalue = 0.027.

Figure 5.3 Time effect on WOMAC Physical Function Subscale in the overall THE LO Study Cohort



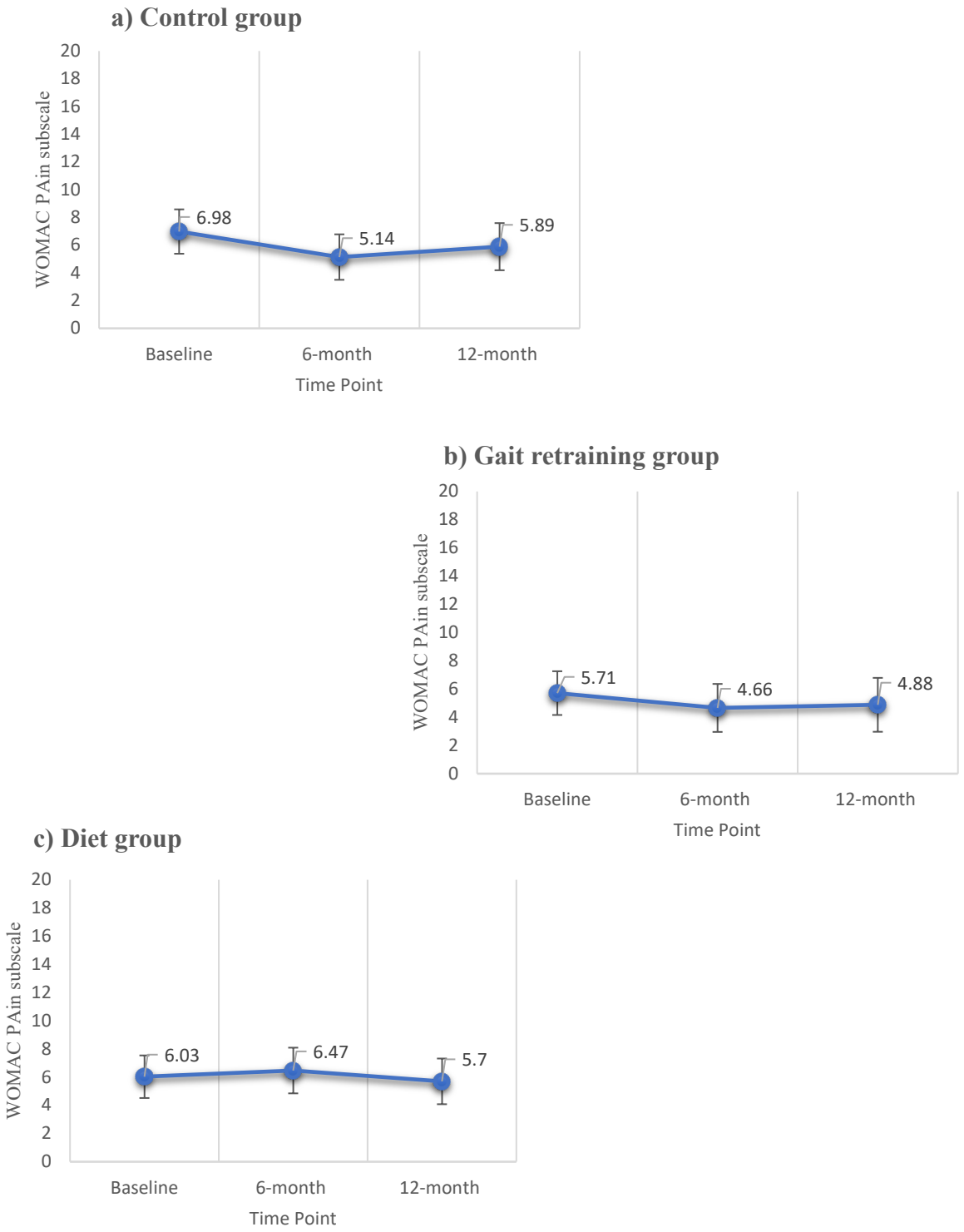
Graph shows time effect on WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index Physical Function Subscale 0-68, where higher score indicates worse physical function. Results expressed as mean and 95% Confidence Intervals (error bars) at each time point.
Post hoc t tests for all pairwise comparisons in the linear mixed model of time effect demonstrated significant physical function improvement when comparing baseline to 6 months: P value= 0.021; baseline to 12 months: P value= 0.001and 6 months to 12 months: P value=0.013. This indicates continuous significant improvement over the entire 12 months.

Table 5.3 Group changes over time in WOMAC pain subscale

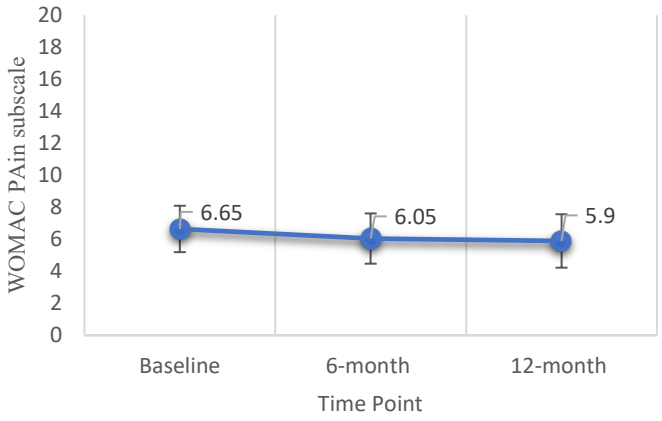
	Baseline	**6-month**	**12-month**	**BL to 6m**	**BL to 12m**
	mean (SD)	*mean (SD)*	*mean (Sd)*	*Statistical difference*	*Statistical difference*
				Mean difference (95%CI)	*Mean difference (95%CI)*
Control	6.98 (3.6)	5.14 (3.74)	5.89 (3.85)	-1.84 (-0.38, -3.31)	-1.09 (0.79, -2.96)
Gait	5.71 (3.52)	4.66 (3.94)	4.88 (4.5)	-1.05 (0.5, -2.58)	-0.83 (1.26, -2.9)
Diet	6.03 (0.3.77)	6.47 (3.95)	5.70 (3.98)	0.45 (1.92, -1.03)	-0.33 (1.5, -2.15)
PRT	6.65 (3.6)	6.05 (3.89)	5.90 (4.16)	-0.6 (0.82, -2.01)	-0.75 (1.07, -2.57)
Combined	6.84 (3.7)	5.63 (3.70)	5.09 (3.98)	-1.22 (-0.2,2.62)	-1.75(-0.03,3.52)

WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index[12] *(pain subscale 0-20, higher score indicating worse pain);*
Results expressed in mean (standard deviation)
Statistical difference expressed as mean difference (95% Confidence Intervals)
PRT= High Intensity Progressive Resistance Training group, Gait= Individualized Gait Retraining group, Diet= Low Glycemic index and High Protein Restricted Calorie Diet group, Combined= PRT+Gait+Diet group,

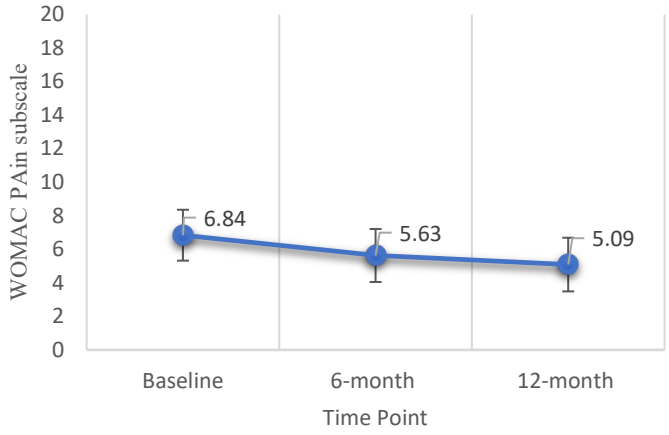
Figure 5.4 Changes over time in WOMAC pain sub-scale within groups



d) PRT group



e) Combined group



Graph shows within groups changes over time in WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, pain subscale 0-20, where higher score indicates worse pain. Results expressed as mean along with 95% coefficient intervals (error bars) at each time point.

Table 5.4 Group changes over time in WOMAC physical function subscale

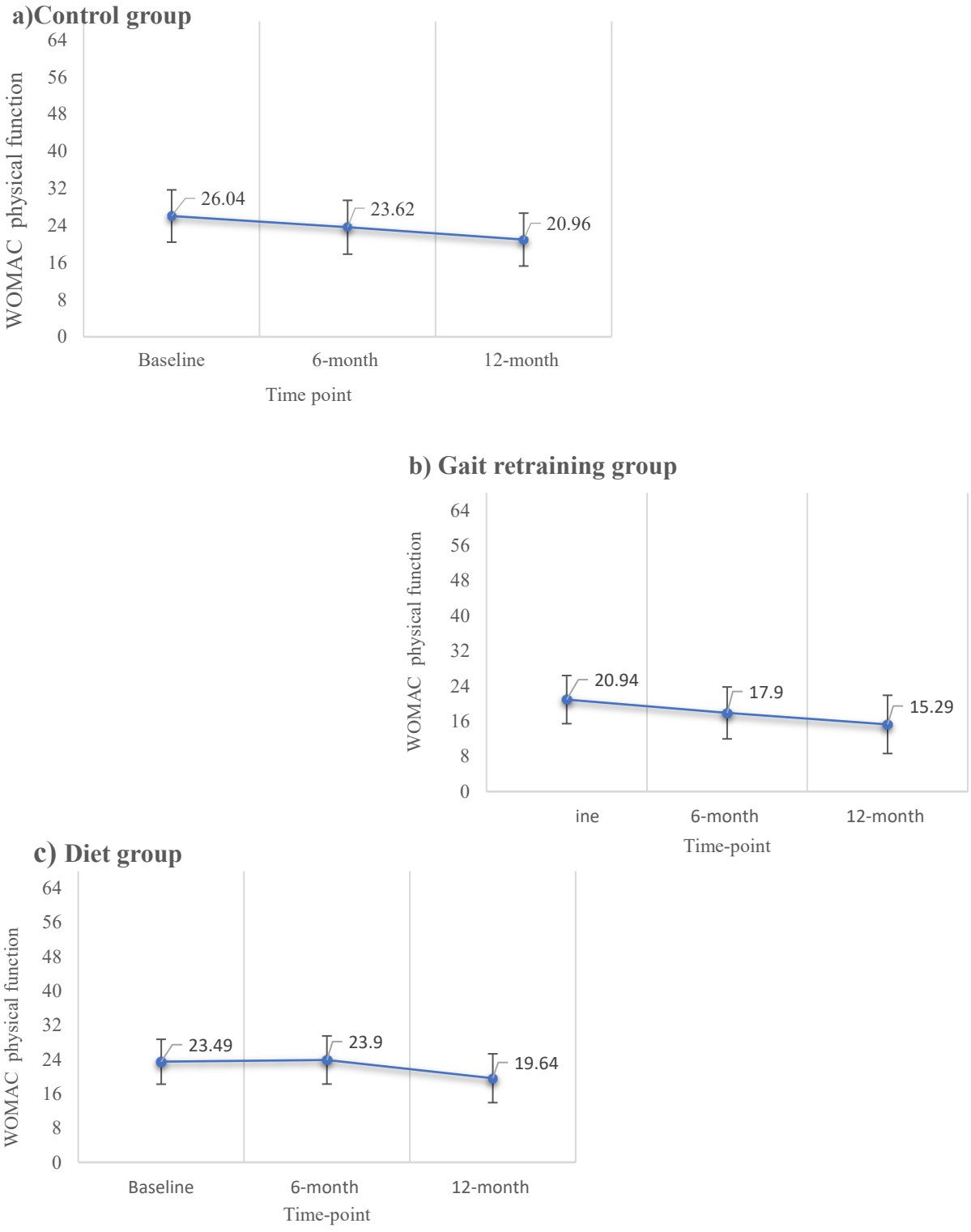
	Baseline	6-month	12-month	BL to 6m	BL to 12m
	mean (SD)	*mean (SD)*	*mean (SD)*	*Statistical difference* *Mean difference (95%CI)*	*Statistical difference* *Mean difference (95%CI)*
Control	26.04 (13.4)	23.62 (13.6)	20.96 (14.2)	-2.43 (2.17, -7.02)	-5.09 (0.95, -11.11)
Gait	20.94 (13.04)	17.9 (14.1)	15.29 (15.9)	-3.04 (1.79, -7.86)	-5.65 (1.06, -12.35)
Diet	23.49 (12.47)	23.9 (13.37)	19.64 (13.55)	0.41 (4.98, -4.17)	-3.86 (1.91, -9.62)
PRT	25.45 (12.7)	20.95 (13.22)	20.95 (13.22)	-4.51 (-0.08, -8.94)	-6.97 (-1.11, -12.83)
Combined	23.63 (13.22)	21.19 (13.23)	19.35 (13.91)	-2.44 (1.9, -6.78)	-4.29 (1.41, -9.97)

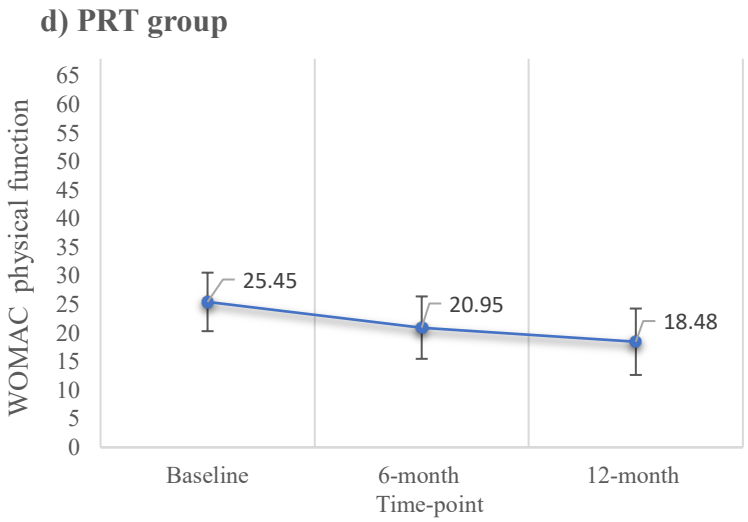
WOMAC= Western Ontario and McMaster Universities Osteoarthritis Index[10] physical function subscale 0-68, higher scores indicate worse function

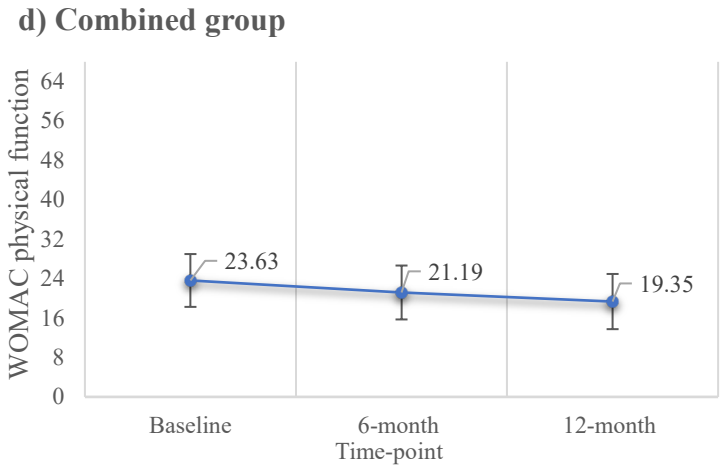
Results expressed in mean (standard deviation)
Statistical difference expressed as mean difference (95% Confidence Intervals)

PRT= High Intensity Progressive Resistance Training group, Gait= Individualized Gait Retraining group, Diet= Low Glycemic index and High Protein Restricted Calorie Diet group, Combined= PRT+Gait+Diet group,

Figure 5.5 Changes over time in WOMAC physical function sub-scale within groups







Graph shows time effect in WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index, physical function subscale 0-68, where higher score indicates worse physical function. Results expressed in mean along with 95% coefficient intervals (error bars) at each time point.

5.5. Discussion

To our knowledge, this is the first study to compare three different types of lifestyle interventions and the accumulative combination of all three to controls over the long term (12 months) in people with medial knee OA and overweight /obesity, which is a common high-risk OA subgroup.[34]

Contrary to our hypothesis, there was no significant Group x Time interaction effect on pain or self-reported physical function. However, there was a Time effect on pain (P=0.027) as well as on physical function (P=0.001). Overall, the entire cohort demonstrated statistically significant improvements in pain (P=0.01) after six months and this improvement was maintained for up to 12 months of intervention (P= 0.027), although (Figure 5.2) from 6 to 12 months, it had plateaued. The average benefits exceeded the MCID reported after other non-surgical interventions in similar cohorts (12%)[33] However, CIs are wide (95%CI -1.7%, -28%), therefore we cannot be confident that a clinically significant reduction in pain would consistently happen.

However, in contrast to pain, across all groups the self-reported physical function showed significant differences in all *post hoc* pairwise comparisons: BL to 6 m, BL to 12 m and 6 m to 12 m: P<0.02 (Figure 5.3) and the MCID indicated in previous studies of 12% improvement from baseline scores were greatly exceeded by the 22% improvement we observed. Similar to pain, a wide range in CIs was observed (95% CI 10.3%, 33%) ,

however even the lower CI was close to the MCID threshold, and so we are close to confident that a meaningful benefit would be observed in other trials of similar interventions.

Pain and physical function have been identified as the most important and relevant OA symptoms reported by patients.[35,36] The mechanisms involved in pain improvements are not well understood yet, however, in studies where patients were treated with anti-inflammatory drugs (ibuprofen), patients perceived similar improvements as our results in pain and physical function;[33] so, it is possible that the interventions worked partially through an anti-inflammatory pathway. Blood samples obtained for this purpose in this cohort have not yet been analysed. However, the addition of multiple benefits to health by exercising and adopting healthy diet habits would theoretically exceed those provided by an anti-inflammatory drug. These important secondary outcomes (e.g., body composition, blood pressure, psychological function, exercise capacity, muscle strength, nutritional adequacy, etc.) have been captured in THE LO Study, but not yet analysed.

It is important to consider that pain could also be affected by reporting bias or the Hawthorne effect, as patents in the control group received attention by our clinicians with weekly telephone calls to assess health status. Moreover, the WOMAC questionnaire was performed during the assessments sessions which provided attention and detailed health evaluation from our clinicians and geriatrician. which may also have been reflected in an improvement on pain rating.[38]

According to our systematic review (Chapter 2), most of the RCTs with exercise interventions have been short term (from 12 weeks up to 6 months),[39–42] and gait retraining studies never been tested for more than 16 weeks.[43–45] Larger sample sizes are needed in future studies to extend our analyses and investigate whether significant differences between groups may occur.

One of the limitations in this analysis is that original sample size estimates were aim to power changes in KAM 1st peak and clinical symptoms were just a secondary outcome. It is possible that a Type II error could partially explain the lack of Group x Time effects on the WOMAC. Therefore, a *post hoc* power calculation was performed to further investigate if there was enough power to exclude a significant benefit from the groups with gait interventions (our originally hypothesised most favourable groups). We calculated the Hedges' bias correct Effect Size of GaitRe vs. Controls (effect size -0.34) and combined vs. Control (effect size: -0.46%) using G-power[46] and we were underpowered (19% and 29%, respectively) to test the null hypothesis for an ES of this magnitude at an alpha of 0.05. The sample size required for the 2 groups would have been 275 people. Therefore, the negative statistical results in this study could potentially be attributed to insufficient power to test the small ES observed.

However, it should be noted that the differences in physical function and pain between groups were above the MCID for these outcomes, suggesting that there may have been a clinically meaningful benefit of gait retraining by itself or added to PRT and Diet, despite the lack of ability to prove statistical significance in this study.

Further analysis of other outcomes obtained in THE LO Study such as performance-based tests of function and exercise capacity will be completed to obtain a better understanding of knee OA patients, and then determine the best intervention to both slow down the disease progression (i.e., reduce KAM) and improve clinical symptoms simultaneously.

In conclusion, after a 12-month intervention with PRT, Diet, GaitRe, Combined interventions or a Control group allocation, overall, the entire cohort significantly improved in pain perception and self-reported physical function. After a linear mixed model analysis with the intention to treat analysis, there was no effect of group assignment, however, there were significant improvements in pain and physical function at 6 and 12 months irrespective of group assignment. The MCIDs for both pain and physical function were exceeded, suggesting the changes were clinically meaningful. Further analyses of THE LO Study dataset will be conducted to understand the most important mediators of the improvement in clinical symptoms, and whether they were related to changes in body weight, muscle strength, inflammation, macronutrient composition of diet, self-efficacy, depressive symptoms, or other potential covariates and outcomes we targeted and measured.

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CHAPTER 6.

DISCUSSION

6.1. The Purpose of this Thesis

The overall purpose of this thesis was to improve the understanding and delivery of lifestyle interventions as a critical part of the management of knee osteoarthritis (OA). This aim began with a review the current evidence base of randomised clinical trials with lifestyle interventions which included the knee adduction moment (KAM) during gait, due to its central role in disease progression. This review of the literature provided evidence to design and implement for the first time a novel long term lifestyle intervention to address the risk factors for elevated KAM and knee OA progression. We hypothesised that this intervention would have a positive impact on clinical symptoms of pain and physical function, mediated in part via gait modification of load distribution over the tibiofemoral compartment of the knee joint, as well as targeted improvements in muscle function and body composition.

To achieve this overall thesis aim, five chapters are presented.

- **Chapter One** provided a background and overview of the current impact of osteoarthritis and the necessity to find optimal approaches to target the disease with a holistic, patient-centered program with positive health impact.
- **Chapter Two** was a systematic review of randomised control trials examining lifestyle interventions targeting the KAM as a surrogate measurement of abnormal knee joint load distribution in individuals diagnosed with knee OA aiming to reduce the knee joint loading.

- **Chapter Three** describes the protocol for a novel combination of three different lifestyle interventions to target the joint loading of the knee during gait of overweight/obese patients with medial knee OA**.** Train High Eat Low for Osteoarthritis (THE LO Study): protocol for a randomised control trial. This RCT was a 12-month intervention carried out at The University of Sydney Cumberland campus over eight years where 110 participants were randomised into Gait retraining (GaitRe), High intensity progressive resistance training (PRT), low glycemic/ high protein, energy-restricted diet (Diet), or the combination of all of them in comparison to controls.
- **Chapter Four** describes a test-retest reliability analysis which was conducted to determine the potential differences between pre- and post- analysis of the three-dimensional (3D) modeling anthropometric measurements, vital analysis that should be conducted a *priori* and reported in any 3D motion capture study. In order to support future studies and help researchers and academics we developed a checklist tool that summaries minimum requirement for 3D motion gait analysis that can be implemented in any future study.
- **Chapter Five** presents the results of the secondary clinical outcomes of THELO Study: pain and self-reported physical function after 12-months of intervention or control conditions.

6.2. Key Findings

Chapter One provided a background and overview of the current impact of OA which is increasing globally in prevalence, morbidity and health care burden. Knee OA is of

particular importance due its impact on mobility, pain and function, as well as a vicious cycle of deconditioning which increases the risk of many other chronic co-morbidities and disability. None of the treatment approaches for OA of the knee have yet been able to slow the trajectory of disease progression ultimately leading to joint replacement surgery as the only option for advanced disease. Among the many risk factors identified (obesity, low muscle strength, low physical activity levels), the KAM stands out as the most important, potentially modifiable risk factor for disease progression. Medical management to date has focused on the pharmacological treatment of pain, which is not a disease-modifying approach in OA. Thus, a focus on the evidence that KAM itself may be improved with targeted interventions in this cohort was warranted.

As part of the systematic review outlined in **Chapter 2**, three different modalities of interventions targeting KAM 1^{ST} peak to evaluate knee joint loading were found: exercise, gait retraining and weight loss diet. Only 11 randomised controlled trials with a total of 1,061 participants a crossed all trials met the criteria. Significant group x time effects on KAM 1^{st} peak when comparing group intervention vs. controls were reported in 3[1–3] out of 4 gait retraining trials. Two of them implemented individualised gait strategies and the third implemented medial knee thrust, By contrast, only one[4] out of seven exercise intervention trials (P<0.05) employing a proprioceptive training (balance) intervention reduced KAM, the remainder of the resistance exercise trials were negative.

Thus, was some ability to reduce KAM 1^{st} peak by gait retraining interventions, although these trials showed inconsistent improvements in clinical outcomes (pain and physical

function). Many gaps remain, as there was no ability to synthesise data via meta-analysis due to the significant variability in intervention protocols. Also, the trials with one exception (The IDEA Study of diet and exercise) were relatively short (up to 6 months only), and all but the IDEA study had small sample sizes as well. Thus, despite the promising findings of some of the gait retraining studies, there is far from a robust, consistent conclusion that can be drawn as to how to modify KAM in this cohort. Many more theoretically grounded studies are needed, as well as ones which demonstrate that improvements in medical joint loading actually lead to slower cartilage degeneration over time.

The gaps identified in Chapter 2 required the design of a new approach to disease modification in knee OA. The protocol designed was the novel evidence-base lifestyle intervention including gait retraining, high intensity progressive resistance training (PRT)and a high protein/low glycaemic index, energy-restricted diet: THE LO Study is presented in **Chapter 3**. This trial directly compared isolated effects of these 3 interventions as well as all of them in combination (combined group) compared to control group. This non-pharmacological intervention targeted middle and older overweight / obese adults with medial knee OA, with the intention to cover the main profile patient who suffer this condition. To our knowledge, THE LO Study was the first long term study (12 months) conducted to compare three different interventions individually and the combination in people overweight/ obese with medial knee OA. More than 150 outcomes were assessed and as most of them are still to be analysed. THE LO was based on the idea that disease progression was multifactorial, and the best outcomes would only be achieved if the modifiable risk factors of obesity, muscle weakness, sedentary behaviour,

and abnormal knee loading were addressed simultaneously. In addition, the trial had to be long term, as the feasibility of sustaining behavioural changes over many months or years was something most previous trials were unable to demonstrate. The specific dietary intervention was a significant departure from previous low-fat diets (such as in the IDEA Study), as the low GI/high protein composition of THE LO diet was designed to retain lean tissue and lower insulin resistance and inflammation, in addition to having been shown to promote better long-term weight loss compared to calorie-restriction/low fat diets.

In **Chapter 4** we evaluated THE LO Study protocol implemented to perform 3D gait analysis and found it does not meet the current standards required according to the 2023 Australia and New Zealand Clinical Motion Analysis Group (ANZ-CMAG) clinical practice recommendations. We note that the trial was conducted before these guidelines were issued. The main deficiencies identified concerned staff training, reliability of marker placement, and absence of protocols established *a priori* for data processing and constant quality control.

We also conducted a test-retest reliability study of the 3D kinematic gait modelling parameters collected in THE LO Study (2012-2018). Contrary to our hypothesis, it showed significant differences in pre-post sample t-tests in 26 out of 135 (19%) pairs of comparison. More than 60% of measured variables exhibited low-to-moderate reliability and high variances. Thus, we concluded that KAM analysis in this RCT would not be reliable and could not proceed.

Challenges in marker placement accuracy, especially in overweight or obese individuals, and the need for consistent methodological procedures are acknowledged. This investigation emphasises the importance of a specific gait quality assurance protocol and adherence to the new ANZ-CMAG clinical practice recommendations to ensure reliable data in future 3D gait studies. A summary of the clinical practice recommendations in a check list format was developed as a reference for future studies as part of this Chapter.

Exploratory analysis of the secondary outcomes of THE LO study of pain and self-reported physical function in adults with medial knee OA was conducted and presented in **Chapter 5**. There was no significant Group x Time interactions, however both pain ($p= 0.027$) and physical function ($p=0.0001$) improved over the 12 months across the whole cohort.

A reduction of -14.8% in pain clinically exceeds the MCID reported in literature (12%) although the CIs had a large variation [95%CI (-1.7%, -28%)], and the upper CI was outside of the clinically meaningful improvement range. The greatest improvement was observed at 6 months, followed by plateau without significant effect from 6 months to 12 months.

Overall, the physical function improvement (21.5%) exceeds the MCID 12% in the literature, and the CIs, although wide, are almost all within the clinically meaningful range (10.3%, 33%) suggesting that this is a robust effect that we can almost always be confident of occurring. Interestingly post hoc pairwise comparisons demonstrated

significant improvements in all time-point pairs: baseline-6 months, baseline-12 months and 6 months-12 months. Thus, physical function continued improving significantly from 6 to 12 months and this may suggest that even greater impact on physical function might be observable after 12 months of intervention.

This continuous improvement in physical function after the initial intervention period is particularly encouraging, as it points to the potential for sustained and possibly even greater improvements with prolonged interventions. Therefore, future studies should consider extending the duration of intervention to fully capture the long-term benefits on physical function.

Equally important are the feasibility and safety of the interventions. Despite the high-intensity nature of the progressive resistance training and a long term energy deficit in the diet group, participant adherence was high, and dropout rates were low. The low incidence of adverse events further supports the clinical relevance and safety of all our interventions for individuals with knee OA. The combination of significant improvements in pain and function, along with the high feasibility and low risk of adverse outcomes, underscores the potential of these interventions to be integrated into clinical practice. However, the variability in pain outcomes suggests that personalised approaches may be necessary to maximise benefits across different individuals.

In conclusion, this study emphasises the importance of long-term interventions for managing knee OA, particularly in improving physical function, and highlights the need

for further research to optimise pain management strategies. The results underscore the potential for such interventions to be both effective and safe, providing a pathway for improving quality of life in individuals with this chronic condition.

6.3. Limitations

There are a number of limitations to this thesis, which are briefly summarised below:

- As part of our Systematic Review in Chapter 2, a large variation in sample size (from 17 to 454 participants), intervention length (from 4 to 72 weeks), type of intervention, participants characteristics profile, severity, and location of knee OA, were identified therefore meta-analysis was not plausible.

- Optimum lifestyle intervention(s) has not yet been identified. Firstly, in terms of gait retraining, the challenge is to how the implementation and what specific movement adaptation of an individual in their activities of daily living is required in order to optimise the most efficient movement strategy option and improve their pain and function in individuals with knee OA.

- Recruitment in THE LO Study took longer than expected. Initially we were planning to recruit 125 participants; after six years only 110 participants were

recruited. This had implications as staff changes over time necessarily occurred, affecting the precision of the data collection protocol, as outlined in Chapter 4.

- Quality assurance in 3D motion gait analysis is one of the most important elements in a longitudinal study. This limitation, identified within this thesis, highlights the importance of detailed a priori protocol with constant revision, updates are needed, therefore some caution was taken and decision to perform a test-retest reliability analysis previous to evaluate KAM.

- For the secondary outcome variables explored in Chapter 5, the sample size was a limitation as power was not determined for WOMAC questionnaire outcomes. Instead, initial estimations were to power the study to show changes KAM 1st peak, and clinical symptoms were a secondary outcome. Therefore, it is possible that Type II errors could partially explain the lack of Group x Time interactions in this study for clinical outcomes.

6.4. Concluding Remarks

This thesis set out to 1) Review the current evidence of clinical trials with lifestyle interventions which have the knee adduction moment (KAM) as an outcome evaluating knee forces during gait in patients with knee OA. 2) Present for the first time a novel long term lifestyle intervention (THE LO Study) to address the risk factors for knee OA progression with a positive impact in clinical symptoms, and finally 3) Aanalyse the

primary and secondary outcomes of THE LO Study (KAM and clinical symptoms pain and physical function). To comprehensively address this aim, I have utilised a broad spectrum of scientific methodologies and study designs, including a systematic review, reliability analysis, and analysis of a novel randomised controlled trial. The findings in this longitudinal project provide critical insights into the requirements for robust implementation of RCT intervention studies and provide drive to potential directions of lifestyle changes in people with knee OA.

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APENDIX

Appendix 1 THE LO Study publication

Journal of Physiotherapy xxx (2015) xxx–xxx

Journal of PHYSIOTHERAPY

journal homepage: www.elsevier.com/locate/jphys

Appraisal Trial Protocol

Train High Eat Low for Osteoarthritis study (THE LO study): protocol for a randomized controlled trial

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Abstract

Introduction: Osteoarthritis (OA) is one of the most prevalent chronic conditions among older adults, with the medial tibiofemoral joint being most frequently affected. The knee adduction moment is recognized as a surrogate measure of the medial tibiofemoral compartment joint load and therefore represents a valid intervention target. This article provides the rationale and methodology for THE LO study (Train High, Eat Low for Osteoarthritis), which is a randomized controlled trial that is investigating the effects of a unique, targeted lifestyle intervention in overweight/obese adults with symptomatic medial knee OA. **Research question**: Compared to a control group given only lifestyle advice, do the effects of the following interventions result in significant reductions in the knee adduction moment: (1) gait retraining; and (2) combined intervention (which involves a combination of three interventions: (a) gait retraining, (b) high-intensity progressive resistance training, and (c) high-protein/low-glycaemic-index energy-restricted diet)? It is hypothesized that the combined intervention group will be superior to the isolated interventions of the high-protein/low-glycaemic-index diet group and the progressive resistance training group. Finally, it is hypothesized that the combined intervention will result in a greater range of improvements in secondary outcomes, including: muscle strength, functional status, body composition, metabolic profile, and psychological wellbeing, compared to any of the isolated interventions or control group. **Design**: Single-blinded, randomized controlled trial adhering to the CONSORT guidelines on conduct and reporting of non-pharmacological clinical trials. **Participants**: One hundred and twenty-five community-dwelling people are being recruited. Inclusion criteria include: medial knee OA, low physical activity levels, no current resistance training, body mass index $\geq$ 25 kg/m^2 and age $\geq$ 40 years. **Intervention and control**: The participants are stratified by sex and body mass index, and randomized into one of five groups: (1) gait retraining; (2) progressive resistance training; (3) high-protein/low-glycaemic-index energy-restricted diet (25 to 30% of energy from protein, 45% of energy from carbohydrates, $<$ 30% of energy from fat, and glycaemic index diet value $<$ 50); (4) a combination of these three active interventions; or (5) a lifestyle-advice control group. All participants receive weekly telephone checks for health status, adverse events and optimisation of compliance. **Measurements**: Outcomes are measured at baseline, 6 and 12 months. The primary outcome is the peak knee adduction moment during the early stance phase of gait. The secondary outcome measures are both structural (radiological), with longitudinal reduction in medial minimal joint space width at 12 months, and clinical, including: change in body mass index; joint pain, stiffness and function; body composition; muscle strength; physical performance/mobility; nutritional intake; habitual physical activity and sedentary behaviour; sleep quality; psychological wellbeing and quality of life. **Discussion**: THE LO study will provide the first direct comparison of the long-term benefits of gait retraining, progressive resistance training and a high-protein/low-glycaemic-index energy-restricted diet, separately and in combination, on joint load, radiographic progression, symptoms, and associated co-morbidities in overweight/obese adults with OA of the knee.

Trial Registration: Australia and New Zealand Clinical Trials Register. **Registration Number**: ACTRN12612000501842. **Was this trial prospectively registered**: No. **Date of trial registration**: 9 May 2012 (date of first enrolment 1 February 2012). **Funding**: This project was funded by the National Health and Medical Research Council. **Funder approval number**: NHMRC Grant ID 1006769. **Anticipated completion date**: December 2016. **Provenance**: Not invited. Peer-reviewed. **Corresponding author**: Maria A Fiatarone Singh, MD, FRACP, Exercise, Health and Performance Faculty Research Group, Faculty of Health Sciences, University of Sydney, 75 East Street, Lidcombe, NSW 2141, Australia. Email: Maria.fiataronesingh@sydney.edu.au

Full protocol: Available on the eAddenda at doi:10.1016/j.jphys.2015.05.020

http://dx.doi.org/10.1016/j.jphys.2015.05.020

Please cite this article in press as: Guerrero Y, et al. Train High Eat Low for Osteoarthritis study (THE LO study): protocol for a randomized controlled trial. *J Physiother.* (2015), http://dx.doi.org/10.1016/j.jphys.2015.05.020

Appendix.2 Reliability analysis

Variable		***Timepoint comparison***	***Grand mean***	***Paired Samples Test***			***MDD***	***SEM***	***ICC test***			***CV%***
				Mean Diff. (SD)	*T-value*	*P-value*			*ICC*	*95% CI UB*	*LB*	
Sagital plane (Flex-Ext)	Trunk AB (°)	BL to 6m	-9.931	0.994 (4.202)	1.004	0.330	8.236	2.971	**0.364**	-0.102	0.701	-30%
		BL to 12m	-9.197	-0.474(4.753)	-0.423	0.677	9.316	3.361	**0.117**	-0.385	0.551	-37%
		6m to 12m	-9.694	-1.469(1.630)	**-3.822**	**0.001**	3.195	1.153	0.846	0.359	0.952	-12%
	Hip (°)	BL to 6m	20.283	0.3381(5.979)	0.240	0.813	11.719	4.228	**0.678**	0.314	0.867	21%
		BL to 12m	19.591	1.7221(5.298)	1.379	0.186	10.385	3.746	0.719	0.404	0.884	19%
		6m to 12m	19.422	1.3841(3.045)	1.928	0.071	5.970	2.154	0.879	0.692	0.954	11%
	Knee (°)	BL to 6m	23.295	0.257(5.37)	0.20	0.84	10.53	3.800	**0.55**	0.12	0.81	16%
		BL to 12m	23.743	-0.638(4.88)	-0.55	0.59	9.57	3.453	**0.67**	0.30	0.86	15%
		6m to 12m	23.615	-0.896(3.70)	-1.03	0.32	7.26	2.618	0.79	0.53	0.92	11%
	Ankle (°)	BL to 6m	-4.795	0.65(3.28)	0.731	0.419	0.890	0.838	**0.414**	6.437	2.322	-48%
		BL to 12m	-4.645	0.35(2.74)	0.801	0.544	0.92	0.541	**0.596**	5.365	1.935	-42%
		6m to 12m	-4.969	-0.30(3.43)	0.668	0.30	0.862	-0.370	0.716	6.728	2.427	-49%
Frontal Plane (Add-Abd)	Trunk (°)	BL to 6m	0.00	0.000(3.392)	0.000	1.000	6.648	2.398	**-0.148**	-0.612	0.351	*
		BL to 12m	3.70E-17	0.000(1.843)	0.000	1.000	3.612	1.303	**0.452**	-0.023	0.756	*
		6m to 12m	1.23E-17	0.000(1.893)	0.000	1.000	3.710	1.338	**0.672**	0.303	0.864	*
	Hip (°)	BL to 6m	3.134	-0.5922(2.905)	-0.865	0.399	5.694	2.054	**0.632**	0.253	0.844	66%
		BL to 12m	2.711	0.2547(3.911)	0.276	0.786	7.666	2.766	**0.148**	-0.360	0.574	102%
		6m to 12m	3.007	0.8469(4.061)	0.885	0.389	7.960	2.872	**0.372**	-0.098	0.707	95%
	Knee (°)	BL to 6m	-5.376	0.407(2.319)	0.74	0.47	4.55	1.640	0.82	0.58	0.93	-31%

Variable		Timepoint comparison	Grand mean	Paired Samples Test			MDD	SEM	ICC test			CV%
				Mean Diff. (SD)	T-value	P-value			ICC	95% CI UB	95% CI LB	
		BL to 12m	-5.967	1.588(3.47)	1.94	**0.07**	6.81	2.456	**0.56**	0.17	0.81	-41%
		6m to 12m	-6.170	1.181(2.08)	**2.41**	**0.03**	4.08	1.471	0.82	0.52	0.93	-24%
	Ankle (°)	BL to 6m	-3.751	-0.75(10.73)	0.496	**0.038**	0.778	-0.298	0.769	21.031	7.587	**-202%**
		BL to 12m	-3.506	-1.24(5.36)	0.908	0.776	0.964	-0.984	**0.339**	10.504	3.789	-108%
		6m to 12m	-3.129	-0.49(8.33)	0.641	0.253	0.85	-0.249	0.806	16.332	5.892	-188%
Coronal Plane (Internal-ext rotation)	Trunk (°)	BL to 6m	1.23E-17	0.000(5.471)	0.000	1.000	10.723	3.868	**0.156**	-0.356	0.580	*
		BL to 12m	-1.23E-17	0.000(5.010)	0.000	1.000	9.821	3.543	**0.465**	-0.006	0.763	*
		6m to 12m	-2.47E-17	0.000(3.521)	0.000	1.000	6.901	2.490	**0.588**	0.168	0.825	*
	Hip (°)	BL to 6m	-1.291	2.6179(7.923)	1.402	0.179	15.529	5.603	0.734	0.429	0.890	-434%
		BL to 12m	-2.526	5.0879(8.951)	**2.411**	**0.027**	17.545	6.330	**0.492**	0.068	0.771	-251%
		6m to 12m	-3.835	2.4700(7.012)	1.494	0.153	13.744	4.958	0.72	0.404	0.884	-129%
	Knee (°)	BL to 6m	-14.024	2.507(7.86)	1.35	0.19	15.41	5.558	**0.56**	0.16	0.81	-40%
		BL to 12m	-11.677	-2.185(12.01)	-0.77	0.45	23.53	8.490	**-0.03**	-0.50	0.44	-73%
		6m to 12m	-12.931	-4.693(8.08)	**-2.46**	**0.02**	15.85	5.717	**0.37**	-0.05	0.69	-44%
	Ankle (°)	BL to 6m	6.836	-3.75(6.43)	0.548	0.123	0.803	-2.475	**0.024**	12.6105	4.549	67%
		BL to 12m	6.268	-2.62(6.96)	0.467	**0.045**	0.756	-1.596	**0.129**	13.643	4.922	79%
		6m to 12m	8.145	1.13(5.88)	0.534	0.107	0.796	0.819	**0.424**	11.525	4.158	51%

B) Joint segments Reliability test

Variable		***Timepoint comparison***	***Grand mean***	***Paired Samples Test***			***MDD***	***SEM***	***ICC test***			***CV%***
				Mean Diff. (SD)	*T-value*	*P-value*			*ICC*	*95% CI UB*	*LB*	
Sagital plane (Flex-Ext)	Trunk Ab-pelvis (°)	BL to 6m	-3.1730	2.687(3.815)	**2.988**	**0.008**	7.477	2.698	**0.629**	0.167	0.852	-85%
		BL to 12m	-3.28	2.909(4.780)	**2.582**	**0.019**	9.369	3.380	**0.447**	0.019	0.745	-103%
		6m to 12m	-4.6270	0.222(4.114)	0.229	0.821	8.063	2.909	**0.563**	0.132	0.812	-63%
	Pelvis (°)	BL to 6m	-3.932	-0.713(4.058)	-0.745	0.466	7.954	2.869	**0.684**	0.335	0.868	-73%
		BL to 12m	-3.300	-1.976(4.073)	-2.058	**0.055**	7.982	2.880	**0.618**	0.232	0.837	-87%
		6m to 12m	-2.944	-1.263(2.595)	-2.065	**0.055**	5.086	1.835	0.741	0.417	0.896	-62%
	Thigh (°)	BL to 6m	13.489	-1.327(3.918)	-1.438	0.169	7.678	2.770	**0.434**	0.001	0.738	21%
		BL to 12m	13.659	-1.667(3.529)	-2.004	0.061	6.917	2.495	**0.441**	0.022	0.739	18%
		6m to 12m	14.322	-0.339(2.785)	-0.517	0.612	5.458	1.969	0.785	0.514	0.914	14%
	Shank (°)	BL to 6m	-9.888	-1.322(2.708)	-2.071	**0.054**	5.307	1.915	**0.633**	0.252	0.845	-19%
		BL to 12m	-10.330	-0.438(2.685)	-0.693	0.498	5.262	1.898	**0.684**	0.334	0.869	-18%
		6m to 12m	-9.669	0.883(2.166)	1.730	0.102	4.246	1.532	0.791	0.523	0.916	-16%
	Foot (°)	BL to 6m	-14.874	0.31(2.93)	0.154	-0.349	0.576	0.453	**0.656**	5.7444	2.072	-14%
		BL to 12m	-15.053	0.67(2.00)	0.658	0.304	0.855	1.420	**0.174**	3.920	1.414	-9%
		6m to 12m	-15.209	0.36(2.21)	0.31	-0.178	0.673	0.685	0.502	4.327	1.561	-10%
Frontal Plane (Add-Abd)	Trunk Ab-pelvis (°)	BL to 6m	0.000	0.000(2.581)	0.000	1.000	5.059	1.825	0.695	0.343	0.875	*
		BL to 12m	0.00	0.000(1.694)	0.000	1.000	3.320	1.198	0.875	0.695	0.951	*
		6m to 12m	1.85E-17	0.000(2.562)	0.000	1.000	5.021	1.811	**0.597**	0.182	0.829	*
	Pelvis (°)	BL to 6m	0.000	0.000(1.909)	0.000	1.000	3.741	1.350	0.745	0.432	0.897	*

Variable		Timepoint comparison	Grand mean	Paired Samples Test			MDD	SEM	ICC test			CV%
				Mean Diff. (SD)	T-value	P-value			ICC	95% CI UB	95% CI LB	
		BL to 12m	0.000	0.000(1.598)	0.000	1.000	3.132	1.130	0.791	0.520	0.917	*
		6m to 12m	0.000	0.000(2.033)	0.000	1.000	3.985	1.438	0.729	0.402	0.890	*
	Thigh (°)	BL to 6m	0.313	0.598(2.041)	1.244	0.230	4.000	1.443	0.874	0.700	0.950	461%
		BL to 12m	0.329	0.565(3.304)	0.726	0.478	6.475	2.336	**0.590**	0.184	0.824	710%
		6m to 12m	0.030	-0.033(3.251)	-0.043	0.966	6.371	2.299	**0.684**	0.323	0.869	*
	Shank (°)	BL to 6m	0.187	-0.346(3.213)	-0.457	0.653	6.297	2.272	**0.447**	-0.023	0.752	*
		BL to 12m	0.174	-0.321(2.773)	-0.491	0.630	5.435	1.961	**0.675**	0.314	0.865	*
		6m to 12m	0.347	0.025(2.317)	0.046	0.964	4.542	1.639	**0.694**	0.340	0.874	**472%**
	Foot (°)	BL to 6m	-0.008	4.41(9.50)	0.651	0.283	0.853	1.968	**0.066**	18.616	6.716	*
		BL to 12m	1.461	1.47(6.41)	0.894	0.744	0.959	0.971	**0.345**	12.562	4.532	310%
		6m to 12m	-0.741	-2.94(7.78)	0.723	0.408	0.886	-1.602	**0.128**	15.254	5.503	-743%
Coronal Plane (Internal-external rotation)	Trunk Ab-pelvis (°)	BL to 6m	-1.13E-16	0.000(5.718)	0.000	1.000	11.208	4.043	**0.32**	-0.184	0.682	*
		BL to 12m	-2.31E-18	0.000(5.259)	0.000	1.000	10.308	3.719	**-0.162**	-0.622	0.339	*
		6m to 12m	-6.17E-17	0.000(6.478)	0.000	1.000	12.696	4.580	**0.094**	-0.413	0.538	*
	Pelvis (°)	BL to 6m	0.000	0.000(3.402)	0.000	1.000	6.668	2.406	0.804	0.545	0.922	*
		BL to 12m	0.000	0.000(4.809)	0.000	1.000	9.426	3.401	**0.477**	0.009	0.768	*
		6m to 12m	0.000	0.000(3.844)	0.000	1.000	7.534	2.718	0.721	0.388	0.886	*
	Thigh (°)	BL to 6m	-4.187	3.190(8.819)	1.534	0.143	17.286	6.236	**0.483**	0.062	0.765	-149%
		BL to 12m	-3.178	1.172(11.065)	0.449	0.659	21.688	7.824	**0.254**	-0.249	0.640	-246%
		6m to 12m	-4.773	-2.018(5.916)	-1.447	0.166	11.595	4.183	0.757	0.470	0.901	-88%
	Shank (°)	BL to 6m	-3.285	0.834(10.102)	0.350	0.730	19.799	7.143	0.837	0.616	0.936	**-217%**

Variable	*Timepoint comparison*	*Grand mean*	*Paired Samples Test*			*MDD*	*SEM*	*ICC test*			*CV%*
			Mean Diff. (SD)	*T-value*	*P-value*			*ICC*	*95% CI UB*	*LB*	
Foot (°)	BL to 12m	-3.029	0.323(10.809)	0.127	0.901	21.185	7.643	0.768	0.477	0.907	**-252%**
	6m to 12m	-3.446	-0.511(6.832)	-0.317	0.755	13.390	4.831	0.928	0.819	0.973	**-140%**
	BL to 6m	-1.874	0.63(5.45)	0.84	0.623	0.937	0.491	**0.629**	10.685	3.854	-206%
	BL to 12m	-2.03	0.94(6.35)	0.762	0.472	0.904	0.631	**0.536**	12.438	4.487	-221%
	6m to 12m	-2.346	0.31(5.50)	0.842	0.625	0.938	0.241	0.812	10.787	3.891	-166%

C) Segment Distances reliability test

Variable		Timepoint comparison	Grand mean	Paired Samples Test			MDD	SEM	ICC test			CV%
				Mean Diff. (SD)	T-value	P-value			ICC	95% CI UB	95% CI LB	
Pelvis Segment	R- L ASIS (m)	BL to 6m	0.327	-0.01(0.037)	-0.649	0.535	0.072	0.026	**0.211**	-0.537	0.750	10%
		BL to 12m	0.315	0.016(0.068)	0.718	0.493	0.134	0.048	**-0.428**	-0.938	0.341	14%
		6m to 12m	0.319	0.024(0.044)	1.660	0.136	0.086	0.031	**0.393**	-0.193	0.809	10%
	Pelvis Length (m)	BL to 6m	0.217	0.008(0.034)	0.741	0.480	0.067	0.024	**0.28**	-0.455	0.778	15%
		BL to 12m	0.219	0.003(0.041)	0.236	0.820	0.081	0.029	**0.041**	-0.733	0.678	14%
		6m to 12m	0.215	-0.005(0.026)	-0.597	0.567	0.052	0.019	**0.544**	-0.154	0.876	9%
	Pelvis Depth (m)	BL to 6m	0.147	-0.003(0.005)	-1.696	0.128	0.010	0.004	0.978	0.899	0.995	2%
		BL to 12m	0.147	-0.002(0.007)	-0.927	0.381	0.013	0.005	0.97	0.882	0.993	3%
		6m to 12m	0.148	0.001(0.005)	0.453	0.663	0.010	0.004	0.981	0.922	0.996	2%
	Sacrum to ASIS (m)	BL to 6m	0.306	0.009(0.024)	1.535	0.143	0.046	0.017	0.839	0.624	0.936	5%
		BL to 12m	0.304	0.014(0.026)	**2.223**	**0.040**	0.051	0.018	0.78	0.472	0.914	6%
		6m to 12m	0.300	0.005(0.017)	1.258	0.225	0.033	0.012	0.895	0.746	0.959	4%
	GT to ASIS (m)	BL to 6m	0.158	0.00540(0.02498)	0.917	0.372	0.049	0.018	0.757	0.466	0.901	11%
		BL to 12m	0.174	-0.02609(0.05891)	-1.879	0.077	0.115	0.042	**-0.259**	-0.592	0.195	24%
		6m to 12m	0.171	-0.03149(0.05187)	**-2.576**	**0.020**	0.102	0.037	**-0.168**	-0.463	0.245	21%
Leg Segment	GT to FC (m)	BL to 6m	0.386	-0.01732(0.02344)	**-3.135**	**0.006**	0.046	0.017	0.791	0.374	0.927	4%
		BL to 12m	0.363	0.02989(0.06611)	1.918	**0.072**	0.130	0.047	**-0.139**	-0.488	0.300	13%
		6m to 12m	0.371	0.04721(0.06072)	**3.299**	**0.004**	0.119	0.043	**-0.165**	-0.415	0.227	12%

	Variable	Timepoint comparison	Grand mean	Paired Samples Test			MDD	SEM	ICC test			CV%
				Mean Diff. (SD)	T-value	P-value			ICC	95% CI UB	95% CI LB	
	Leg length (m)	BL to 6m	0.899	-0.0016(0.0232)	-0.297	0.770	0.046	0.016	0.913	0.784	0.967	2%
		BL to 12m	0.902	-0.0076((0.0217)	-1.485	0.156	0.043	0.015	0.905	0.767	0.963	2%
		6m to 12m	0.902	-0.0060(0.0188)	-1.346	0.196	0.037	0.013	0.938	0.844	0.976	1%
Thigh segment	Distal Radius (m)	BL to 6m	0.063	0.002(0.005)	1.897	0.075	0.010	0.004	0.844	0.620	0.939	6%
		BL to 12m	0.063	0.003(0.009)	1.442	0.168	0.017	0.006	**0.515**	0.102	0.783	10%
		6m to 12m	0.062	0.001(0.009)	0.305	0.764	0.018	0.006	**0.472**	0.006	0.766	10%
	Prox. Radius (m)	BL to 6m	0.118	-0.003(0.018)	-0.643	0.529	0.035	0.012	**0.365**	-0.117	0.705	11%
		BL to 12m	0.114	0.005(0.033)	0.694	0.497	0.065	0.023	**-0.283**	-0.686	0.217	21%
		6m to 12m	0.115	0.008(0.021)	1.655	0.116	0.041	0.015	**0.528**	0.122	0.789	13%
	Thigh Length (m)	BL to 6m	0.436	-0.002(0.024)	-0.293	0.773	0.047	0.017	0.703	0.358	0.878	4%
		BL to 12m	0.426	0.018(0.032)	**2.327**	**0.033**	0.063	0.023	**0.388**	-0.029	0.706	5%
		6m to 12m	0.427	0.019(0.027)	**3.085**	**0.007**	0.052	0.019	**0.443**	-0.005	0.747	4%
Shank segment	Distal Radius (m)	BL to 6m	0.460	0.000(0.002)	0.624	0.541	0.004	0.002	0.702	0.362	0.877	0%
		BL to 12m	0.460	0.001(0.002)	1.076	0.297	0.005	0.002	**0.661**	0.305	0.857	0%
		6m to 12m	0.460	0.000(0.002)	0.686	0.502	0.003	0.001	0.898	0.751	0.960	0%
	Prox Radius (m)	BL to 6m	0.063	0.002(0.005)	1.897	0.075	0.010	0.004	0.844	0.620	0.939	6%
		BL to 12m	0.063	0.003(0.009)	1.442	0.168	0.017	0.006	**0.515**	0.102	0.783	10%
		6m to 12m	0.062	0.001(0.009)	0.305	0.764	0.018	0.006	**0.472**	0.006	0.766	10%
	Shank Length (m)	BL to 6m	0.399	0.007(0.013)	**2.427**	**0.027**	0.025	0.009	0.766	0.427	0.909	2%
		BL to 12m	0.407	-0.009(0.022)	-1.665	0.114	0.043	0.016	**0.651**	0.291	0.852	4%

	Variable	***Timepoint comparison***	***Grand mean***	***Paired Samples Test***			***MDD***	***SEM***	***ICC test***			***CV%***
				Mean Diff. (SD)	*T-value*	*P-value*			*ICC*	*95% CI UB*	*LB*	
		6m to 12m	0.404	-0.016(0.025)	**-2.741**	**0.014**	0.049	0.018	**0.531**	0.089	0.797	4%
Foot Segment	FC to L M (m)	BL to 6m	0.407	0.003(0.012)	1.209	0.243	0.024	0.009	0.859	0.669	0.944	2%
		BL to 12m	0.416	-0.014(0.022)	**-2.714**	**0.015**	0.043	0.016	**0.627**	0.194	0.847	4%
		6m to 12m	0.414	-0.018(0.026)	**-2.878**	**0.010**	0.051	0.018	**0.5**	0.051	0.780	4%
	Distal Radius(m)	BL to 6m	0.046	0.00034(0.0023)	0.624	0.541	0.004	0.002	0.702	0.362	0.877	4%
		BL to 12m	0.046	0.00059(0.0023)	1.076	0.297	0.005	0.002	**0.661**	0.305	0.857	4%
		6m to 12m	0.046	0.00025(0.0015)	0.686	0.502	0.003	0.001	0.898	0.751	0.960	2%
	Proximal Radius (m)	BL to 6m	0.098	-0.00210(0.0074)	-1.213	0.242	0.014	0.005	0.991	0.975	0.996	5%
		BL to 12m	0.098	-0.00237(0.0069)	-1.455	0.164	0.014	0.005	0.991	0.977	0.997	5%
		6m to 12m	0.099	-0.00027(0.0041)	-0.280	0.783	0.008	0.003	0.997	0.993	0.999	3%
	Foot Length (m)	BL to 6m	0.150	-0.00595(0.0099)	**-2.558**	**0.0204**	0.019	0.007	**0.503**	0.072	0.778	5%
		BL to 12m	0.151	-0.00660(0.0084)	**-3.338**	**0.004**	0.016	0.006	**0.482**	0.006	0.775	4%
		6m to 12m	0.154	-0.00065(0.0062)	-0.446	0.661	0.012	0.004	0.827	0.595	0.931	3%
	LM to 2nd M (m)	BL to 6m	0.161	-0.008(0.012)	**-3.014**	**0.008**	0.023	0.008	**0.519**	0.058	0.793	5%
		BL to 12m	0.160	-0.008(0.010)	**-3.229**	**0.005**	0.020	0.007	**0.483**	0.014	0.774	5%
		6m to 12m	0.164	0.000(0.008)	0.194	0.849	0.016	0.006	0.779	0.498	0.912	3%

Australia and New Zealand Clinical Motion Analysis Group (ANZ-CMAG) clinical practice recommendations[1] synthesised check list version

Yes= meet criteria No= did not meet criteria N/R= not reported N/A= not applicable

		YES	NO	N/R	N/A
Requiremnets for motion analysis service					
Staffing	Mandatory training				
	Minimum prefessional qualification and registration				
	Continuing professional development (including gait analysis courses)				
	Student placement requirements				
	Infection control and incident reporting				
Facilities and Equipment	**Clinical assessment and examination area**				
	Adequate location, furnishing and room size for examination area				
	Laboratory space and considerations				
	Level of Building				
	No windows or windows blocked out and completely coverd				
	Wall colour/finish				
	Floor type				
	Room size				
	Minimum equipment to oparate clinical motion analysis				
	Stereophotogrammetry system (optoelectrical cameras)				
	Force platform/s				
	Electromyography (EMG)				
	2D video system				
	Equipment management and maintenance				
	Serial number, company and model				
	Software/firmware versions				
	Known time delays and synchronisation of data				
	Calibration details				
	Schematic drawing/fault tree				
	Electrical safety testing record				
	TGA/Medsafe approved registration number				

Australia and New Zealand Clinical Motion Analysis Group (ANZ-CMAG) clinical practice recommendations[1] synthesised check list version

Continuation 2/3

		YES	NO	N/R	N/A
Patients and stakeholders					
Pre-appointment	Referal process including elegibility criteria				
	Information sheets				
	Consent forms				
	Identification of risks and risk management plans				
	Consumer engagement strategies				
During assessment	Patient history and physical examination				
	Diagnosis and other relevant medical conditions and medications				
	Participation in physical activity				
	Pain and its impact on movement				
	Current client concerns and goals				
	Marker placement for each model used in assessments				
	EMG surface/finewire				
	Patient preparation				
3-dimentional motion analysis					
Data collection	Considerations of possible effects of fatigue and behaviour of patient				
	Skin shift, adipose tissue effects on model, marker placement				
	Record any changes to standard protocol				
	Collect enough data to produce typical gait output for kinematics and kinetics				
	Facilities preparation				
	System calibration				
Data analysis	Clear protocol of processing methods				
	Documentation of 3-dimensional gait data interpolation parameters				
	Method for identifying gait cycle events				
	Identification of the 3-dimensional gait model used and changes				
Data interpretation	Kinematic and kinetic graphs				
	Electromyography reporting				
	Temporo-spatial parameters				
	Combining physical assessment with gait data				
	Clinical interpretation				
	Clinical recommendations				

Australia and New Zealand Clinical Motion Analysis Group (ANZ-CMAG) clinical practice recommendations[1] synthesised check list version

Continuation 3/3

		YES	NO	N/R	N/A
Quality assurance					
Patient records	History taking				
	Clinical examinations				
	List of medications				
Records of staff trainig sessions	Evidence of repeatability comparison with at least 1 member of staff before the new staff member works independently				
	Protocol to explain how the trainer determines when the trainee has reached the required proficiency to complete the task independently				
Marker placement	Repeated data collections should be completed on a single subject				
	Marker placement must be performed by team members with specific experience, and applying validated protocols				
	Evidence of inter and intra-rater reliability for marker placement				
Data procesing	At least one set of data should be processed by all team members responsible for data processing				
	Reliability testing should include event detection: events detected from force plate and events when no force plate data is available				
	Data processing should include technical or clinical judgement processes (e.g. knee cross plane correction, adjustments to hip joint centre)				
Data mangment	All raw data should be stored for future reference or inspection				
Biomechanical models	Description of biomechanical model implemented				
	Strategies implemented to minimise most common concerns/ errors related to the biomechanical models				
	Implementation of Skin tissue artefacts (STA)				
	Imaging and subject specific models				
	Hip joint centre (HJC) location				
	Identification of the 3-dimensional gait model used and changes				
	Pelvic segment - angle sequence				
	Knee kinematics cross talk				
	Foot /ankle graphs				

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

PHYSICIAN SCREEN

Social History

- ☐ Living Situation _____
- ☐ Number of Children _____
- ☐ Occupation _____
- ☐ Retired _____
- ☐ Functional Status _____
- ☐ Hobbies / Recreational Activities _____
- ☐ Driving Status _____
- ☐ Smoking History _____
- ☐ Alcohol History _____

Family History

- ☐ Diabetes _____
- ☐ CV Disease _____
- ☐ HTN _____
- ☐ Obesity _____
- ☐ Other _____

Current Review of Systems

- ☐ CV _____
- ☐ Pulmonary _____
- ☐ Musculoskeletal _____
- ☐ Neurological _____

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☐ Gait & Balance _____

☐ Genitourinary _____

☐ GI _____

☐ Sleep _____

☐ Other _____

Arthritis History / Symptoms

☐ Date of first onset: _____

☐ Joints affected: _____

☐ Occupational injury: _____

☐ Sports injury: _____

☐ **Pain in knees**

Days per month: _____

Severity (1 – 10): _____

☐ **Stiffness in morning**

Minutes of stiffness: _____

Other Symptoms

☐ Locking
☐ Giving way
☐ Creaking / crepitus
☐ Snapping

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
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Timepoint:	Baseline	

Treatments Used

TREATMENT	EVER USED	CURRENTLY USE
NSAIDs	☐ YES ☐ NO	☐ YES ☐ NO
Panadol	☐ YES ☐ NO	☐ YES ☐ NO
Aspirin	☐ YES ☐ NO	☐ YES ☐ NO
Narcotics	☐ YES ☐ NO	☐ YES ☐ NO
Glucosamine	☐ YES ☐ NO	☐ YES ☐ NO
Chondroitin	☐ YES ☐ NO	☐ YES ☐ NO
Fish Oil	☐ YES ☐ NO	☐ YES ☐ NO
Topical treatment	☐ YES ☐ NO	☐ YES ☐ NO
Local heat	☐ YES ☐ NO	☐ YES ☐ NO
Massage	☐ YES ☐ NO	☐ YES ☐ NO
Acupuncture	☐ YES ☐ NO	☐ YES ☐ NO
Chiropractor	☐ YES ☐ NO	☐ YES ☐ NO
Naturopath	☐ YES ☐ NO	☐ YES ☐ NO
Physiotherapy	☐ YES ☐ NO	☐ YES ☐ NO
Hydrotherapy	☐ YES ☐ NO	☐ YES ☐ NO
Ultrasound	☐ YES ☐ NO	☐ YES ☐ NO
Steroid injections	☐ YES ☐ NO	☐ YES ☐ NO
Exercise, type: _____	☐ YES ☐ NO	☐ YES ☐ NO
Surgery, type: _____	☐ YES ☐ NO	☐ YES ☐ NO
Herbs, type: _____	☐ YES ☐ NO	☐ YES ☐ NO

Aggravating Factors

- ☐ Standing
- ☐ Walking
- ☐ Jogging / Running
- ☐ Jumping
- ☐ Stair ascent
- ☐ Stair descent
- ☐ Sitting long periods
- ☐ Chair Rise
- ☐ Squatting / knee bends

- ☐ Knee flexion
- ☐ Knee extension
- ☐ Cold
- ☐ Other: _____

Past Medical History

- ☐ Abdominal / Inguinal Hernia
- ☐ Amputation, Site: _____
- ☐ Angina / CAD
- ☐ Aortic Aneurysm
- ☐ Aortic Stenosis
- ☐ Arrythmias
- ☐ Arterial Hypertension
- ☐ Carcinoma, Site: _____
- ☐ Cataracts
- ☐ Cerebrovascular Disease
- ☐ CHF
- ☐ Cognitive Impairment
- ☐ COPD / CAL
- ☐ Depression
- ☐ DVT
- ☐ Endocarditis
- ☐ Fracture within the past 6 months
- ☐ GERD Disease
- ☐ Gout
- ☐ Haemorrhoids
- ☐ Hyperlipidemia
- ☐ Inflammatory Joint Disease, Site: _____
- ☐ MI, Site: _____
- ☐ Mitral Incompetence
- ☐ Neurological Disease, Site: _____
- ☐ Osteoporosis
- ☐ PE / Pulmonary Infarction
- ☐ Pericarditis
- ☐ Peripheral Neuropathy
- ☐ Peripheral Vascular Disease
- ☐ Progressive / Proliferative Diabetic Retinopathy
- ☐ Renal Disease
- ☐ Retinal Disease
- ☐ Retinal Haemorrhage / Detachment
- ☐ Thyroid Disease

☐ Type 2 Diabetes
☐ Ulcer, Site: _____
☐ Other Acute or Unstable Chronic Disease:

OA

_____

_____

_____

_____

Weight

Young Adult Weight: _____ kg / lbs

Peak Adult Weight: _____ kg / lbs

Lowest Adult Weight: _____ kg / lbs

Hx of Weight Cycling: _____ kg / lbs

Diet Changes

Diets tried in the past: _____

Successful weight loss attempts: _____

Reasons for weight gain / diet changes in the past: _____

_____

_____

_____

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

Physical Examination

HR _____ bpm
BP _____ mmHg

HEENT _____

Heart _____

Chest _____

Abdo _____

Neuro _____

Musc-Skel _____

Neck _____

Back _____

Shoulders _____

Elbows _____

Wrists _____

Fingers _____

Subject ID:		
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Timepoint:	Baseline	

Hips _____

_____

Ankles _____

_____

Feet _____

_____

Derm _____

_____

Other _____

_____

FINDING	RIGHT	LEFT
Hypertrophic changes		
Varus deformity		
Valgus deformity		
Scarring/laceration		
Redness		
Warmth		
Crepitation on ROM		
Swelling, pre-patellar		
Swelling, pes-anserine bursa		
Swelling, popliteal fossa (posterior knee)		
Swelling, semi-membranosus bursa (postero-medial knee)		
Swelling, FCL bursa (lateral knee)		
Swelling, infrapatellar bursa		

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

FINDING	RIGHT	LEFT
Swelling, intra-articular (ballotment, fluid wave)		
Pain on step up to table		
Pain on chair rise		
Pain on ambulation		
Pain, proximal patella		
Pain, tibial tuberosity		
Pain, patello-femoral compression, movement		
Pain, medial joint line, 30 deg, valgus stress, clicking, crepitation, laxity (MCL, meniscus)		
Pain, lateral joint line, 30 deg, varus stress, clicking, crepitation, laxity (FCL/ACL/PCL)		
Pain, posterior, deep, during maximal flexion-post horn		
Pain, suprapatellar plica (medial patella)		
Pain, lateral joint with dorsiflexion, fabella-femoral joint		
Pain, distal to fibular head, peroneal nerve; referred disk		
Pain, pes-anserine bursa (medial, inferior to knee)		
Pain, biceps femoris, FCL bursa		
Pain, semimembranosus bursa		
Pain, straight leg raising, dorsiflexion		
Lateral patellar subluxation, dislocation pain, apprehension at 45 deg		
Medial patellar subluxation, dislocation, pain, apprehension at 0 deg; reduced at 30 deg		
Valgus stress test at 0 degrees, pain, laxity MCL+ACL/PCL		
Anterior drawer test 80 deg, Lachman's test 0 deg		
Posterior drawer test, 80 deg		

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

FINDING	RIGHT	LEFT
Range of motion, knee extension		
Range of motion, knee flexion		
Strength, quadriceps		
Strength, hip flexors		
Strength, hip abduction		
Strength, hip adduction		
Strength, hip flexion		
Strength, dorsiflexion		
Strength, plantarflexion		
Reflexes, knee		
Reflexes, ankle		
Other:		

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

Exclusion Criteria:

Tick any of the following conditions which <u>permanently exclude</u> the subject from participation in the THE LO STUDY:

- ☐ Unstable aortic aneurysm
- ☐ Rapidly progressive or terminal illness (Specify)

_____

- ☐ Severe left ventricular dysfunction/end stage congestive heart failure
- ☐ Severe aortic stenosis
- ☐ Secondary osteoarthritis (traumatic or post-surgical), rheumatic disease, gouty or septic arthritis, Paget's disease, pseudogout, major congenital abnormalities, hemachromatosis, Wilson's disease and other rare forms of arthritis)
- ☐ Magnetic/electronic devices which cannot be removed (e.g. pacemaker)
- ☐ Metal objects in the lower limbs
- ☐ Previous or anticipated (within 6-12 months) joint replacement operation
- ☐ Severe psychosis or behavioural disturbance
- ☐ Surgery to any structure (cartilage, bone, tendons, ligaments, muscle) in or around the knee joint (specify)

_____

Tick any of the following conditions which <u>require medical intervention or re-evaluation prior to participation</u> in the THE LO STUDY:

- ☐ Abnormal resting ECG
- ☐ Agitation and severe claustrophobia
- ☐ Angina (unstable)
- ☐ Arrhythmias or heart block (uncontrolled)
- ☐ Breathing problem or motion disorder
- ☐ Cardiac surgery (within last 6 months)
- ☐ Cataract extraction (within last month)
- ☐ CHF (uncontrolled)
- ☐ Cognitive impairment (severe)
- ☐ COPD / CAL (uncontrolled)
- ☐ Diabetes (uncontrolled, eg. HbA_{1c} > 10%)
- ☐ Deep venous thrombosis (acute)
- ☐ Endocarditis
- ☐ Fracture (delayed union)
- ☐ Haemorrhoids
- ☐ Hernia (unrepaired or symptomatic; abdominal or inguinal)
- ☐ Hypertension (uncontrolled; arterial or pulmonary)
- ☐ Inflammatory joint disease (acute)
- ☐ Knee joint injury within the past 6 months
- ☐ Knee Injections (e.g. Corticosteroids – cortisone); no more than 2 in the last 5 years, and only one in the last 6 months.
- ☐ Myocardial infarction (acute; within last 6 months)
- ☐ Neurological disease (rapidly progressive or unstable)
- ☐ Pericarditis (acute)
- ☐ Pulmonary embolism or infarction (acute)
- ☐ Retinopathy, recently treated, unsable
- ☐ Severe functional limitation (unable to walk unaided)
- ☐ Other (eg. Other acute illness or unstable chronic disease) (specify) _____

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

Inclusion Criteria:
Tick the following inclusion criteria enabling the subject to participate in the PRT in Osteoarthritis Study:

- ☐ Primary osteoarthritis of at least one knee
  - ☐ right ____most affected, use for x-ray
  - ☐ left ____most affected, use of x-ray
  - ☐ both

Criteria used to make OA diagnosis:

- ☐ Knee pain
- ☐ + at least 1 of 3:
  - ☐ Age > 50 years
  - ☐ Stiffness < 30 minutes
  - ☐ Crepitus
- ☐ + Osteophytes

[Source:__XRAYS___Previous MRI__THE LO X-Ray__Arthroscopy __Ultrasound __Other]

- ☐ Aged 40 years or more
- ☐ No unstable disease (see exclusion criteria)
- ☐ Ambulatory without human assistance
- ☐ No specific contraindications to PRT exercise (see exclusion criteria)

Is the subject able to be included in the study at this time? ☐ YES ☐ NO

If no:
- ☐ Permanently Excluded
- ☐ Requires re-evaluation

Plan: _____

Presumptive diagnosis of knee pain if *not* PRIMARY OA:

- ☐ Secondary OA: _____
- ☐ Congential disease: _____
- ☐ Other arthritis: _____
- ☐ Trauma: _____
- ☐ Meniscus tear: _____
- ☐ Ligament taxity/tear: _____
- ☐ Bursitis: _____
- ☐ Patello-femoral disease
- ☐ Baker's cyst
- ☐ Peroneal nerve pain
- ☐ Referred pain from back, hip
- ☐ Other: _____

Physician Signature: _____ Date: ____/____/____

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

CONDITIONS TABLE

CONDITION	WHAT TO WATCH FOR

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

MEDICATIONS

MEDICATION	DOSE/FREQUENCY (eg 500mg/2d)

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

ASSESSMENT A CHECKLIST

Assessment	Completed (Tick)	Date	Not completed due to:
Informed Consent			
Medications			
Reports/Scans			
Anthropometry:			
Mass (kg)			
Height (m)			
Waist circumference			
Blood Pressure			
DEXA SCAN			
Bloods			
Breakfast			
Physician Screen			
Gait analysis			
6MWT			
1RMs:			
Leg Press			
Leg Extension (L)			
Leg Extension (R)			
Leg Flexion			
Hip Abd (L)			
Hip Abd (R)			
Hip Add (L)			
Hip Add (R)			
Chest Press			
Seated Row			
Triceps Pushdowns			
Questionnaires (optional)			
Take Home Info Pack:			

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

Actigraphs			**Returned:**
24h Urine & 3d Food Record			

GAIT ANALYSIS

Most Affected Knee (circle): LEFT / RIGHT

Habitual Shoe Description:

☐ X

☐ Bare foot ☐ Running shoe / jogger ☐ High heel (>3cm)

☐ Flat shoe / sandshoe ☐ Low heel (2-3 cm) ☐ Other: _____

Pain Scale:

"On a scale of 0 to 10, what number would you give your pain right now in your worst affected knee?"

Before Testing (circle)…	**After Testing (circle)…**
0 1 2 3 4 5 6 7 8 9 10	0 1 2 3 4 5 6 7 8 9 10

SHOES / BARE FEET (circle)

☐ 1 x **Static Reference Position** trial (30 markers)

☐ 1 x **Dynamic Reference Position** trial (26 markers)

☐ 6 x **Walking trials** at the participant's usual pace and form (26 markers)
Trial No: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

☐ 6 x **Sit-to-Stand**, count to 6, return to sit trials without using arms (26 markers)
Trial No: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

SHOES / BARE FEET (circle)

☐ 1 x **Static Reference Position** trial (30 markers)

☐ 1 x **Dynamic Reference Position** trial (26 markers)

☐ 6 x **Walking trials** at the participant's usual pace and form (26 markers)
Trial No: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

☐ 6 x **Sit-to-Stand**, count to 6, return to sit trials without using arms (26 markers)
Trial No: ☐ 1 ☐ 2 ☐ 3 ☐ 4 ☐ 5 ☐ 6

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

Protocol complete: ☐ Yes ☐ No
Deviations from protocol: ☐ Yes ☐ No

If yes, please comment: _____

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

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
- ☐ Separated

Residence
In what type of accommodation do you live?

- ☐ House (own)
- ☐ House (rented)
- ☐ Unit (own)
- ☐ Unit (rented)
- ☐ Retirement village
- ☐ Hostel
- ☐ Nursing home
- ☐ Board / rooming house

How long have you lived at this address?
Years _____Months _____

Living Situation
With whom do you live?

- ☐ Alone
- ☐ Spouse / partner
- ☐ Family
- ☐ Paid carer
- ☐ Friend
- ☐ Other residents

Total number of persons in the household
_____ People

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

Education

What is the highest grade or year of school you completed?

- ☐ never /kindergarten 0
- ☐ primary school 1 2 3 4 5 6
- ☐ high school 7 8 9 10 11 12
- ☐ tertiary 13 14 15 16
- ☐ post graduate 17 18 19 20

Work

Do you currently work for pay either for yourself or someone else?

- ☐ yes
- ☐ no

How many hours per week do you work for pay?

_____hours / week

Do you currently work as a volunteer?

- ☐ yes
- ☐ no

How many volunteer hours / week do you work?

_____hours / week

Annual Income

In what range is your annual income?

- ☐ < $ 15,000
- ☐ $ 15,000- $30,000
- ☐ >$30,000

Pension

Do you receive a pension?

- ☐ Nil
- ☐ DVA
- ☐ Age pension
- ☐ Widows pension
- ☐ Disability Pension

Private Health Insurance

Do you have a private health insurance?

- ☐ yes
- ☐ no

if yes, specify_____

Hospital Admissions

During the past 12 months, how many different times did you stay in hospital over night?

_____ number of times

_____ number of days in hospital

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

Smoking

Have you ever smoked cigarettes, cigars or a pipe on a daily basis?

☐ yes
☐ no

Do you currently smoke at least 1 cigarette, cigar or pipe per day?

☐ yes
☐ no

If yes, how many cigarettes, cigars or pipes do you smoke on an average day?

_____ per day

Alcohol

During the past 30 days, about how many days did you drink any alcoholic beverages (beer, wine, liquor)

☐ almost every day
☐ 3-4 times a week
☐ once or twice a week
☐ 2-3 times a month
☐ once a month
☐ none

Comment: _____

_____

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

GDS

☐ (1) NOT DONE

INSTRUCTIONS: Check the best answer for how you felt over the past week.

1. Are you basically satisfied with your life?	☐ Yes	☐ No
2. Have you dropped many of your activities and interests?	☐ Yes	☐ No
3. Do you feel that your life is empty?	☐ Yes	☐ No
4. Do you often get bored?	☐ Yes	☐ No
5. Are you hopeful about the future?	☐ Yes	☐ No
6. Are you bothered by thoughts that you just cannot get out of your head?	☐ Yes	☐ No
7. Are you in good spirits most of the time?	☐ Yes	☐ No
8. Are you afraid that something bad is going to happen to you?	☐ Yes	☐ No
9. Do you feel happy most of the time?	☐ Yes	☐ No
10. Do you often feel helpless?	☐ Yes	☐ No
11. Do you often get restless and fidgety?	☐ Yes	☐ No
12. Do you prefer to stay at home, rather than go out and do new things?	☐ Yes	☐ No
13. Do you frequently worry about the future?	☐ Yes	☐ No
14. Do you feel that you have more problems with memory than most?	☐ Yes	☐ No
15. Do you think it is wonderful to be alive now?	☐ Yes	☐ No
16. Do you often feel downhearted and blue?	☐ Yes	☐ No
17. Do you feel pretty worthless the way you are now?	☐ Yes	☐ No
18. Do you worry a lot about the past?	☐ Yes	☐ No
19. Do you find life very exciting?	☐ Yes	☐ No

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

20. Is it hard for you to get started on new projects? ☐ Yes ☐ No
21. Do you feel full of energy? ☐ Yes ☐ No
22. Do you feel that your situation is hopeless? ☐ Yes ☐ No
23. Do you think that most people are better off than you are? ☐ Yes ☐ No
24. Do you frequently get upset over little things? ☐ Yes ☐ No
25. Do you frequently feel like crying? ☐ Yes ☐ No
26. Do you have trouble concentrating? ☐ Yes ☐ No
27. Do you enjoy getting up in the morning? ☐ Yes ☐ No
28. Do you prefer to avoid social gatherings? ☐ Yes ☐ No
29. Is it easy for you to make decisions? ☐ Yes ☐ No
30. Is your mind as clear as it used to be? ☐ Yes ☐ No

Total Score _____

Subject ID:		
Subject Name:		
Date:	AxA: 1	AxB:22-
Assessor Initials:		
Timepoint:	Baseline	

PASE

Physical Activity Scale for the Elderly And Paffenbarger Physical Activity Index © New England Research Institute

Please write down the **exact** number of hours or minutes and days for the relevant activities, even if the category is listed more broadly, such as 1-2 days for example

LEISURE TIME ACTIVITIES

1. Over the past 7 days, how often did you participate in sitting activities such as reading, watching TV or doing handcrafts?

[0] never → Go to Q.2

[1] seldom (1-2 days)

[2] sometimes (3-4 days)

[3] often (5-7 days)

1a. What were these activities?

_____

1b. On average, how many hours per day did you engage in these sitting activities <u>on these days</u>?

[1] less than 1 hour
[2] 1 but less than 2 hours
[3] 2 – 4 hours
[4] more than 4 hours

2. Over the past 7 days, how often did you take a walk outside your home or yard for any reason? For example for fun or exercise, walking to work, walking the dog etc?

[0] never → Go to Q.3

[1] seldom (1-2 days)

[2] sometimes (3-4 days)

[3] often (5-7 days)

2a. On average, how many hours per day did you spend walking <u>on these days</u>?

[1] less than 1 hour
[2] 1 but less than 2 hours
[3] 2 – 4 hours
[4] more than 4 hours

2b. What was the **<u>total</u>** distance (kms/miles/blocks) that you walked in the past 7 days? (1 mile = 12 blocks: 1km = 0.625miles).

Total number of blocks walked in the past **week** _____, or km _____, or miles _____

[1] less than 1 mile
[2] 0ne but less than 2 miles
[3[two to 4 miles
[4] more than 4 miles

3. How many flights of stairs did you **climb up** in the past 7 days? (one flight = 10 steps).

   Total number of steps climbed in the past **week** _____, or flights of steps _____.

   [1] less than 1 flight
   [2] 0ne but less than 2 flights
   [3] two to 4 flights
   [4] more than 4 flights

4. Over the past 7 days, how often did you engage in **light** sport or recreational activities such as 'light' cycling on an exercise bike, lawn bowls, bowling, water aerobics, golf with a cart, yoga, tai chi, fishing from a boat or pier or other similar activities?

   [0] never → Go to Q.5

   [1] seldom (1-2 days) →
   [2] sometimes (3-4 days) →
   [3] often (5-7 days) →

   4a. What were these activities?
   _____

   4b. On average, how many hours per day did you engage in these light sport or recreational activities on these days?
   [1] less than 1 hour
   [2] 1 but less than 2 hours
   [3] 2 – 4 hours
   [4] more than 4 hours

5. Over the past 7 days, how often did you engage in **<u>moderate</u>** sport or recreational activities such as doubles tennis, ballroom dancing, golf without a cart, softball or other similar activities?

[0] never → Go to Q.6

[1] seldom (1-2 days) → 5a. What were these activities? _____

5b. On average, how many hours per day did you engage in these moderate sport or recreational activities <u>on these days</u>?
[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

[2] sometimes (3-4 days) → 5a. What were these activities? _____

5b. On average, how many hours per day did you engage in these moderate sport or recreational activities <u>on these days</u>?
[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

[3] often (5-7 days) → 5a. What were these activities? _____

5b. On average, how many hours per day did you engage in these moderate sport or recreational activities <u>on these days</u>?
[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

6. Over the past 7 days, how often did you engage in **<u>strenuous</u>** sport and recreational activities such as jogging, swimming, cycling, singles tennis, aerobic dance, skiing (downhill or cross country) or other similar activities?

[0] never → Go to Q.7

[1] seldom (1-2 days) → 6a. What were these activities? _____

6b. On average, how many hours per day did you engage in these strenuous sport or recreational activities <u>on these days</u>?
[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

[2] sometimes (3-4 days) → 6a. What were these activities? _____

6b. On average, how many hours per day did you engage in these strenuous sport or recreational activities <u>on these days</u>?
[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

[3] often (5-7 days) → 6a. What were these activities? _____

6b. On average, how many hours per day did you engage in these strenuous sport or recreational activities <u>on these days</u>?
[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

7. Over the past 7 days, how often did you exercise specifically to increase muscle strength and endurance such as lifting weights or pushups etc?

[0] never → Go to Q.8

[1] seldom (1-2 days) → 7a. What were these activities? _____

7b. On average, how many hours per day did you engage in exercise to increase muscle strength/endurance <u>on these days</u>?
[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

[2] sometimes (3-4 days) → 7a. What were these activities? _____

7b. On average, how many hours per day did you engage in exercise to increase muscle strength/endurance <u>on these days</u>?
[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

[3] often (5-7 days) → 7a. What were these activities? _____

7b. On average, how many hours per day did you engage in exercise to increase muscle strength/endurance <u>on these days</u>?
[1] less than 1 hour [2] 1 but less than 2 hours
[3] 2 – 4 hours [4] more than 4 hours

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HOUSEHOLD ACTIVITIES

8. During the past 7 days, have you done any light housework such as dusting or washing dishes?
   [1] No [2] Yes

9. During the past 7 days, have you done any heavy housework or chores such as vacuuming, scrubbing floors, washing windows or carrying wood?
   [1] No [2] Yes

10. During the past 7 days, did you engage in any of the following activities?

	No	Yes
a. Home repairs like painting, wallpapering, electrical etc	0	1
b. Lawn work or yard care including snow or leaf removal, wood chopping etc	0	1
c. Outdoor gardening	0	1
d. Caring for another person such as a dependent child, dependent spouse or another adult	0	1

WORK-RELATED ACTIVITIES

11. During the past 7 days did you work for pay or as a volunteer?
    [1] No [2] Yes

11a. How many hours per week did you work for pay and/or as a volunteer? _____hours
11b. Which of the following categories best describes the amount of physical activity required on your job and /or volunteer work?

(1) Mainly sitting with light arm movements (eg. Office work, watch maker, seated assembly line worker, bus driver etc)
(2) Sitting or standing with some walking (eg. Cashier, general office worker, light tool and machinery worker)
(3) Walking with some handling of materials generally weighing less than 50 pounds (eg. Mailman, waitress, construction worker, heavy tool and machinery worker)
(4) Walking and heavy manual work often requiring handling of materials weighing over 50 pounds (eg. Lumberjack, stone mason, farm or general labourer.

Comments: _____

_____

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WOMAC

Western Ontario and McMaster Universities OA Index (Bellamy N. et al. Journal of Rheumatology. 15(12):1833-40, 1988)

Instructions to participants
In section A, B and C questions will be asked in the following formats and you should give your answer by putting an "X" in one of the boxes.

For example:
1. If you put your "X" in the left-hand box, that is

☒ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

Then, you are indicating you have no pain.

2. If you put your "X" in the right-hand box, that is

☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☒ Extreme

Then, you are indicating you have extreme pain.

Notes:
1. The further to the right you place your "X", the more pain you are experiencing.
2. The further to the left you place your "X", the less pain you are experiencing.
3. Please do not place your "X" outside the box.

Section A

Instructions to participants
The following questions concern the amount of pain you have experienced as a result of your arthritis in your knees. For each situation, please enter the amount of pain experienced in the last **48 hours**. Please answer by putting a "X" in one of the boxes.

HOW MUCH PAIN DO YOU HAVE?

1. Walking on a flat surface.

☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

2. Going up or down stairs.

☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

3. At night while in bed.

☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

4. Sitting or lying.

☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

5. Standing upright.

☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

Section B

Subject ID:		
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Instructions to participants
The following questions concern the amount of joint stiffness (not pain) you have experienced as a result of your arthritis in your knees. For each situation, please enter the amount of stiffness experienced in the last **48 hours**. Stiffness is a sensation of restriction or of slowness in ease with which you move your joints. Please answer by putting a "X" in one of the boxes.

6. How severe is your stiffness after first waking in the morning?
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

7. How severe is your stiffness after lying or sitting or resting later in the day?
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

Section C

Instructions to participants
The following questions concern your physical function. By this we mean your ability to move around and to look after yourself. For each of the following situation, please indicate the degree of difficulty experienced in the last **48 hours** due to your arthritis in your knees. Please answer by putting an "X" in one of the boxes.

WHAT DEGREE OF DIFFICULTY DO YOU HAVE?

8. Descending stairs
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

9. Ascending stairs
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

10. Rising from sitting
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

11. Standing
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

12. Bending to the floor
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

13. Walking on the flat
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

14. Getting in / out of the car
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

15. Going shopping
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

16. Putting on socks / stockings
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

17. Rising from bed
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

18. Taking off socks / stockings
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

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19. Lying in bed
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

20. Getting in / out of the bath
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

21. Sitting
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

22. Getting on / off the toilet
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

23. Heavy domestic duties
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

24. Light domestic duties
☐ None | ☐ Mild | ☐ Moderate | ☐ Severe | ☐ Extreme

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EWART SELF EFFICACY SCALE

This form asks you how much physical activity you think you can cope with right now. On a scale of 0 to 100, please choose a number that signifies how confident you are that you could do each activity now.

Lifting Objects	**Confidence**
Lift nothing	
Lift a 5 pound (approx. 2 kg) object	
Lift a 10 pound (approx. 5 kg) object	
Lift a 20 pound (approx. 10 kg) object	
Lift a 30 pound (approx. 15 kg) object	
Lift a 40 pound (approx. 20 kg) object	
Lift a 50 pound (approx. 25 kg) object	
Lift a 60 pound (approx. 30 kg) object	
Lift a 70 pound (approx. 35 kg) object	
Lift a 80 pound (approx. 40 kg) object	
Lift a 90 pound (approx. 45 kg) object	
Lift a 100 pound (approx. 50 kg) object	
Lift a 120 pound (approx. 60 kg) object	
Total	

Walking at a steady pace (3 miles per hour or approximately 5 kilometres per hour) without stopping	**Confidence**
Walking 1 block (2 mins)	
Walking 2 blocks (4 mins)	
Walking 3 blocks (6 mins)	
Walking 4 blocks (8 mins)	
Walking ½ mile [approx. 0.8 km] (10 mins)	
Walking 3/4 mile [approx. 1.2 km] (15 mins)	
Walking 1 mile [approx. 1.6 km] (20 mins)	
Walking 1.5 miles [approx. 2.4 km] (30 mins)	
Walking 2 miles [approx. 3.2 km] (40 mins)	
Walking 2.5 miles [approx. 4.0 km] (50 mins)	
Walking 3 miles [approx. 4.8 km] (60 mins)	
Walking 3.5 miles [approx. 5.6 km] (1 hr, 10 mins)	
Walking 4 miles [approx. 6.4 km] (1 hr, 20 mins)	
Walking 4.5 miles [approx. 7.2 km] (1 hr, 30 mins)	
Walking 5 miles [approx. 8.0 km] (1 hr, 40 mins)	
Total	

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<u>Jogging</u> at a steady pace (5 miles per hour or approximately 8 kilometres per hour) without stopping

	Confidence
Jog 1 block (1 min)	
Jog 2 blocks (2 mins)	
Jog 3 blocks (3 mins)	
Jog 4 blocks (4 mins)	
Jog ½ mile [approx. 0.8 km] (6 mins)	
Jog 3/4 mile [approx. 1.2 km] (8 mins)	
Jog 1 mile [approx. 1.6 km] (12 mins)	
Jog 1.5 miles [approx. 2.4 km] (18 mins)	
Jog 2 miles [approx. 3.2 km] (24 mins)	
Jog 2.5 miles [approx. 4.0 km] (30 mins)	
Jog 3 miles [approx. 4.8 km] (36 mins)	
Jog 3.5 miles [approx. 5.6 km] (42 mins)	
Jog 4 miles [approx. 6.4 km] (48 mins)	
Jog 4.5 miles [approx. 7.2 km] (54 mins)	
Jog 5 miles [approx. 8.0 km] (60 mins)	
Total	

<u>Climbing stairs</u> at a steady pace without pausing	**Confidence**
Walk up several steps	
Walk up 1 flight of stairs	
Walk up 2 flights of stairs	
Walk up 3 flights of stairs	
Walk up 4 flights of stairs	
Walk up 5 flights of stairs	
Walk up 6 flights of stairs	
Walk up 7 flights of stairs	
Walk up 8 flights of stairs	
Total	

<u>Push-ups</u> at a steady pace without pausing	**Confidence**
Do 1 push-up	
Do 3 push-ups	
Do 6 push-ups	
Do 10 push-ups	
Do 15 push-ups	
Do 20 push-ups	
Do 30 push-ups	
Do 35 push-ups	
Do 40 push-ups	
Total	

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NHANES

I am going read a list of activities with which some people have difficulty. Please tell me if you have:

0= no difficulty
1= some difficulty
2= much difficulty
3= unable to do
4= never do
5= don't know
6= inappropriate

Read choices. Probe if necessary. If answer is 1-6 then ask A-D.

Category	Q. #	Question	Score
DG	3	Dress yourself including tying shoes, working zippers, and doing buttons?	
PRI	5	Stand up from an armless straight chair (such as a dining room chair)?	
PRI	6	Get in and out of bed?	
EAT	7	Prepare meals?	
EAT	8	Cut your meat?	
EAT	9	Lift a full glass or cup to your mouth?	
EAT	10	Open a new milk carton?	
WALK	11	Walk a quarter mile (2-3 blocks)? If code = 0, go to Q13	
WALK	12	Walk from one room to another (on the same floor)?	
WALK	13	Walk up and down at least two steps?	
HYG	15	Get in and out of the bathtub?	
HYG	16	Wash and dry your whole body?	
HYG	17	Get on and off the toilet?	
DG	18	Comb your hair?	
REA	19	Reach and get a 5lb object (such as a bag of sugar) from just above your head?	
REA	20	Bend down and pick up clothing?	
GRIP	22	Open jars that have not been previously opened?	
GRIP	23	Use a pen or pencil to write with?	
ERR/CH	24	Get in and out of a car?	
ERR/CH	25	Run errands and shop?	
ERR/CH	26	Do light chores such as vacuuming?	
ERR/CH	27	Lift and carry a full bag of groceries?	
ERR/CH	28	Do heavy chores around the house or yard (washing windows, walls and floors)?	

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If subject answers 1-6 on questions from previous page, ask the following:

Q. #	A. Do you have help from another person? NO=0 YES=1	B. Do you have help from a mechanical aid/device? NO=0 YES=1	C. If yes, how much difficulty do you now have? (Code 0-6)
3			
5			
6			
7			
8			
9			
10			
11			
12			
13			
15			
16			
17			
18			
19			
20			
22			
23			
24			
25			
26			
27			
28			

Scoring

Category	Score	Category	Score
1. Dressing (qu: 3, 18)		6. Reach (qu: 19, 20)	
2. Arise (qu: 5, 6)		7. Grip (qu: 22, 23)	
3. Eating (qu: 7, 8, 9, 10)		8. Errands/chores (24, 25, 26, 27, 28)	
4. Walking (qu: 11, 12, 13)		9. Disability score (average 8 categories)	
5. Hygiene (qu: 15,16,17)			

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SF-36

SF-36v2™ Health Survey (To be completed by the subject)

☐ (1) NOT DONE

Instructions:
This survey asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Thank you for completing this survey!

For each of the following questions, please mark an ☒ in the one box that best describes your answer.

1. In general, would you say your health is:

Excellent	Very Good	Good	Fair	Poor
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. Compared to one week ago, how would you rate your health in general now?

Much better now than one week ago	Somewhat better now than one week ago	About the same as one week ago	Somewhat worse than one week ago	Much worse than one week ago
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

3. The following questions are about activities you might so during a typical day. Does your health now limit you in these activities? If so, how much?

	Yes, limited a lot	Yes, limited a little	No, not limited at all
a. Vigorous activities such as running, lifting heavy objects, participating in strenuous sports	☐ 1	☐ 2	☐ 3
b. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling or playing golf	☐ 1	☐ 2	☐ 3
c. Lifting or carrying groceries	☐ 1	☐ 2	☐ 3
d. Climbing several flights of stairs	☐ 1	☐ 2	☐ 3
e. Climbing one flight of stairs	☐ 1	☐ 2	☐ 3
f. Bending, kneeling or stooping	☐ 1	☐ 2	☐ 3
g. Walking more than a mile	☐ 1	☐ 2	☐ 3
h. Walking several hundred yards	☐ 1	☐ 2	☐ 3
i. Walking one hundred yards	☐ 1	☐ 2	☐ 3
j. Bathing or dressing yourself	☐ 1	☐ 2	☐ 3

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Timepoint:	Baseline	

4. During the <u>past week</u>, how much of the time have you had any of the following problems with your work or other regular daily activities <u>as a result of your physical health</u>?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
b. <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
c. Were limited in the <u>kind</u> of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
d. Had <u>difficulty</u> performing the work or other activities (for example, it took extra effort)	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**

5. During the <u>past week</u>, how much of the have you had any of the following problemswith your work or other regular daily activities <u>as a result of any emotional problems</u> (such as feeling depressed or anxious)?

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Cut down on the <u>amount of time</u> you spent of work or other activities	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
b. <u>Accomplished less</u> than you would like	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
c. Did work or other activities <u>less carefully than usual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**

6. During the <u>past week</u>, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups?

Not at all	Slightly	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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7. How much <u>bodily</u> pain have you had during the <u>past week</u>?

None	Very mild	Mild	Moderate	Severe	Very Severe
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6

8. During the <u>past week</u>, how much did <u>pain</u> interfere with your normal work (including both work outside the home and housework)?

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

9. These questions are about how you feel and how things have been with you <u>during the past week</u>. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the <u>past week</u>…

	All of the time	Most of the time	Some of the time	A little of the time	None of the time
a. Did you feel full of life?	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
b. Have you been very nervous?	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
c. Have you felt so down in the dumps that nothing could cheer you up?	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
d. Have you felt calm and peaceful?	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
e. Did you have a lot of energy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
f. Have you felt downhearted and depressed?	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
g. Did you feel worn out?	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
h. Have you been happy?	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
i. Did you feel tired?	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**

10. During the <u>past week</u>, how much of the time has your <u>physical health or emotional problems</u> interfered with your social activities like visiting friends, relatives, etc.)?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

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11. How TRUE or FALSE is <u>each</u> of the following statements for you?

	Definitely true	Mostly true	Don't know	Mostly false	Definitely false
a. I seem to get sick a little easier than other people	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
b. I am as healthy as anybody I know	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
c. I expect my health to get worse	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**
d. My health is excellent	☐ 1	☐ 2	☐ 3	☐ 4	☐ **5**

THANK YOU FOR COMPLETING THESE QUESTIONS!

Subject ID:		
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THREE-FACTOR EATING QUESTIONNAIRE

One point is given for each item in Part I and for each item (numbered question) in Part II. The correct answer for the true/false items is underlined and bside it is the number of the factor it measures. The direction of the question in Part II is determined by splitting the responses at the middle. If the item is labelled '+', those responses above the middle are given a zero. Vice versa for those with a '—'. For example, anyone scoring 3 or 4 on the first item in Part II (item No. 37) would receive 1 point. Anyone scoring 1 or 2 would receive a zero.

Part I

No.	Question	True / False (circle)	
1.	When I smell a sizzling steak or see a juicy piece of meat, I find it very difficult to keep from eating, even if I have just finished a meal.	T	F
2.	I usually eat too much at social occasions like parties and picnics.	T	F
3.	I am usually so hungry that I eat more than 3 times a day.	T	F
4.	When I have eaten my quota of calories, I am usually good about not eating any more.	T	F
5.	Dieting is so hard for me because I just get too hungry.	T	F
6.	I deliberately take small helpings as a means of controlling my weight.	T	F
7.	Sometimes things just taste so good that I keep eating even when I am no longer hungry.	T	F
8.	Since I am often hungry, I sometimes wish that an expert would tell me that 'I have had enough' or that 'I can have something more to eat.'	T	F
9.	When I feel anxious, I find myself eating.	T	F
10.	Life is too short to worry about dieting.	T	F
11.	Since my weight goes up and down, I have gone on reducing diets more than once.	T	F
12.	I often feel so hungry that I just have to eat something.	T	F
13.	When I am with someone who is overeating, I usually overeat	T	F

too.

14.	I have a pretty good idea of the number of calories in common food.	T	F
15.	Sometimes when I start eating, I just can't seem to stop.	T	F
16.	It is not difficult for me to leave something on my plate.	T	F
17.	At certain times of the day, I get hungry because I have gotten used to eating then.	T	F
18.	While on a diet, if I eat food that is not allowed, I consciously eat less for a period of time to make up for it.	T	F
19.	Being with someone who is eating often makes me hungry enough to eat as well.	T	F
20.	When I feel blue, I often overeat.	T	F
21.	I enjoy eating too much to spoil it by counting calories or watching my weight.	T	F
22.	When I see a real delicacy, I often get so hungry that I have to eat right away.	T	F
23.	I often stop eating when I am not really full as a conscious means of limiting the amount that I eat.	T	F
24.	I get so hungry that my stomach often feels like a bottomless pit.	T	F
25.	My weight has hardly changed at all in the last ten years.	T	F
26.	I am always hungry so it is hard for me to stop eating before I finish the food on my plate.	T	F
27.	When I feel lonely, I console myself by eating.	T	F
28.	I consciously hold back at meals in order not to gain weight.	T	F
29.	I sometimes get very hungry late in the evening or at night.	T	F
30.	I eat anything I want, any time I want.	T	F
31.	Without even thinking about it, I take a long time to eat.	T	F
32.	I count calories as a conscious means of controlling weight.	T	F
33.	I do not eat some foods because they make me fat.	T	F

34. I am always hungry enough to eat at any time. T F

35. I pay a great deal of attention to changes in my figure. T F

36. While on a diet, if I eat a food that is not allowed, I often then splurge and eat other high calorie foods. T F

Part II

Directions: Please answer the following questions by circling the number above the response that is appropriate to you.

37. How often are you dieting in a conscious effort to control your weight?

1	2	3	4
Rarely	Sometimes	Usually	Always

38. Would a weight fluctuation of 5 lbs affect the way you live your life?

1	2	3	4
Not at all	Slightly	Moderately	Very much

39. How often do you feel hungry?

1	2	3	4
Only at mealtimes	Sometimes between meals	Often between meals	Almost always

40. Do your feelings of guilt about overeating help you to control your food intake?

1	2	3	4
Never	Rarely	Often	Always

41. How difficult would it be for you to stop eating halfway through dinner and not eat for the next four hours?

1	2	3	4
Easy	Slightly difficult	Moderately difficult	Very difficult

42. How conscious are you of what you are eating?

1	2	3	4
Not at all	Slightly	Moderately	Extremely

43. How frequently do you avoid 'stocking up' on tempting foods?

1	2	3	4
Almost never	Seldom	Usually	Almost always

44. How likely are you to shop for low calorie foods?

1	2	3	4
Unlikely	Slightly unlikely	Moderately likely	Very likely

45. Do you eat sensibly in front of others and splurge alone?

1	2	3	4
Never	Rarely	Often	Always

46. How likely are you to consciously eat slowly in order to cut down on how much you eat?

1	2	3	4
Unlikely	Slightly likely	Moderately likely	Very likely

47. How frequently do you skip dessert because you are no longer hungry?

1	2	3	4
Almost never	Seldom	At least once a week	Almost every day

48. How likely are you to consciously eat less than you want?

1	2	3	4
Unlikely	Slightly likely	Moderately likely	Very likely

49. Do you go on eating binges even though you are not hungry?

1	2	3	4
Never	Rarely	Sometimes	At least once a week

50. On a scale of 0 to 5, where 0 means no restraint in eating (eating whatever you want, whenever you want it) and 5 means total restraint (constantly limiting food intake and never 'giving in'). what number would you give yourself?

0	Eat whatever you want, whenever you want
1	Usually eat whatever you want, whenever you want it
2	Often eat whatever you want, whenever you want it
3	Often limit food intake, but often 'give in'
4	Usually limit food intake, rarely 'give in'
5	Constantly limiting food intake, never 'giving in'

51. To what extent does this statement describe your eating behaviour? 'I start dieting in the morning, but because of any number of things that happen during the day, by evening I have given up and eat what I want, promising myself to start dieting again tomorrow.'

1	2	3	4
Not like me	Little like me	Pretty good description of me	Describes me perfectly

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SOCIAL SUPPORT & EXERCISE SURVEY

Below is a list of things people might do or say to someone who is trying to exercise regularly. If you are not trying to exercise, then some of the questions may not apply to you, but please read and give an answer to every question.

Please rate each question ***twice***. Under ***family***, rate how often anyone living in your household has said or done what is described during the last three months. Under ***friends***, rate how often your friends, acquaintances, or co-workers have said or done what is described during the last three months.

Please write one number from the following rating scale in each space:

none	rarely	a few times	often	very often	does not apply
1	2	3	4	5	8

During the ***past three months***, my family (or members of my household) or friends:

	Family	**Friends**
11. Offered to exercise with me.		
12. Gave me helpful reminders to exercise ("Are you going to exercise tonight?").		
13. Gave me encouragement. to stick with my exercise program.		
14. Changed their schedule so we could exercise together.		
15. Discussed exercise with me.		
16. Complained about the time I spend exercising.		
17. Criticized me or made fun of me for exercising.		
18. Gave me rewards for exercising (bought me something or gave me something I like).		
19. Planned for exercise on recreational outings.		
20. Helped plan activities around my exercise.		
21. Asked me for ideas on how they can get more exercise.		
22. Exercised with me.		
23. Talked about how much they like to exercise.		

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SELF-EFFICACY FOR EXERCISE

Instructions: Many people report that it is more difficult to get themselves to exercise under some conditions than others.

Imagine if the "The LO Study" involved you performing a strength training program for 12 months. By using the scale below, please rate how CONFIDENT you would be that you could participate in strength training under each of the following conditions over the NEXT 12 MONTHS.

Please write in a confidence rating for EVERY LINE. Do NOT leave any lines blank.

Confidence Scale:

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
Not at all Confident					Somewhat confident					Absolutely confident

Over the next six months I could strength train:

	Confidence Rating (0-100%)
1. When tired…	
2. During or following a personal crisis…	
3. When feeling depressed…	
4. When feeling anxious…	
5. During bad weather…	
6. When slightly sore from the last time I exercised…	
7. When on vacation…	
8. When there are competing interests (like my favourite TV show)…	
9. When I have a lot of work to do…	
10. When I haven't reached my exercise goals…	
11. When I don't receive support from family or friends…	
12. Following complete recovery from an illness which has caused me to stop exercising for a week or longer…	
13. When I have no one to exercise with…	
14. When my schedule is hectic…	

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SELF- EFFICACY FOR EXERCISE AND OUTCOME EXPECTATIONS FOR EXERCISE FOR MINORITY OLDER ADULTS

SECTION A. Self-Efficacy for Exercise Scale

Now I am going to give little situations that might affect your participation in exercise. For each one, use this scale where 0 is Not Confident and 10 is Very Confident, to tell me how confident you are right now that you could exercise 2 times a week for 60 minutes each time, in each of these situations:

	Not Confident										**Very Confident**
1. If the weather was bothering you	0	1	2	3	4	5	6	7	8	9	10
2. If you were bored by the program or activity	0	1	2	3	4	5	6	7	8	9	10
3. If you felt pain when exercising	0	1	2	3	4	5	6	7	8	9	10
4. If you had to exercise alone	0	1	2	3	4	5	6	7	8	9	10
5. If you did not enjoy it	0	1	2	3	4	5	6	7	8	9	10
6. If you were too busy with other activities	0	1	2	3	4	5	6	7	8	9	10
7. If you felt tired	0	1	2	3	4	5	6	7	8	9	10
8. If you felt stressed	0	1	2	3	4	5	6	7	8	9	10
9. If you felt depressed	0	1	2	3	4	5	6	7	8	9	10

SECTION B. Outcome Expectations for Exercise Scale

Now I'm going to read you nine different statements about the benefits of exercising, like walking, jogging, swimming, biking, stretching, or lifting weights. On this scale from 1 to 5, where 1 means you Strongly Disagree, and 5 means you Strongly Agree, please state how much you agree or disagree with each statement.

1. Exercise makes me feel better physically

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

2. Exercise makes my mood better in general

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

3. Exercise helps me feel less tired

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

4. Exercise makes my muscles stronger

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

5. Exercise is an activity I enjoy doing

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

6. Exercise gives me a sense of personal accomplishment

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

7. Exercise makes me more alert mentally

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

8. Exercise improves my endurance in performing my daily activities (personal care, cooking, shopping, light cleaning, taking out the garbage)

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

9. Exercise helps to strengthen my bones

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

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CORE SELF-EVALUATION

A. I am confident that I will get the success I deserve in life

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

B. Sometimes I feel depressed

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

C. When I try, I generally succeed

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

D. Sometimes when I fail, I feel worthless

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

E. I complete tasks successfully

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

F. Sometimes, I do not feel in control of my regular daily activities

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

G. Overall, I am satisfied with my life

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

H. I am filled with doubts about my competence

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

I. I determine what will happen in my life

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

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J. I do not feel in control of the outcomes in my daily life

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

K. I am capable of coping with most of my problems

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5

L. There are times when things look pretty bleak and hopeless to me

Strongly Disagree	Disagree	Neither agree or disagree	Agree	Strongly Agree
1	2	3	4	5