Impact of lifestyle and digital health interventions on vascular function and cardiometabolic health

Sayan Mitra

A thesis submitted to fulfil requirements for the degree of

Doctor of Philosophy (Medicine)

Fontana Healthy Longevity Research Group, Charles Perkins Centre

Central Clinical School, Faculty of Medicine and Health

The University of Sydney

2024

Primary supervisor Professor Luigi Fontana

Co-supervisors Dr Sophie Cassidy, Dr Cynthia Kroeger, and Dr Na Liu

Statement of originality

This is to certify that to the best of my knowledge; the content of this thesis is my own work. This thesis has not been submitted for any degree or other purposes.

I certify that the intellectual content of this thesis is the product of my own work and that all the assistance received in preparing this thesis and sources have been acknowledged.

Sayan Mitra, MBBS MPH MPhil
Monday, 16 December 2024

Abstract

The rising prevalence of abdominal obesity, type 2 diabetes, hypertension, and dyslipidaemia poses a significant global challenge in the fields of cardiometabolic health and vascular ageing. This challenge is primarily driven by sedentary lifestyles, inadequate dietary habits, and the demographic trend towards an ageing population. These elements collectively contribute to the development of atherosclerosis and other vascular modifications, consequently increasing the risk of cardiovascular diseases (CVD), the foremost cause of morbidity and mortality globally. Additionally, the widespread difficulty in adopting and maintaining necessary lifestyle modifications presents a substantial barrier, significantly hampering efforts to prevent or mitigate cardiometabolic diseases and related escalating health care costs.

The principal research gap in addressing these concerns lies in the identification and implementation of strategies that effectively encourage and sustain lifestyle improvements across different age groups. While the risk factors and their impact on vascular health are well understood, there is a notable lack of effective methods to ensure long-term adherence to healthier lifestyles, especially in communities with varied backgrounds. Moreover, there is an urgent requirement for more comprehensive research into specialised digital health tools, which promise to offer accessible and cost-effective means to enhance cardiometabolic health and prevent vascular ageing worldwide.

This thesis investigates how lifestyle choices impact vascular health and examines the role of digital health tools in promoting healthier lifestyles. Starting with a foundational understanding of lifestyle's effects on cardiovascular health (Chapter 1), the research initially focuses on a large population database (UK Biobank) to explore the relationship between lifestyle behaviours and its impact on cardiovascular health (Chapter 2), specifically looking into carotid intima-media thickness as a surrogate marker for future cardiovascular disease events. This study highlights the connection between everyday habits, cardiometabolic risk factors and vascular health, setting the groundwork for a deeper investigation.

Recognising the limitations of observational studies in proving cause and effect, we advance to a controlled clinical setting with the LIVEPLUS Protocol, a study designed to closely examine how lifestyle changes affect vascular health through a randomised controlled trial (Chapter 3). This approach allows for a detailed study of the impact of diet and exercise over six months, providing clear evidence of the benefits of a comprehensive lifestyle intervention (Chapter 4).

Acknowledging the difficulty in maintaining lifestyle changes over time, the thesis then explores the concept of digital health interventions as a method to increase long-term commitment to healthy habits (Chapter 5). This exploration includes a thorough literature review on gamification in health interventions, setting the stage for applying these concepts in a practical setting with the MIRTH Protocol, which integrates digital health interventions into the LIVEPLUS study to encourage sustained lifestyle improvements (Chapter 6).

A modified MIRTH protocol is then applied as a digital health intervention approach and the outcomes are examined in Chapter 7, comparing the results to existing literature to understand how digital health

intervention affects lifestyle behaviours and, consequently, vascular health. The thesis concludes with a comprehensive synthesis of the findings from the cross-sectional study, the systematic review, and the LIVEPLUS and MIRTH studies, discussing their implications within the broader context of digital health interventions and lifestyle changes for vascular health improvement (Chapter 8). This final chapter ties together the various elements of the research, offering a critical perspective on their significance and suggesting directions for future research in the field.

Acknowledgements

Completing this PhD thesis has been an immensely rewarding experience, and I am deeply thankful to everyone who has supported and guided me along the way.

First and foremost, I want to express my heartfelt gratitude to my supervisors, Professor Luigi Fontana, Dr Sophie Cassidy, Dr Cynthia Kroeger, and Dr Na Liu. Your expertise, guidance, and unwavering support have been instrumental in shaping my research and academic growth. I have been inspired by your dedication and feel incredibly fortunate to have had the opportunity to learn from each of you. Special thanks to Luigi for your candour and the candid discussions we shared, and to Cynthia for your mentorship, which has significantly influenced my development as a researcher.

I am also deeply indebted to my collaborators, Dr Kenny Xu, Dr Raaj Biswas, Associate Professor Bibhas Chakraborty, Dr Andrea Nova, Professor Leah Avery, Dr Imre Hunyor, Dr Robin Huang, and Dr Philip Darke. Your invaluable guidance on my projects, insights, and contributions have been crucial to the success of my work. I am grateful for your patience, encouragement, and the profound knowledge you have shared with me. A special mention goes to Kenny for your friendship and to Raaj for your exceptional mentorship, which has greatly enhanced my research skills.

To the clinic staff who have made me feel so welcome when collecting data for my project: my sincere thanks to Pauline Scott, David Martins, and Catherine Yates. My thanks also to Reeja (Jia) Nasir, Sally McClintock, and Seren Ucak for your unrelenting assistance with various clinical measurements. Your support has been indispensable, and I am grateful for your readiness to help.

My gratitude extends to my colleagues in the lab, whose camaraderie and support have been a source of strength. Dr Andrius Masedunskas, I have learnt so much from you and deeply appreciate your willingness to share your expertise. Your mentorship has been incredibly valuable to me. Tian and Isabella, your unwavering support and friendship have made the lab a more collaborative and enjoyable place to work.

A special note of thanks goes to my family, whose love and support have been my foundation throughout this journey. I am deeply thankful to my parents for their unconditional support and belief in me. To my brother, your advice and encouragement have been invaluable. To my friends, thank you for your compassion, camaraderie, and the light-hearted silly moments that have provided much-needed relief during challenging times. Your presence in my life has been a blessing.

Lastly, I am grateful to everyone who has contributed, directly or indirectly, to the completion of this thesis. Your support and encouragement have been pivotal, and I am deeply thankful for your kindness and generosity.

This thesis is a testament to the collective effort and support of a wonderful community. Thank you all for being part of this journey.

Table of Contents

List of figures

List of tables

List of abbreviations

AIx	Augmentation index
AP	Augmentation pressure
BMI	Body mass index
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CHD	Coronary heart disease
CIMT	Carotid intima media thickness
CPC	Charles Perkins Centre
CRBI	cardiometabolic risk biomarker index
CRP	C-reactive protein
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
df	Degrees of freedom
DHI	Digital health interventions
FMD	Flow mediated dilation
HbA1c	haemoglobin A1c
HDL	high-density lipoprotein
HF	heart failure
HTN	hypertension
ILP	Intensive lifestyle program
IMT	Intima media thickness
IPAQ	International Physical Activity Questionnaire
IQR	Inter quartile range
LAP	Low attenuation plaque
LDL	low-density lipoprotein
LIVEPLUS	Lifestyle
MARS	Mobile apps rating scale
MI	myocardial infarction
MIRTH	Messages improving resting heart health
MRT	Micro randomised trial
PWA	Pulse wave analysis
PWV	Pulse wave velocity
RPA	Royal Prince Alfred (hospital)
SBP	Systolic blood pressure
SEVR	Subendocardial viability ratio
T2DM	Type 2 diabetes mellitus
WHR	waist-to-hip ratio

Authorship attribution statement

Chapter 3 of this thesis is published as a study protocol in the Journal of Nutrition and Health Aging. I was involved in the design and drafting of the manuscript.

> Cassidy S, Kroeger CM, Wang T, **Mitra S**, Liu C, Ribeiro R, Dai A, Lau J, Huang R, Masedunkas A, Jose S Liu N, Avery L, Yang J, McGrady M, Lo S, George J, Cistulli P, Khor L, Kozor R, Ugander M, Wilcox I, Hunyor I, Fontana L. Impact of an Intensive Lifestyle Program on Low Attenuation Plaque and Myocardial Perfusion in Coronary Heart Disease: A Randomised Clinical Trial Protocol. Nutrition and Healthy Aging, 2022: 9-22, doi: 10.3233/NHA-210146

Chapter 5 of this thesis is currently under review by npj Digital Medicine for publication as an original research article. I was involved in the conceptualisation and design of this study, including literature search, study screening, acquisition, data extraction and interpretation, qualitative and statistical analyses, meta-analysis, generating original figures, and drafting of the manuscript. I was responsible as corresponding author for submitting the manuscript.

> **Mitra S**, Kroeger CM, Wang T, Masedunskas A, Cassidy S, De Ciutiis I, Hooijenga P, Huang R, Liu N, Fontana L. Effectiveness of Gamified vs Non-Gamified Digital Health Apps on Cardiovascular Risk: A Systematic Review and Meta-Analysis. npj Digital Medicine. NPJDIGITALMED-09818. (Stage: Manuscript under revision)

Chapter 6 of this thesis is published as a study protocol in JMIR Research Protocols. I was involved in the conceptualisation, design, and drafting of the manuscript. I was responsible as corresponding author for submitting the manuscript.

> **Mitra S**, Kroeger CM, Xu J, Avery L, Masedunskas A, Cassidy S, Wang T, Hunyor I, Wilcox I, Huang R, Chakraborty B, Fontana L. Testing the effects of app-based motivational messages on physical activity and resting heart rate through smartphone app compliance in patients with vulnerable coronary artery plaques: Protocol for a microrandomized trial. JMIR Res Protoc. 2023;12:e46082, doi: 10.2196/46082

In addition to the statements above, in cases where I am not the corresponding author of a published item, permission to include the published material has been granted by the corresponding author.

Sayan Mitra, MBBS MPH MPhil
Monday, 16 December 2024

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

Professor Luigi Fontana, MD PhD FRACP
Monday, 16 December 2024

Publications and presentations

Peer reviewed publications included in this thesis

1. **Mitra S**, Kroeger CM, Xu J, Avery L, Masedunskas A, Cassidy S, Wang T, Hunyor I, Wilcox I, Huang R, Chakraborty B, Fontana L. Testing the effects of app-based motivational messages on physical activity and resting heart rate through smartphone app compliance in patients with vulnerable coronary artery plaques: Protocol for a microrandomized trial. JMIR Res Protocols. 2023;12:e46082.
2. Cassidy S, Kroeger CM, Wang T, **Mitra S**, Liu C, Ribeiro R, Dai A, Lau J, Huang R, Masedunkas A, Jose S Liu N, Avery L, Yang J, McGrady M, Lo S, George J, Cistulli P, Khor L, Kozor R, Ugander M, Wilcox I, Hunyor I, Fontana L. Impact of an intensive lifestyle program on low attenuation plaque and myocardial perfusion in coronary heart disease: A randomised clinical trial protocol. Nutrition and Healthy Aging. 2022;7(9-22).

Peer-reviewed publications not contained within this thesis

1. **Mitra S**. The cumulative effect of insufficient sleep on adolescent obesity: Evidence from a Spanish cohort, European Journal of Preventive Cardiology, Volume 30, Issue 12, September 2023, Pages 1289–1290, doi:10.1093/eurjpc/zwad175
2. Wang T, Kroeger CM, Cassidy S, **Mitra S**, Ribeiro R, Jose S, Masedunskas A, Senior A, Fontana L. Vegetarian dietary patterns and cardiometabolic risk in people with or at high risk of cardiovascular disease: A systematic review and meta-analysis. JAMA Network Open. 2023;6(7):e2325658. doi:10.1001/jamanetworkopen.2023.25658

Conference proceedings included in this thesis

1. **Mitra S**, Biswas R, Nova A, *et al.* Investigating lifestyle determinants of carotid intima-media thickness: cross-sectional insights from the UK biobank cohort. European Heart Journal. 2024. 45(Suppl 1). doi:10.1093/eurheartj/ehae666.2722
2. **Mitra S**, Kroeger C, Wang T, *et al*. The Impact of Gamified Smartphone App Interventions on Behaviour and Metabolic Outcomes in Individuals at Risk of Cardiovascular Disease. Studies in Health Technology and Informatics. 2024 Aug;318:172-173. doi:10.3233/SHTI240913
3. **Mitra S**, Kroeger C, Wang T, *et al*. Gamified smartphone-app interventions on behaviour and metabolic profile in patients at risk of cardiovascular disease. Studies in Health Technology and Informatics. 2024 Jan;310:1542-1543. doi:10.3233/shti231284
4. Wang T, Cassidy S, Kroeger C, **Mitra S**, Ribeiro R, Masedunskas A, Huang R, Fontana L. P23-080-23 Impact of an intensive lifestyle program on low attenuation plaque and myocardial perfusion in coronary heart disease: A randomised clinical trial protocol. Current Developments in Nutrition. 2023 Jul 1;7:100188

Conference proceedings not contained within this thesis

1. Wang T, Nova A, Cassidy S, Fazia T, **Mitra S**, Kroeger CM, Masedunskas A, Bernardinelli L, Willett WC, Fontana L. Association of a healthy plant-based heart-protective diet with reduced cardiovascular disease incidence and mortality: findings from the UK Biobank Study. European Heart Journal. 2024. 45(Suppl 1). doi:10.1093/eurheartj/ ehae666.2647
2. Wang T, Nova A, Cassidy S, Kroeger C, **Mitra S**, Masedunskas A, Fazia T, Bernardinelli L, Fontana L. P23-079-23 Heart-protective diet scores, cardiometabolic risk and cardiovascular disease incidence and mortality: a prospective study from UK biobank. Current Developments in Nutrition. 2023 Jul 1;7:100187
3. Wang T, Kroeger C, Cassidy S, **Mitra S**, Ribeiro R, Jose S, Masedunskas A, Fontana L. The effect of different vegetarian diets on cardiometabolic profile in people with or at high risk of cardiovascular diseases: A systematic review and meta-analysis. Current Developments in Nutrition. 2022 Jun;6(Suppl 1):53

Conference presentations

1. **Mitra S**, *et al*. Investigating lifestyle determinants of carotid intima-media thickness: cross-sectional insights from the UK biobank cohort. European Society of Cardiology (ESC) Congress 2024, London, UK.
2. **Mitra S,** *et al*. Investigating the impact of lifestyle on carotid intima-media thickness through a UK biobank cross-sectional study. American College of Cardiology (ACC) Asia 2024, New Delhi, India
3. **Mitra S,** *et al*. The impact of gamified smartphone app interventions on behaviour and metabolic outcomes in individuals at risk of cardiovascular disease. HIC 2024, Brisbane, Australia
4. **Mitra S**, *et al*. Revolutionizing Cardiovascular Health: Assessing the Impact of Intensive Lifestyle Interventions on CVD population with Low Attenuation Plaque (LIVEPLUS protocol). IBTN 2024, Montreal, Canada.
5. **Mitra S**, *et al*. App-Based Motivational Messages for Physical Activity and Heart Rate in Coronary Plaque Patients: Microrandomized Trial Protocol. International Behavioural Trials Network (IBTN) 2024, Montreal, Canada.
6. **Mitra S**, Biswas RK, Nova A, Hooijenga P, Cassidy S, Kroeger CM, Fontana L. Association between diet quality and vascular ageing in the UK Biobank population. Australian Public Health Conference 2023, Hobart, Tasmania, Australia
7. **Mitra S**, *et al*. Gamified Smartphone-App Interventions on Behaviour and Metabolic Profile in Patients at Risk of Cardiovascular Disease. MedInfo 2023, Australasian Institute of Digital Health, Sydney, Australia
8. **Mitra S**, *et al*. Gamified Smartphone-App Interventions on Behaviour and Metabolic Profile in Patients at Risk of Cardiovascular Disease. Medicine in a Virtual Age, October 4-6, 2022, Nature Conferences (Online)

In preparation or review

1. **Mitra S**, *et al*. Carotid intima-media thickness, cardiovascular disease, and risk factors in 29,000 UK Biobank adults. American Journal of Preventive Cardiology. (Stage: Manuscript AJPC-D-24-00305 under consideration.)
2. **Mitra S**, *et al*. Effectiveness of Gamified vs Non-Gamified Digital Health Apps on Cardiovascular Risk: A Systematic Review and Meta-Analysis. npj Digital Medicine. (Stage: Manuscript NPJDIGITALMED-09818 under consideration.)

Rationale for chapters

From Chapter 1 to Chapter 2:

Having established a foundational understanding of how lifestyle impacts coronary heart disease and cardiometabolic health, as well as the role of digital health/mHealth interventions (Chapter 1), we now turn to a specific instance of this relationship. In Chapter 2, we investigate a cross-section of the UK Biobank population, focusing on the influence of lifestyle behaviours on carotid intima-media thickness. This study offers a more focused lens on the correlation between lifestyle factors and vascular function, setting the stage for deeper exploration.

From Chapter 2 to Chapter 3:

While the cross-sectional study (Chapter 2) provided valuable insights, the inherent limitations of such studies, particularly in establishing causality, prompt us to further our investigation through a more controlled approach. In Chapter 3, we progress to a randomised controlled trial – the LIVEPLUS Protocol – to rigorously examine the influence of lifestyle on vascular function. This shift from observational to experimental research allows us to explore these relationships with greater precision.

From Chapter 3 to Chapter 4:

Building on the framework established in the LIVEPLUS Protocol, Chapter 4 presents a detailed analysis of the intervention's impact over a six-month period. This longitudinal sub-study within LIVEPLUS zeroes in on the direct effects of diet and physical activity on vascular function, providing tangible evidence of lifestyle modification outcomes.

From Chapter 4 to Chapter 5:

Recognising the challenges in maintaining long-term adherence to lifestyle interventions, Chapter 5 shifts focus to an innovative approach: gamification. Through a systematic literature review, we explore how gamification might bolster the effectiveness of health interventions, setting a conceptual foundation for integrating these strategies into our research.

From Chapter 5 to Chapter 6:

With the groundwork on gamification laid out, Chapter 6 introduces the MIRTH Protocol, a practical application of gamification within the context of the LIVEPLUS study. This chapter bridges the conceptual understanding of gamification from the literature review to its practical implementation, exploring how it can enhance lifestyle behaviour changes.

From Chapter 6 to Chapter 7:

The practical implications of the MIRTH Protocol come to life in Chapter 7, where we look into the outcomes of this gamified approach. By comparing these results with the systematic review and existing literature, we gain a deeper understanding of how gamification influences lifestyle behaviours and, in turn, vascular health.

From Chapter 7 to Chapter 8:

Finally, Chapter 8 synthesises the findings from the entire journey – from the LIVEPLUS protocol to the MIRTH case study – within the broader landscape of lifestyle interventions and vascular health. This discussion not only ties together the different strands of my dissertation but also critically examines their implications and potential directions for future exploration.

1 Chapter 1: Introduction and literature review

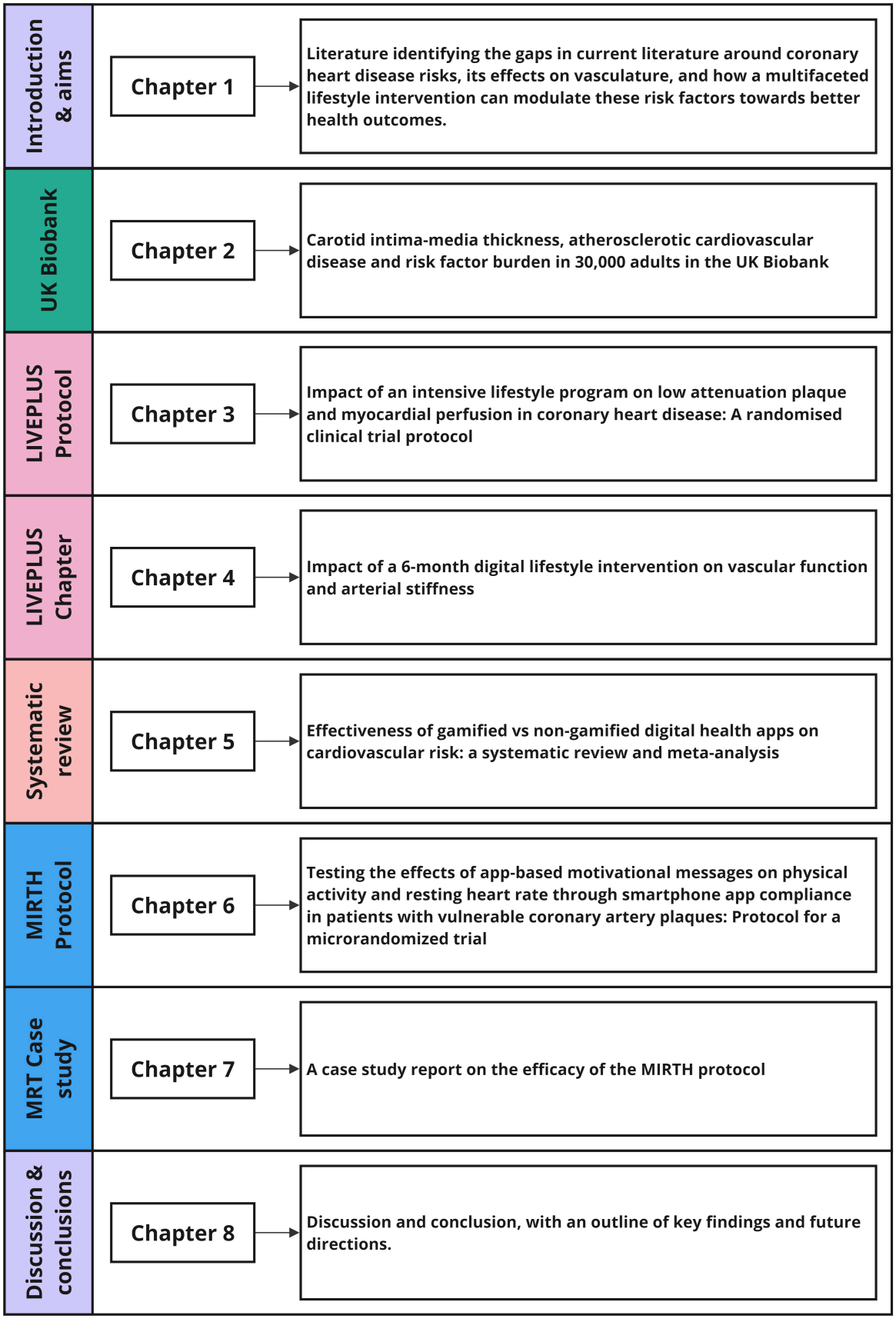


Figure 1.1 Thesis outline and chapter overview.

1.1 General introduction

Cardiovascular disease (CVD) remains a significant public health challenge worldwide, contributing substantially to global morbidity and disability. Atherosclerotic CVD, characterised by the narrowing of arteries due to plaque build-up, often leads to severe health outcomes, including coronary heart disease (CHD), heart failure, peripheral vascular disease, ischemic stroke and vascular dementia.[1] The World Health Organization reports that CVDs are the leading cause of death globally, with an estimated 17.9 million humans dying from CVDs in 2019, representing 32% of all global deaths. Of these deaths, 85% were due to heart attacks and strokes.[2] Coronary heart disease (CHD), also known as ischemic heart disease, affected an estimated 244.1 million people globally in 2020, with a higher prevalence in males (141.0 million) compared to females (103.1 million).[3]

The prevalence of atherosclerotic CVD is closely linked to lifestyle factors common in Western societies.[4] A sedentary lifestyle combined with diets high in saturated fats, refined carbohydrates, salt and processed foods significantly contributes to the development and progression of atherosclerotic CVD.[5] These behaviours promote central obesity, type 2 diabetes, dyslipidaemia, hypertension, and escalating atherosclerotic CVD rates.[6] The convenience-oriented Western lifestyle, characterised by fast food, insufficient physical activity, sleep deprivation and mental stress exacerbates this burden.[7] Additionally, behavioural factors such as tobacco use and excessive alcohol consumption, along with environmental factors like air pollution, further increase the risk.[8] These risk factors often result in intermediate conditions such as elevated blood pressure, insulin resistance, glucose intolerance, as well as low-grade chronic inflammation and clonal haematopoiesis, which collectively heighten the likelihood of atherosclerotic CVD.[9]

Amidst these challenges, there has been a marked increase in the use of digital tools for the prevention and management of CHD in recent years. These technologies offer potential innovative solutions to promote healthier lifestyles and provide timely interventions. Mobile health applications, wearable fitness trackers, and telemedicine platforms are becoming integral components of healthcare, empowering individuals to monitor their health and engage in proactive disease management. Digital tools facilitate personalised care, improve patient adherence to treatment plans, and enable healthcare providers to deliver more efficient and effective care.

This thesis investigates the interplay between lifestyle factors, cardiometabolic and digital health innovations in addressing atherosclerotic CVD, and in particular CHD. The thesis structure is set out in **Figure 1.1**.

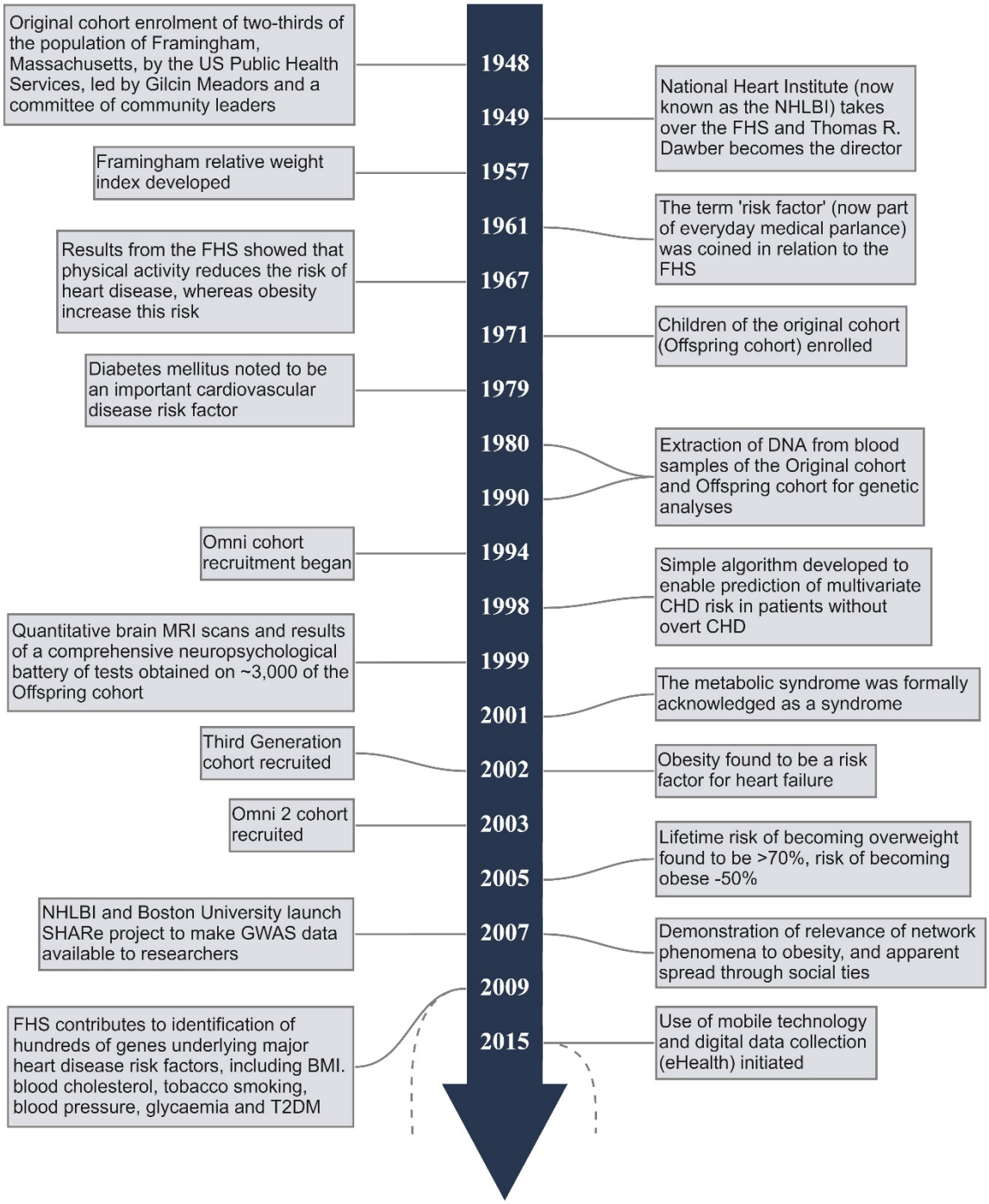


Figure 1.2 Milestones from the Framingham Heart Study (FHS).
Showing initiation of the eHealth era.[10] CHD, coronary heart disease; FHS, Framingham Heart Study; GWAS, genome-wide association study; NHLBI, National Heart, Lung, and Blood Institute; SHARe, SNP Health Association Resource, T2DM, type 2 diabetes mellitus. From Wilson, Am J Hypertens (1994).[11]

1.1.1 Coronary heart disease

Coronary heart disease (CHD), also known as coronary artery disease, is characterised by chronic inflammation and the deposition of atherosclerotic plaques within the subendothelial space of the coronary arteries. These plaques, composed of lipids, cholesterol, and inflammatory cells, often originate during childhood and progressively expand throughout life, particularly in the presence of abnormal cardiometabolic risk factors.[12] Atherosclerosis, a chronic inflammatory triggered by lipid accumulation in the arterial wall, may remain asymptomatic for decades.[13] However, the destabilisation of inflammed plaques can result in erosion or fissuring, leading to thrombus formation and acute ischemic events.[14] The primary risk factors for atherosclerosis include non-modifiable factors such as age and a family history of CHD, alongside several modifiable risk factors, including smoking, elevated low-density lipoprotein (LDL) cholesterol levels, type 2 diabetes, and hypertension.[15] Additional contributors to atherosclerotic CVD, particularly CHD and myocardial infarction, include abdominal obesity, low high-density lipoprotein (HDL) levels, hypertriglyceridemia, elevated plasma levels of lipoprotein (a) and homocysteine, chronic inflammation (elevated high-sensitivity C-reactive protein), clonal haematopoiesis, physical inactivity, and psychosocial stress. The Framingham Heart Study (**Figure 1.2**) initiated in 1948, has been foundational in identifying the predictive significance of major cardiometabolic risk factors. This longitudinal cohort study established hypertension, hypercholesterolaemia, and smoking as major contributors to CVDs, shaping current understanding and preventative strategies for cardiovascular and cardiometabolic health.[10]

1.1.1.1 Prevalence of CHD in Australia

Despite advances in healthcare, CHD remains Australia ‘s leading cause of disease burden and death. The 2017-2018 National Health Survey reported 2.8% of adults (approximately 580,000 people) had CHD,[16] with prevalence rising to 14% among those aged 75 and older.[17] In 2020, 56,700 acute coronary events occured (155 every day),[18] while 39,500 strokes were recorded.[18] In 2019, atherosclerotic CVD caused 42,300 deaths (25% of all deaths),[19] and in 2018, CHD led to17,500 deaths, including 7,300 from heart attacks.[20] Since 1980, CHD mortality rates have fallen by 82% due to improved treatment and preventive care, with greater reductions in older adults.[21]

1.1.1.2 Aetiology

The aetiology of CHD is fundamentally linked to atherosclerosis, which is driven by lipid accumulation, endothelial injury, inflammation, and plaque formation, compounded by modifiable lifestyle factors and genetic predispositions that collectively increase cardiovascular risk. Atherosclerosis is initiated by the deposition of low-density (LDL) lipoproteins and triglyceride-rich lipoproteins (TGRL) within the sub-endothelial space of arterial walls.[22] These lipoproteins undergo oxidative modification, releasing bioactive oxidised phospholipids that induce endothelial dysfunction and activate immune cells including monocytes and T cells, triggering chronic inflammation. [23] This inflammatory cascade promotes smooth muscle cell migration and proliferation, leading to the formation of a subendothelial collagen cap that initially stabilises the plaque by separating it from circulating blood.[24,25] Plaque formation is central to atherosclerosis,[24] characterised by the deposition of cholesterol, lipids, and other substances within the arterial wall,[26] which leads to luminal narrowing, arterial stiffening,[27] and heightened vulnerability to disruption.[28] The process begins with endothelial dysfunction, allowing

oxidised low-density lipoprotein (ox-LDL) to penetrate the intima,[29] where it attracts and transforms monocytes which then become lipid-laden foam cells. This creates a necrotic core within the plaque, which is exacerbated by the release of cytokines and formation of neutrophil extracellular traps, further promoting inflammation[30, 31] and thrombosis.[32] However, as the plaque expands, the arterial lumen progressively narrows, ultimately obstructing blood flow, which can clinically manifest as angina (**Figure 1.3**).[29] In advanced stages, plaque disruption, whether through fibrous cap rupture[33] or endothelial erosion,[24, 31] exposes thrombogenic material to the bloodstream, precipitating thrombotic events such as myocardial infarction and ischemic stroke.[34, 35]

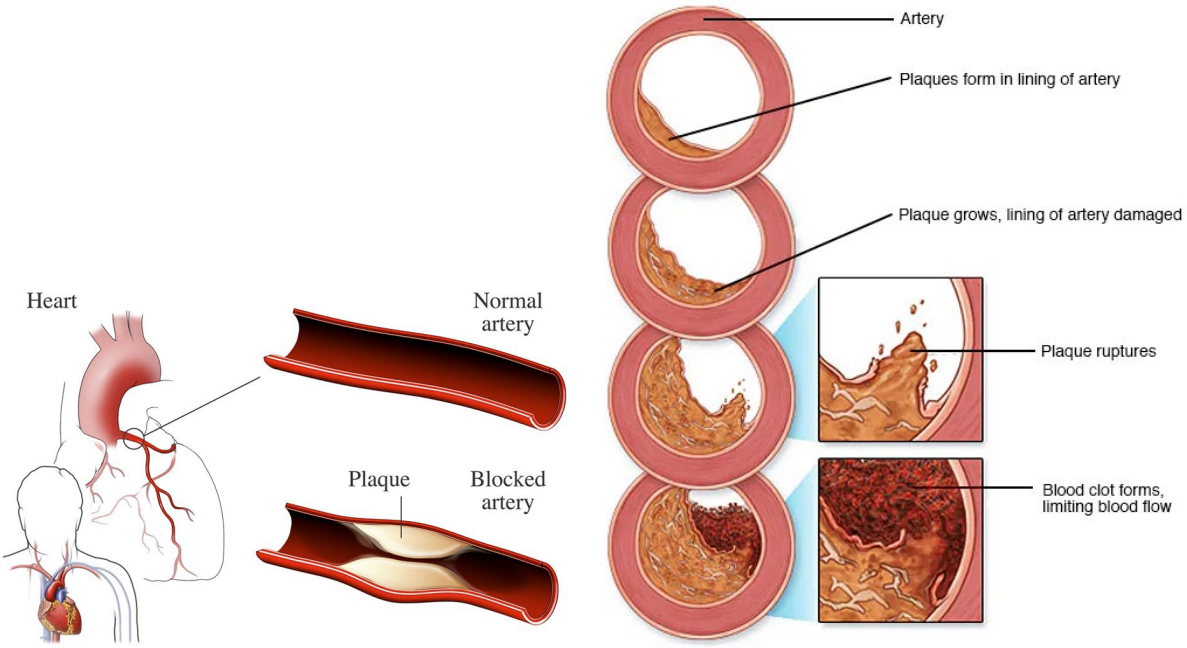


Figure 1.3 Normal versus a blocked artery, and plaque progression.
From: Causes and Risk Factors, NIH (2023)[36] & Myocardial Ischemia, Mayo Clinic (2023).[37]

1.1.1.3 Risk factors

Epidemiologic and randomised studies have consistently shown that various risk factors significantly contribute to the development of atherosclerotic CVDs and major adverse cardiovascular events by amplifying their combined effects on morbidity and mortality.[38-40] Non-modifiable (biological) risk factors for CHD include age, gender, ethnicity and family history.[12] In contrast, modifiable (behavioural) risk factors, such as smoking, elevated levels of LDL and TGRL, hypertension, type 2 diabetes, high sensitive C-reactive protein play a substantial role (**Figure 1.4**).[41] The progression and exacerbation of atherosclerotic CVD are determined not only by the presence and magnitude of these risk factors but also by their persistence over time.

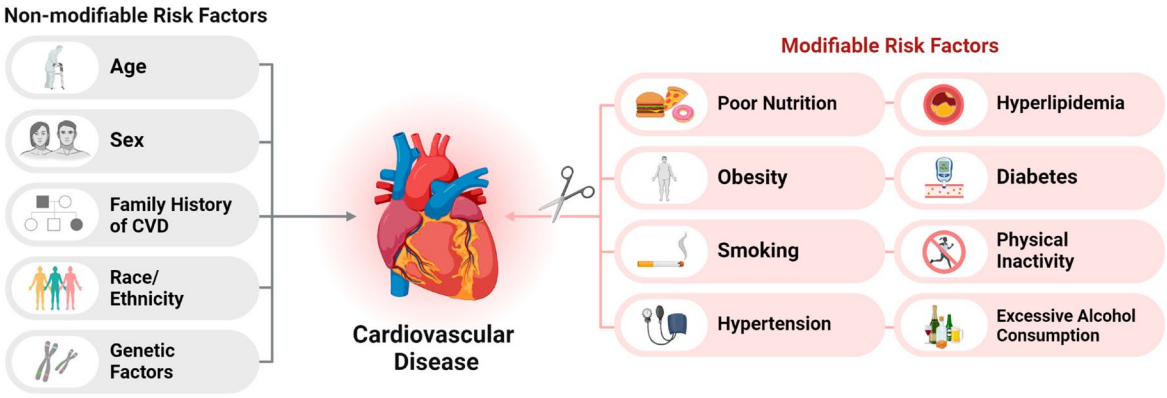


Figure 1.4 Risk factors (modifiable and non-modifiable) for CHD.
From Singar *et al.*, Nutrients (2024).[42]

Biological non-modifiable risk factors for CHD include age, with men over 45 and women over 55 being at higher risk.[43, 44] Gender also plays a role, as men[45] and post-menopausal women[46] are more susceptible. A family history of heart disease is a potent predictor; the CARDIO2000 study found that it increased the risk of a non-fatal acute coronary event by approximately fourfold in males and threefold in females.[47, 48] Ethnic background impacts risk levels as well, with South Asian and certain indigenous populations showing higher susceptibility to cardiometabolic diseases.[49]

Classical modifiable (behavioural) cardiometabolic risk factors for CHD and atherosclerotic CVDs in (smoking[11], BMI, elevated LDL-cholesterol, hypertension[50], and type 2 diabetes[51]) have been increasingly managed through highly effective and now inexpensive LDL-lowering and antihypertensive pharmacological treatments, leading to a general reduction in both LDL levels and blood pressure. However, the rise in central (abdominal) obesity, and related insulin resistance/glucose dysmetabolism, physical inactivity and high-calorie diets has increased the prevalence of metabolic syndrome.[52, 53] This syndrome, marked by increased waist circumference, elevated triglycerides (≥1.7 mmol/L or drug treatment for elevated triglycerides), low HDL-cholesterol (<1.0 mmol/L in men, <1.3 mmol/L in women or drug treatment for reduced HDL-C), elevated blood pressure (≥130 systolic or ≥85 diastolic or drug treatment for hypertension), and raised fasting blood glucose (>5.6 mmol/L or drug treatment for elevated glucose), has markedly increased in Australia.[54] The 2000 Australian Diabetes, Obesity, and Lifestyle study (AusDiab) found that 19% of Australians aged 25 and over met the criteria for a diagnosis of metabolic syndrome.[55] According to the Australian Institute of Health and Welfare 2017-18, 25% of children aged 2-17 years, 57.7% of young adults aged 25-34 years, and 82.9% of men aged 45-54 years have a BMI higher than 25 kg/m^2, and 60% of men and 66% of women had a waist circumference indicating a higher risk of metabolic complications.[56]

1.1.2 Atherosclerotic plaque types

The composition and structural characteristics of plaques vary significantly, influencing their stability: calcified plaques, primarily composed of hardened calcium deposits, are generally stable; however, they contribute to arterial stiffness.[57] In contrast, non-calcified, lipid-rich plaques possess a higher propensity for rupture and acute cardiovascular events.[58] Mixed plaques,[59] containing both calcified[60] and non-calcified components,[61] exhibit variable stability,[62] while low-attenuation plaques,[63] identifiable

through CT imaging[64] due to their low density, present a particularly high risk of rupture.[65] Detailed characterisation of plaque composition is crucial for risk stratification,[66] as certain types are more strongly associated with acute coronary syndromes and major cardiovascular events.[67]

1.1.3 Vascular endothelium

The vascular endothelium is an essential component of the circulatory system, contributing to the regulation of smooth muscle cell function, thrombus formation, inhibition of leukocyte and platelet adhesion, and maintenance of capillary function.[68] Positioned between the vessel lumen and the smooth muscle cell layer, the endothelial cells (tunica intima) align their long axes parallel to the capillary or blood vessel axis, forming a critical interface between underlying tissues and the blood or lymph.[69] As a single cell layer, the vascular endothelium responds to haemodynamic changes via membrane receptors and regulates homeostasis by synthesising and releasing various molecules, including prostacyclins, endothelins, endothelial cell growth factors, interleukins, plasminogen inhibitors, and nitric oxide (NO).[68] These macromolecules play a crucial role in maintaining vascular tone, particularly under severe pathological conditions. Among them, nitric oxide has been extensively studied since the 1980s.[68, 70] Its reduced bioavailability, known as endothelial dysfunction, is recognised as the initial step in the progression of atherosclerotic cardiovascular disease,[71] which is the leading cause of mortality worldwide.[72]

1.1.4 Arterial stiffness and cardiometabolic health

Arterial stiffness is widely acknowledged as a significant predictor of cardiovascular events, dementia, death, and is associated with a range of cardiovascular diseases, exacerbated by aging and various disorders including hypertension, diabetes, and renal disease.[73-76] Measurement techniques such as pulse wave velocity (PWV) are essential for assessing arterial stiffness, with non-invasive methods being highlighted for their diagnostic and predictive value in evaluating cardiovascular risk and therapeutic efficacy. Lifestyle modifications, pharmacological treatments, and addressing modifiable risk factors are emphasised as shown in **Table 1.1** for their effectiveness in reducing arterial stiffness, with further research needed to explore the impact of these interventions on cardiovascular outcomes.[77]

Table 1.1 A tabular summary of the current evidence on the effects of arterial stiffness on cardiometabolic health.

Author, year	Main findings
Agbaje *et al.,* 2022[78]	Arterial stiffness is a strong predictor of cardiovascular events and all-cause mortality in middle-aged and old adults. Linked to hypertension, overweight/obesity, and insulin resistance in adolescents and young adults. Preventing or decreasing arterial stiffness during adolescence may confer cardiometabolic health benefits later in life.
Ecobici *et al.,* 2017[79]	Arterial stiffness is an independent predictor of cardiovascular disease in patients with hypertension. Pulse wave velocity (PWV) is the gold standard for non-invasive assessment of arterial stiffness. Changes in terms of lifestyle and drug therapy have some positive effects on improving arterial stiffness.
Feola *et al.,* 2021[80]	Arterial stiffness, assessed using pulse wave velocity (PWV), is a strong independent predictor of cardiovascular events. The aetiology of arterial stiffening should be related to degenerative/calcified processes, while the thickening of the walls should be much more related to the atherosclerotic processes.
Quinn *et al.,* 2012[81]	Arterial stiffness is associated with a range of linked pathophysiological changes within the circulation, including increased pulse pressure, left ventricular hypertrophy, subendocardial ischaemia, vessel endothelial dysfunction and cardiac fibrosis. Measurement of arterial stiffness is independently associated with adverse cardiovascular outcomes across many groups and in the general population.
Sacre *et al.,* 2014[82]	There is an association between aortic and proximal arterial stiffness and cardiovascular and all-cause mortality, independent of conventional risk factors. Physical activity and dietary habits influence the rate of

Author, year	Main findings
	arterial stiffening in healthy ageing. Clinical randomised controlled trials have shown that exercise and dietary interventions can modulate arterial biomechanical properties beyond their impact on blood pressure and other conventional risk factors.
Sakuragi *et al.,* 2010[83]	Arterial stiffness is an independent predictor of cardiovascular risk. There are various methods for measuring arterial stiffness. Arterial stiffness can be modified by medical and lifestyle therapy.
Stehouwer *et al.,* 2007[84]	Arterial stiffness can be estimated by quantifying pulse pressure, distensibility, compliance coefficients, pulse wave velocity, and wave reflection. Diabetes, metabolic syndrome, and insulin resistance are associated with greater arterial stiffness. Vigorously treating hypertension with pharmacological agents is the most powerful therapy available for reducing arterial stiffness.
Zieman *et al.,* 2005[85]	Arterial stiffness is associated with increased risk of cardiovascular events, dementia, and death. Lifestyle changes and therapies that reduce arterial stiffness include weight loss, exercise, salt reduction, alcohol consumption, and neuroendocrine-directed therapies.

1.1.5 Lifestyle

Lifestyle factors play a crucial role in both the prevention and management of CHD.[86] Unhealthy behaviours such as physical inactivity, tobacco use, and excessive alcohol consumption contribute to the development of CHD by fostering plaque accumulation in the coronary arteries.[87] Conversely, regular physical activity,[88] adherence to a healthy diet, tobacco abstinence, and effective stress management can prevent CHD and its associated complications.[87] Lifestyle modification is vital not only for primary prevention but also for managing CHD.[52] Incorporating healthy behaviours alongside pharmacological and procedural interventions can significantly reduce symptoms and decrease the likelihood of future cardiac events. Evidence shows that a heart-healthy lifestyle, including smoking cessation, a nutritious diet, and regular exercise, prevents CHD and its complications. However, adherence to these beneficial behaviours is often insufficient, and participation in cardiac rehabilitation programs remains low among individuals with established CHD. Research gaps persist in understanding the barriers to adopting and maintaining these healthy lifestyle practices, particularly concerning dietary habits[89] and physical activity levels. Addressing these gaps is essential for improving the uptake and sustainability of heart-healthy behaviours, thereby enhancing overall CHD outcomes.

1.1.5.1 Diet and CHD

Western dietary patterns, dominated by ultra processed foods high in carbohydrates, sodium, and red meat, lead to an imbalance in inflammatory markers, with an increase in proinflammatory cytokines and a decrease in anti-inflammatory responses.[90] In contrast, a Mediterranean diet, rich in fruits, vegetables, whole grains, nuts, and legumes, has been associated with reduced inflammation[91] and lower rates of cardiovascular disease (CVD).[92] Furthermore, emerging evidence highlights the role of gut microbiota, which influences cardiovascular health.[93] For example, compounds such as L-carnitine, betaine, and choline metabolised by gut bacteria into trimethylamine N-oxide (TMAO), have been linked to heightened risks of diabetes, hypertension, and atherosclerosis. This highlights the impact of diet on inflammation and gut microbiota, emphasising their collective role in CHD risk.[94]

1.1.5.1.1 Diet and CHD prevention

Dietary patterns significantly influence CHD risk by affecting obesity, hypertension, uncontrolled diabetes.[95] Diets low in saturated fats and rich in fibre and plant-based foods offer protective effects[96], with studies showing a Mediterranean diet reduces CHD and mortality risk, while high-fat, low-carbohydrate diets have been associated with higher riskd.[97, 98] Preventive dietary strategies include

portion control, increased intake of fruits, vegetables, and whole grains, and limited consumption of processed meats, sugary drinks, and sodium.[99] Current guidelines recommend diets abundant in plant-based foods and low in processed ingredients to reduce heart disease risk, highlighting specific preventive dietary choices.[5, 92, 100]

1.1.5.1.2 Diet and CHD management

For individuals managing CHD, diet remains a core strategy to control disease progression and improve health outcomes.[101] A balanced (as mentioned above) can help lower cholesterol, manage weight, reduce diabetes risk, and improve blood pressure. The Mediterranean diet and daily consumption of small quantities of nuts are particularly effective in reducing CHD risk, with evidence supporting a reduction in heart disease risk by up to 25%.[97, 102] Dietary guidelines for CHD management emphasise a variety of nutrient-dense foods, minimal added sugar and salt, whole grains, plant-based proteins, and non-tropical oils like olive oil, tailored to support cardiovascular health.[5]

1.1.5.1.3 Pesco vegetarian diets and CHD

The 5:2 pesco-vegetarian diet combines intermittent fasting with a pesco-vegetarian lifestyle,[103] involving five days of unrestricted eating and two days of reduced calorie intake (500-600 calories) focused on fish and plant-based foods.[104] This approach promotes a calorie deficit for weight management and metabolic health, while fish and seafood provide omega-3 fatty acids, supporting heart and cognitive health.[103] This diet combines the benefits of a vegetarian and fish-based nutrition consumption with the metabolic effects of intermittent fasting, offering a potential advantage over Western diet high in unhealthy fats and animal protein.[105, 106] Chapter 4 of this thesis presents a 6-month sub-study from the LIVEPLUS trial exploring the effects of this diet over 12 months.

1.1.5.1.4 Fasting and CHD

In modern societies, the habit of consuming three meals a day contrasts with the continuous food access provided to many laboratory animals. Such patterns, coupled with reduced physical activity, contribute to a rise in metabolic conditions.[107, 108] Historically, humans, like many animals, adapted to environments with intermittent food scarcity, developing mechanisms to sustain physical and cognitive performance during period without food.[109] This principle forms the basis of intermittent fasting (IF), which alternates between extended fasting (16-48 hours) and periods of eating.[110, 111]

Mammals, including humans, use energy reserves stored in the liver and adipose tissue to endure fasting. The evolution of metabolic, endocrine, and nervous systems supports sustained performance even in the absence of food intake.[112] IF has various forms,[113] including Time-Restricted Feeding (TRF), Alternate Day Fasting (ADF), and the 5:2 Method. TRF restricts eating to an 8-hour period each day, ADF alternates low-calorie and regular eating days, and the 5:2 approach[114] allows for normal intake five days a week with reduced intake on two days. Despite IF's rising popularity, its safety and effectiveness require further research.[115] Studies indicate similar weight loss effects for ADF, 5:2, and traditional daily energy restriction (DER), but little is known about nutrient adequacy when following IF,[114] which may risk deficiencies with prolonged use.[116, 117]

Human research has mainly examined IF's impact on weight loss and metabolic health in overweight and obese individuals.[117, 118] Randomised controlled trials have shown that IF methods including ADF

and the 5:2 method promote weight loss and metabolic improvement, often on par with continuous energy restriction (CER). Benefits include reductions in body fat, cholesterol, triglycerides, and insulin resistance, as well as improvements in cardiovascular markers such as blood pressure and resting heart rate.[109, 113] IF diets have shown high adherence rates, with participants generally avoiding excessive intake on non-fasting days.[118] Lean mass preservation is not adversely affected, especially when paired with resistance training.[119]

However, long-term effects of IF on weight stability and overall health are not fully understood, and limited data exist on IF's role in weight gain prevention for normal-weight individuals. Some participants report increased hunger and challenges with daily tasks on fasting days, particularly those who are not overweight. While the potential of IF is significant, further comprehensive studies are essential to establish its safety and effectiveness across different populations. A new ongoing study by Fontana *et al.,* (2022)[120] suggests that fasting alone may not be intense enough for human needs.[121]

1.1.5.2 Physical activity and CHD

One of the key contributing factors to the development of CHD is physical inactivity.[122] In epidemiological studies, physical activity encompasses any leisure activity that increases energy expenditure, while exercise training is defined as structured, repetitive, and goal-oriented physical activity. Regardless of one's physical activity or exercise status, cardiorespiratory fitness, as measured by metabolic equivalents (METs) or peak oxygen uptake, can be determined through a maximum stress test.[123] For this thesis, we consider exercise as a form of structured physical activity.

Routine physical activity/exercise induces vascular responses such as lymphangiogenesis, cardiac angiogenesis, and endothelium-dependent vasodilation. These responses contribute to improved cardiovascular health by enhancing the growth of lymphatic and blood vessels and promoting the dilation of blood vessels, which improves blood flow and reduces cardiovascular risk.[124] Furthermore, regular exercise causes an increase in the size and dilatory capacity of coronary arteries and the formation of collateral blood vessels.[125] The improvement in endothelial function also contributes to better flow-mediated dilation.

Regular physical activity results in enhanced contractile ability and electrical stability of the heart, as well as increased stroke volume both during rest and physical activity.[125] This leads to a higher maximal cardiac output and a reduced heart rate at rest and during submaximal cardiac output. Additionally, regular physical activity affects the coagulation properties of blood by reducing platelet aggregation and enhancing fibrinolytic activity, which may be due to reduced levels of plasminogen activator inhibitor-1. It also has anti-inflammatory effects, including decreased plasma fibrinogen concentrations, C-reactive protein levels, and white blood cell count.[126] Exercise influences systemic responses such as adaptations in skeletal muscle, vessels, brown adipose tissue, and gut microbiota.

The metabolic adaptations during physical activity and post-exercise recovery involve an enhancement of lipid oxidation.[127] The transport of blood lipids undergoes alterations, leading to a higher ratio of high-density lipoprotein (HDL) to low-density lipoprotein (LDL) and increased activity of lipoprotein lipase which results in an increased utilisation of circulating triglycerides as fuel and their clearance even

during periods of inactivity.[128] Furthermore, the activation of this enzyme accelerates the conversion of very low-density lipoprotein (VLDL) to HDL.[129] Regular exercise also enhances the sensitivity of the liver, skeletal muscle, and adipose tissue to insulin, resulting in decreased fasting insulin levels and improved insulin response to glucose, accompanied by an increase in the rate of glucose disposal.[130]

In the past decade, there has been a growing body of literature that demonstrates the positive effects of moderate-intensity physical activity on cardiovascular health (**Figure 1.5**). Moderate intensity is defined in various ways, such as expending more than 6 METs, or roughly 5 Kcal to 7.5 Kcal per minute, exercising at 60-70% of maximum heart rate, or 60% of VO_2 max. This translates to physical activity that elevates the heart rate and breathing rate, yet still allows for conversation, such as brisk walking, swimming, and cycling. METs, or metabolic equivalents, are a unit of measure for the rate at which the body expends energy. A single MET is equivalent to the energy expenditure of an individual at rest. An activity with a MET value of 4 indicates that the individual is expending four times the energy compared to when they are at rest. VO_2 max, also referred to as maximal oxygen uptake, represents the maximum volume of oxygen that can be utilised by the body during exhaustive aerobic exercise while breathing air at sea level. It is indicative of the capacity of the heart to pump oxygen throughout the body and reflects the highest rate of oxygen consumption attainable during exercise performed at maximal intensity.[131]

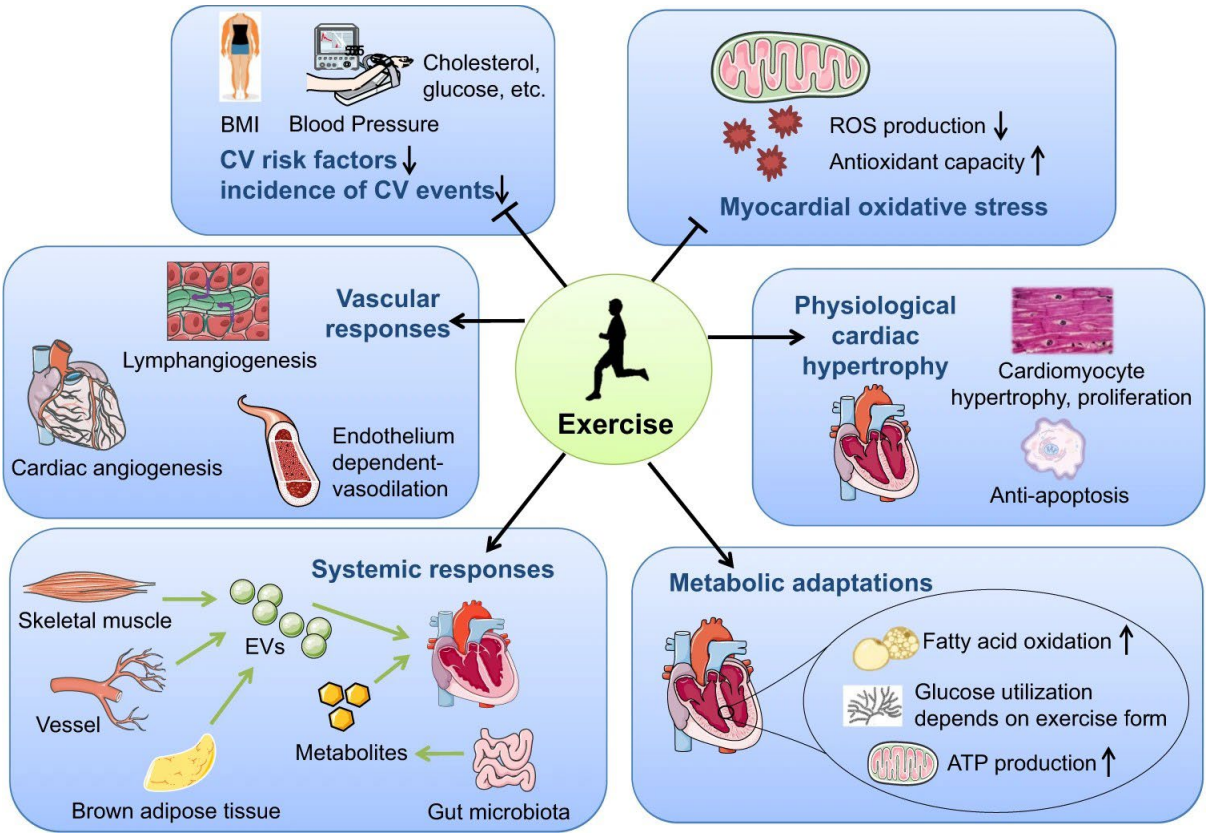


Figure 1.5 Impact of physical activity and exercise on cardiovascular health.
From Chen *et al.*, Sig Transduct Target Ther. (2022).[124]

Emerging evidence from large-scale epidemiological studies, such as the British Regional Heart Study (BRHS) and the Iowa Women's Health Study, highlight the pivotal role of regular physical activity in

mitigating cardiovascular disease risks and enhancing overall heart health across diverse populations. The BRHS is a comprehensive and long-term investigation of cardiovascular disease that commenced in 1978. This study had 7735 male participants aged between 40 and 59, selected randomly from general practices in 24 towns in the United Kingdom. A standardised questionnaire was used to collect data on leisure-time physical activities, including walking, cycling, and sports, as well as other health-related habits.[132] The BRHS identified the impact of lifestyle factors on CVD risk and mortality, while contributing to the understanding of age-related health challenges including frailty and cognitive impairment in older adults.[132] The Iowa Women's Health Study recruited a sample of 40,417 postmenopausal women aged 55-69 from a random selection of Iowa female drivers and monitored their health for a period of up to seven years. The results indicated that women who had the least physical activity had roughly twice the cardiovascular mortality rate when compared to the women who had the highest levels of physical activity. Those who engaged in moderate physical activities four or more times per week demonstrated a 47% reduction in risk compared to women who participated in these activities infrequently or not at all. Furthermore, women who participated in vigorous physical activities four or more times a week exhibited an 80% reduction in risk as compared to women who participated in these activities rarely or never.[133]

Both studies collectively emphasise the critical role of fitness and physical activity in promoting cardiovascular health and preventing disease. They highlight that regular, moderate-to-vigorous physical activity can significantly reduce the risk of developing or dying from cardiovascular diseases, making fitness a key component of a healthy lifestyle. These findings suggest that the advantages of physical activity extend to all genders, age groups, and health statuses, supporting its integration into daily life to enhance public health outcomes. Furthermore, an 8-year follow-up study showed that men without pre-existing CHD who engaged in moderate or moderately vigorous physical activities had their risk of heart disease reduced by 50% compared to those who remained inactive. The findings also indicated that men with pre-existing CHD had a similar inverse association up to moderate levels of activity. However, no additional benefits were observed in participants who engaged in vigorous physical activity.[134]

Cardiovascular fitness, an indicator for physical activity levels, has also been linked to mortality (**Figure 1.6**) as evidenced in a study by Leitzmann *et al.*, where participants who engaged in moderate-intensity physical activity for over three hours per week had a 27% reduction in mortality risk.[135] Studies have shown that higher levels of cardiorespiratory fitness (CRF) are linked to a lower risk of CHD and overall mortality among healthy individuals.[136, 137] Lee *et al*. further confirmed the strong correlation between cardiorespiratory fitness and reduced all-cause mortality, emphasising the effectiveness of structured physical activity training in achieving high cardiovascular fitness, regardless of leisure-time physical activities.[138] The Copenhagen City Heart Study, spearheaded by Schnohr *et al.*, found that the intensity, rather than duration, significantly influences all-cause and coronary heart disease mortality reduction. Particularly, fast cycling was associated with a noteworthy increase in life expectancy, independent of the total cycling time.[139, 140 141]

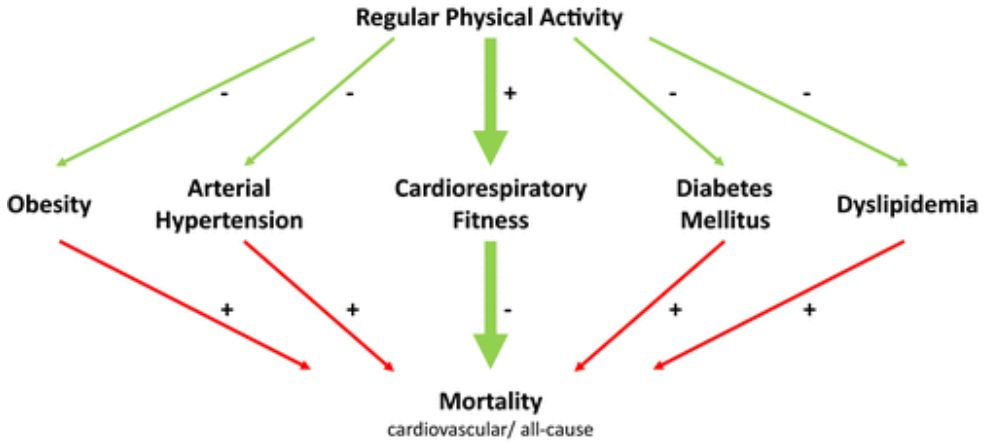


Figure 1.6 Impact of regular physical activity on mortality.
Obesity, arterial hypertension, diabetes mellitus, and dyslipidaemia contribute to increased mortality (+). Regular physical activity improves fitness (+) and counteracts the development of risk factors (−). From Winzer *et al.*, JAHA (2018).[141]

1.1.5.3 Mental health strategies

Stress reduction and mindfulness, while closely intertwined, are distinct concepts with unique contributions to mental health and well-being. Stress reduction is a broad term that includes a variety of techniques aimed at lowering stress levels, such as physical activities, relaxation methods, and psychological strategies. Mindfulness, conversely, is a more focused practice that involves maintaining one's attention on the present moment in a non-judgmental way, facilitating the acknowledgment and acceptance of thoughts, feelings, and bodily sensations.[142] This practice is not only a pivotal aspect of stress reduction, particularly through programs like Mindfulness-Based Stress Reduction (MBSR), but it also serves to enhance mental awareness and foster a calmer, more focused state of mind. Mindfulness embodies the skill of focusing on one's physical and mental experiences during everyday activities with openness, curiosity, and acceptance. It involves self-regulating attention to remain cognisant of the present, thereby improving the recognition of current mental processes, and it encourages an attitude of acceptance towards these experiences. Additionally, mindfulness involves "remembering" to keep certain thoughts or feelings in awareness, contributing to one's overall well-being. Seen as both a practice and a dispositional trait, mindfulness varies among individuals in their natural capacity to remain present and attentive, highlighting its role not just in stress reduction but also in enhancing dispositional mindfulness, which indicates the diverse ability of individuals to engage with and benefit from mindfulness practices in their daily lives.

A recent study involving 382 participants in the United States found a significant link between dispositional mindfulness and better cardiovascular health. Specifically, individuals with high levels of mindfulness were found to have an 86% higher likelihood (prevalence ratio of 1.86, 95% CI 1.08 to 3.19) of exhibiting good cardiovascular health compared to those with lower levels of mindfulness. While research directly connecting mindfulness to cardiovascular events remains scarce, an expanding evidence base suggests mindfulness may influence key risk factors for cardiovascular disease. These factors include physical activity, smoking habits, dietary patterns, obesity, blood pressure, lipid profiles, and diabetes management, as detailed in the study's findings **Figure 1.7**.[143]

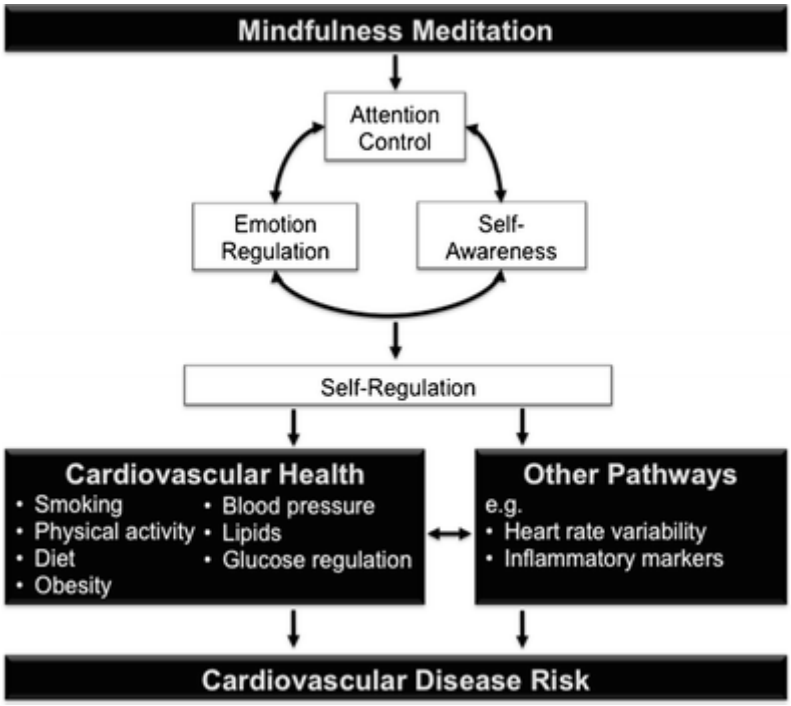


Figure 1.7 Conceptual framework suggesting plausible mechanisms by which mindfulness meditation may influence cardiovascular disease risk.
From Loucks *et al.*, Curr Cardiol Rep (2015).[144]

Dozens of studies have reported on the health benefits of meditation. According to the National Health Interview Survey, 8% of US adults practice some form of meditation. Up to 14% to 24% of patients with CVD have been reported to use or to have used some form of mind-body therapy, and 2% to 3% use or have used some form of meditation. In addition, half of CVD patients are interested in participating in a clinical trial of alternative therapies, and 17% are interested in participating in a clinical trial of meditation. Many modern mindfulness and meditation practices are delivered via digital platforms, including mobile apps and wearables, making them integral to the emerging digital health landscape.[145-147] Hence, mindfulness and meditation may be an attractive cost-effective adjunct to more traditional medical therapies.[148]

1.1.6 Digital lifestyle interventions

Digital health refers to the use of digital technologies including mobile health apps, wearable devices, telemedicine platforms, electronic health records, and personalised medicine to enhance healthcare delivery and promote individual well-being by enabling self-monitoring, remote consultations, data-driven insights, and tailored treatments. By leveraging these tools, digital health aims to empower individuals, improve access to healthcare, enhance care quality, and promote preventive care, representing a shift toward more patient-centred, efficient, and data-informed healthcare systems. Digital lifestyle interventions leverage technology platforms and devices to promote healthy habits and tackle conditions such as obesity, heart disease, type 2 diabetes, and depression.[149] Their goal is to improve health and well-being through digital support and guidance, showing significant promise in modern health management. For instance, mobile apps for healthy eating offer personalised meal plans, recipes, and tracking tools to assist users in making healthier choices and managing calorie intake. Features like social networking and gamification encourage ongoing healthy behaviours.[150]

Similarly, wearable technology, such as fitness trackers, supports physical activity by providing real-time data on activity levels, heart rate, and sleep, alongside coaching features to aid in achieving fitness goals.[151] These interventions represent a growing field aimed at enhancing health outcomes through digital innovation (**Figure 1.8**).

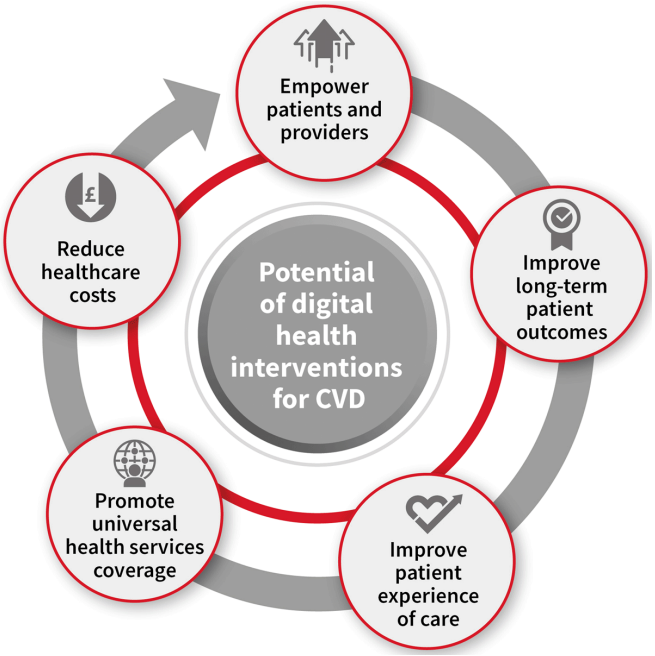


Figure 1.8 The potential of digital health interventions for CVD.
From Tromp *et al.*, Global Heart (2022).[152]

The rapid increase in the use of digital lifestyle interventions highlights the role of technology in offering convenient, personalised, and interactive health solutions, leading to improved health behaviours, outcomes, and patient self-care engagement. However, these interventions come with challenges, including the risk of privacy and security breaches related to the handling of personal health data. Additionally, access disparities present a significant obstacle, with those of lower socioeconomic status or limited digital literacy facing difficulties in using these digital tools, potentially excluding them from the benefits these interventions provide. Several digital health lifestyle strategies have been proposed for the prevention of cardiometabolic diseases, including:

- Mobile health apps: Mobile health apps can be designed to track physical activity levels, monitor diet, and provide feedback and encouragement to users. For example, apps can provide real-time feedback on physical activity and food intake, set achievable goals, and provide rewards for reaching those goals. mHealth is further defined in section 1.1.6.2.
- Telehealth interventions: Telehealth interventions, such as telemedicine, allow individuals to access healthcare services remotely, including access to specialist physicians, nurses, and other healthcare professionals. This can help individuals receive timely, appropriate care and improve their management of chronic conditions.
- Social media-based interventions: social media-based interventions can use online communities to support individuals in adopting healthy behaviours and habits. For example, online communities

can provide access to health information, peer support, and other resources to help individuals manage their health and reduce their risk of developing cardiometabolic diseases.

- Virtual reality-based interventions: Virtual reality-based interventions can use immersive experiences to simulate different health behaviours and help individuals learn about their impact on their health. For example, virtual reality simulations can demonstrate the impact of unhealthy behaviours, such as smoking and excessive alcohol consumption, and encourage individuals to adopt healthier behaviours.
- Wearable technology: Wearable technology, such as fitness trackers and smartwatches, can provide real-time feedback on physical activity levels, heart rate, and other health-related parameters. This information can help individuals monitor their health, make informed decisions about their lifestyle, and take proactive steps to reduce their risk of developing cardiometabolic diseases.

1.1.6.1 Behaviour-change strategies

In the 21st century, digital medicine prioritises the promotion of health behaviour change and the delay of non-communicable chronic diseases onset. A key strategy involves using digital health technologies to foster healthier lifestyles and support sustained behaviour change.[153] To combat cardiometabolic diseases, several behaviour change theories guide the development of digital interventions.[154] These models offer frameworks for understanding the psychological, social, and environmental factors that influence health behaviours, enabling the design of more targeted and effective interventions.

The Transtheoretical Model,[155] provides a stage-based approach to behaviour change, outlining a progression from precontemplation through to maintenance.[156] This model allows digital interventions to be tailored to an individual's readiness for change, facilitating gradual and sustained progress.[156] The Health Belief Model focuses on individuals' perceptions of susceptibility to illness, the severity of potential outcomes, and the benefits and barriers associated with health-promoting actions. This framework is particularly relevant for designing interventions aimed at increasing engagement with preventive health behaviours, such as physical activity or dietary improvements.[157] The Self-Determination Theory highlights the importance of intrinsic motivation and the satisfaction of psychological needs for autonomy, competence, and relatedness. This theory is particularly valuable in digital medicine, as interventions can be designed to foster user engagement and long-term adherence by supporting these intrinsic drivers.[158] Additionally, Social Cognitive Theory emphasises the reciprocal interaction of personal, behavioural, and environmental factors, incorporating concepts such as self-efficacy and observational learning.[159] This is frequently applied in digital platforms that use gamification or peer modelling to reinforce positive behaviours.[160] Other model, such as the Theory of Planned Behaviour, focus on the role of intention, attitudes, perceived norms, and behavioural control in driving actions, offering a framework for interventions aimed at deliberate decision-making processes.[161] The Social Ecological Model broadens this perspective, recognising the influence of multiple levels including individual, social, and structural, on behaviour, making it a useful tool for addressing systemic barriers to health.[162] Finally, Social Norms Theory underscores the influence of perceived norms, which digital interventions can leverage by correcting misperceptions to encourage healthier behaviours.[163] Digital

interventions are designed to align with these theories, tailoring content and strategies to meet individuals at their respective stages of change. For example, the Transtheoretical Model helps identify whether a person is ready to act,[155] while interventions informed by the Health Belief Model enhance perceptions of risk and benefits, fostering a stronger sense of urgency and purpose.[157] Strategies rooted in Self-Determination Theory seek to support autonomy by allowing users to set their own goals, enhance competence through skill-building and feedback, and provide relatedness through social features or community support.[158] These interventions typically include educational content, personalised feedback, and social support to foster awareness, motivation, and sustained action towards healthier behaviours.[164, 165] For instance, apps might highlight personal progress, use peer comparisons to provide context, or present tailored strategies to overcome barriers.[166] By addressing both personal and environmental factors, digital health platforms aim to improve individuals' perceptions of disease susceptibility, severity, and the benefits of behaviour modification while minimising perceived barriers.[167, 168] This comprehensive, theory-driven approach underscores the potential of digital health platforms in promoting healthy behaviours, increasing disease risk awareness, and facilitating sustainable health behaviour changes.[164, 169] Although further research is needed to fully assess the efficacy of these strategies in preventing cardiometabolic diseases, they offer a promising and innovative avenue to improve public health outcomes by empowering individuals to take control of their health behaviours.[166]

1.1.6.2 mHealth

Mobile health (mHealth) leverages mobile technologies to enhance healthcare services, offering significant potential in disease prevention and management. A major advantage of mHealth is its capability to gather and track health data in real time, enabling clinicians to detect health risks early and prevent diseases.[170] For instance, wearable devices including smartwatches can track one's physical activity, heart rate, and sleep patterns, helping to identify early signs of diseases such as cardiovascular conditions (**Figure 1.9**).[171] Moreover, mHealth empowers patients with tools and resources for managing their health, including mobile apps that offer guidance on healthy living, diet, exercise, and medication reminders, thereby facilitating disease prevention.[172] Another key benefit is mHealth's facilitation of instant communication between patients and healthcare providers, enhancing care quality, speeding up service delivery, and fostering patient engagement in prevention programs. Through mHealth, patients can securely message their doctors, engage in telemedicine consultations, and access their medical records and test results on their mobile devices.[173] Additionally, mHealth improves the precision and promptness of health information, giving patients access to the latest health guidelines and practices to inform and engage them in their health management.[174] mHealth stands as a crucial tool in disease prevention and management by collecting real-time data, providing health management tools, enabling instant patient-provider communication, and delivering accurate health information. Through interventions such as text messages, mobile applications, and wearables, mHealth supports behavioural changes that can prevent cardiometabolic diseases, highlighting its importance in modern healthcare strategies.[175] Using these strategies in researching mHealth's benefits, three meta-analyses comparing mHealth interventions to traditional care methods for increasing physical activity have shown promising results. A detailed analysis of 21 randomised controlled trials (RCTs) indicated that mHealth

interventions significantly reduced sedentary behaviour and led to non-significant improvements in overall physical activity, moderate to vigorous intensity physical activity, and walking compared to conventional care.[176] A subsequent meta-analysis of 15 randomised controlled trials found that using computer, mobile, and wearable technology effectively reduced sedentary behaviour, with noticeable decreases in sitting time for up to six months post-implementation. This reduction was specifically noted in studies with a short follow-up period.[177] Yet another study, a meta-analysis, investigated the effectiveness of mobile smartphone-based health programs on enhancing physical activity and reducing obesity in young adults. The analysis found a statistically significant improvement in both physical activity levels and weight loss among the participants. This evidence indicates that mobile health programs can successfully boost physical activity and facilitate weight loss in young adults.[178]

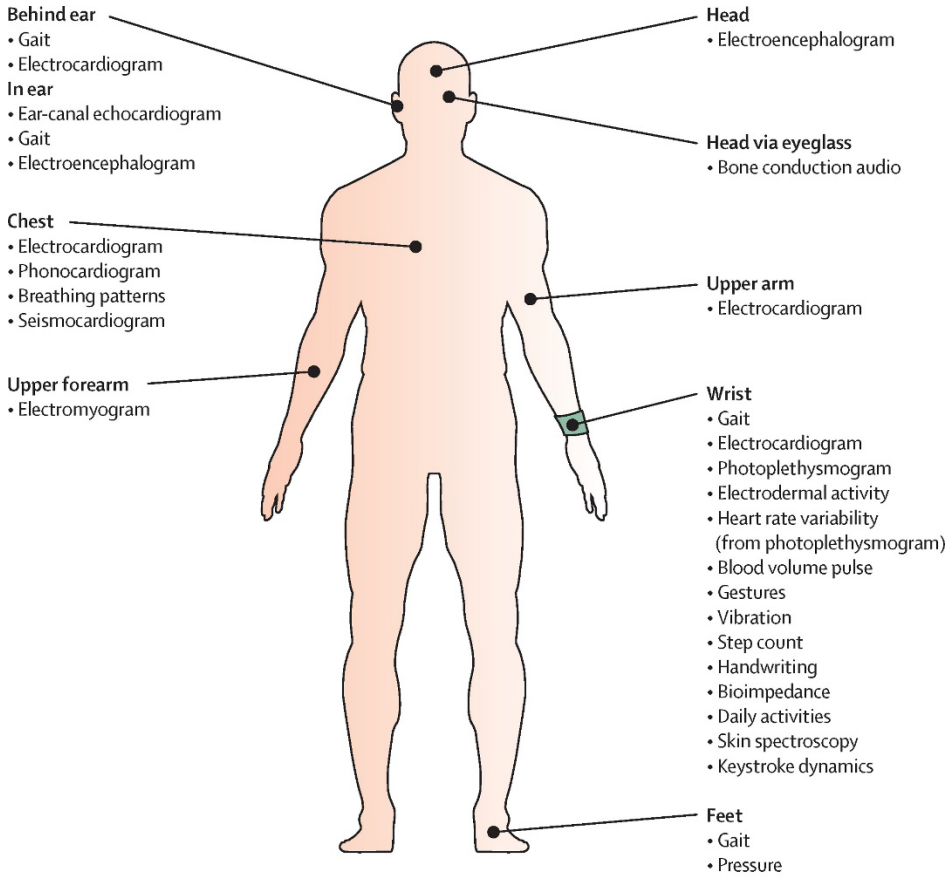


Figure 1.9 Wearable devices, including smartwatches, are evolving with diverse sensors for health monitoring and specific medical uses, offering continuous, shareable data to enhance algorithm accuracy and functionality.
Figure adapted from Chikwetu *et al.*, The Lancet Digital Health (2023).[179]

1.1.6.3 Gamification

Gamification, the application of game design principles in non-game settings, is increasingly used to enhance engagement, motivation, and behavioural change in healthcare.[180] By integrating elements such as competition, achievements, rewards, and social interaction into digital health platforms, gamification aims to make health management tasks more interactive and enjoyable.[181] Features such as goal setting, progress tracking, virtual rewards, and social sharing foster user engagement and support positive health outcomes (**Figure 1.10**).[182] Modern technologies, including smartphones and

wearable devices,[183] enable personalised experiences, improving adherence to treatments and participation in health-promoting behaviours. A primary advantage of gamification lies in its ability to make health behaviour change more enjoyable, motivating individuals to adopt habits such as regular exercise and healthy eating.[184] Mobile apps that gamify exercise, for example, encourage physical activity through goal setting, feedback, and tracking. Gamification also fosters social connection, creating supportive communities where individuals with similar health goals can share experiences and engage in friendly competition. For instance, gamified platforms for diabetes management facilitate patient engagement and treatment adherence by encouraging collaboration and accountability.[185, 186] Despite its potential, gamification faces challenges, including limited evidence of its effectiveness in disease prevention and the perception among some users that it trivialises serious health issues.[187] Additionally, high development costs and limited access to technology in low-income or rural areas may hinder its adoption. Nonetheless, gamification offers a promising approach to making chronic disease management more engaging, ultimately improving patient compliance and reducing the burden of care.[165]

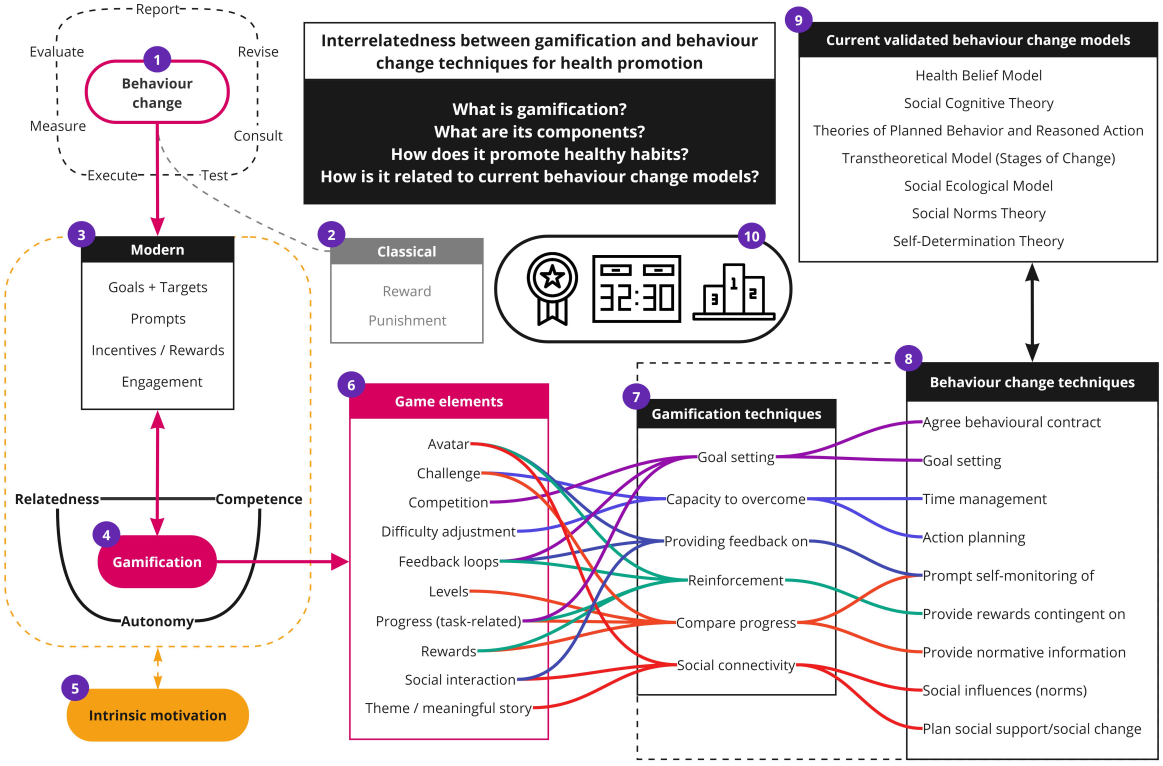


Figure 1.10 Summary overview of the relationship between gamification ingredients and validated health behavioural change techniques.

1. Behaviour change methods involve a pattern of testing and adapting to the changing environment of the individual/population.
2. Classical behaviour change methods involved rewards or punishment.
3. Modern behaviour change methods have moved away from the archaic principle of rewards.
4. Gamification involves a symbiotic relationship between autonomy, relatedness, and competence.
5. Intrinsic motivation: The activity is undertaken because it is internally rewarding where the goal comes from within, and the outcomes of the goal satisfy the basic psychological needs for autonomy, competence, and relatedness.
6. Game elements includes motivation triggering activities.
7. Game techniques are the key to successfully implementing gamification in any intervention.

8. Behaviour change techniques are the end goal of all gamification interventions.
9. List of current validated behaviour change models often used for health interventions – with most having major limitations. For example, the Health Belief Model does not account for a person's attitudes, beliefs, or other individual determinants that dictate a person's acceptance of a health behaviour.
10. Badges, points, and leader boards can be given/implemented as digital goods for motivation.

The growing focus on incorporating gamification into digital healthcare is driven by issues like unequal access to healthcare services, patients not following treatment plans, and rising healthcare costs. Advances in electronic technology, especially the advanced features of smartphones including accelerometers, sensors, and GPS, have significantly contributed to the use of gamification in various sectors, including healthcare. These technologies facilitate effective health interventions through gamified approaches. Technological progress has inspired innovation and creativity, leading to the development of advanced healthcare systems designed to encourage healthy living and improve well-being.[188]

Many mHealth applications and serious games have shown limited long-term engagement because they depend mainly on external rewards. To unlock the full benefits of gamification in healthcare, it's crucial to develop e-Health solutions grounded in theories that tap into the core components and psychological effects of game mechanics.[188] Gamification can aid clinicians in disease prevention by making health behaviour changes enjoyable and engaging, creating a supportive social atmosphere, and offering feedback on patient progress. However, more research is necessary to comprehend its effectiveness fully and overcome the challenges of its implementation.

1.1.6.4 Just-in-time adaptive intervention

The just-in-time adaptive intervention (JITAI) strategy is designed to deliver timely, personalised support that responds dynamically to an individual's changing needs and context. Using mobile technologies and sensors, JITAIs adaptively support health behaviour change by recognising and responding to the fluctuations in a person’s behaviour, environment , or state.[189] This strategy is particularly valuable in addressing complex health issues such as substance use, mental health, and chronic disease management, where real-time, context-sensitive interventions can significantly enhance both engagement and therapeutic outcomes. For instance, in a smoking cessation program, a JITAI might suggest distraction activities or support at moments when cravings are detected, tailored to the user’s specific needs and preferences.[190]

A key element of JITAIs is determining optimal timing and methods for delivering tailored support, known as adaptive treatment strategies or dynamic treatment regimens. JITAIs typically comprise various intervention components that can activate or deactivate based on real-time data, such as physical activity levels, location, or self-reported cravings. For example, in a physical activity intervention, a JITAI might set a daily step goal and provide motivational prompts when activity drops below a certain level.[191] The challenge in developing effective JITAIs lies in understanding how to dynamically adjust these components to meet individual needs across changing situations. The next section discusses how micro-randomised trials (MRTs)[192] provide a powerful methodology for evaluating and optimising these adaptive interventions.

1.1.6.5 Micro randomised controlled trials

Micro-randomised trials (MRTs) are an experimental framework designed to rigorously evaluate JITAIs by allowing for frequent within-participant randomisation of intervention components over time.[190] In an MRT, participants are randomised repeatedly, often multiple times per day, to receive or not receive specific intervention components. This approach enables researchers to assess the real-time effects of individual intervention components, as well as how these effects may vary based on time, context, and individual characteristics. MRTs are essential for understanding how interventions work in naturalistic settings, optimising JITAIs by identifying which components are most effective at different moments and under specific conditions.

The value of MRTs lies in their ability to provide detailed data on both the timing and contextual relevance of interventions, helping researchers fine-tune JITAI components for maximum effectiveness. For instance, an MRT might reveal that certain prompts for physical activity are most effective in the afternoon or under particular environmental conditions.[193] By capturing the interaction between intervention components and contextual variables, MRTs provide a robust framework for developing personalised health interventions (***Textbox 1.1***).[190] With the widespread availability of mobile devices and sensors, MRTs make it feasible to deliver JITAIs that adapt precisely to each user's circumstances, making MRTs a powerful tool in the design of contextually adaptive, effective health interventions.

***Textbox* 1.1** MRTs can help researchers answer questions such as:

- How do the immediate and delayed outcomes of an intervention component compare and differ?
- To what extent do the immediate and delayed effects of an intervention component change over time?
- Which characteristics (fixed or changing over time) influence the immediate or delayed effects of an intervention component?

1.1.6.6 Digital health generated biomarkers

Traditional biomarkers in health assessments typically include physiological indicators such as blood pressure, heart rate, and body temperature, which offer insights into the cardiovascular system.[194] Biochemical markers, measured through blood and urine tests, reveal the functioning of organs, the presence of infections, or the status of metabolic processes.[195, 196] Genetic markers, identified through DNA analysis, can predict susceptibility to certain diseases, response to medications, and provide information on inherited traits.[197] These biomarkers serve as critical indicators for assessing the physiological and metabolic states associated with various health conditions, enabling clinicians to monitor disease progression and evaluate the efficacy of therapeutic interventions (**Figure 1.11**).

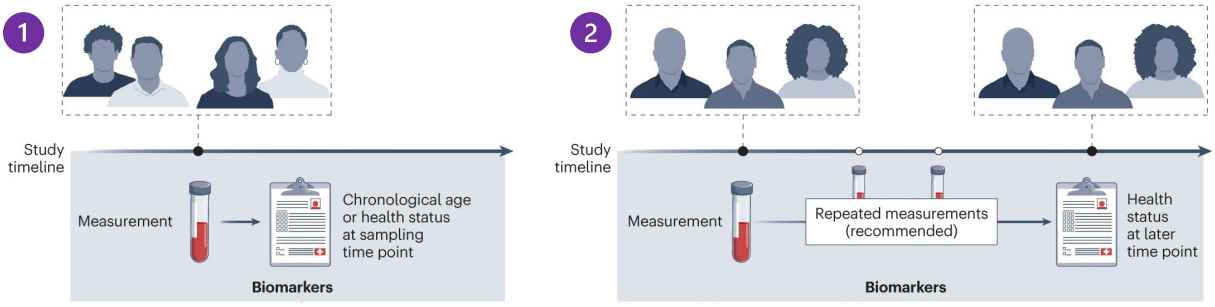


Figure 1.11 Biomarkers are typically verified through two research designs: (1) Cross-sectional and (2) Longitudinal.
Cross-sectional studies measure biomarkers at one time-point, only indicating correlations at that time. Longitudinal studies assess if biomarkers can predict future age-related changes by examining data over time. Figure adapted from Ferrucci *et al.* Nature Medicine (2024).[198]

Digital biomarkers are a relatively new phenomenon in the field of medical science.[199] They refer to a wide range of physiological, behavioural, and environmental variables that can be collected, stored, and analysed through digital technologies such as wearable devices, smartphones, and other sensors (**Figure 1.12**). These variables are used to monitor various aspects of health and well-being, including vital signs, physical activity, sleep patterns, mood, stress levels and more. The data generated by these digital biomarkers can then be used by healthcare providers and researchers to gain insights into a person's health and inform the development of personalised health and wellness programs.[200] Digital biomarkers have rapidly become a promising tool in precision medicine, providing real-time valuable information about an individual's health status.

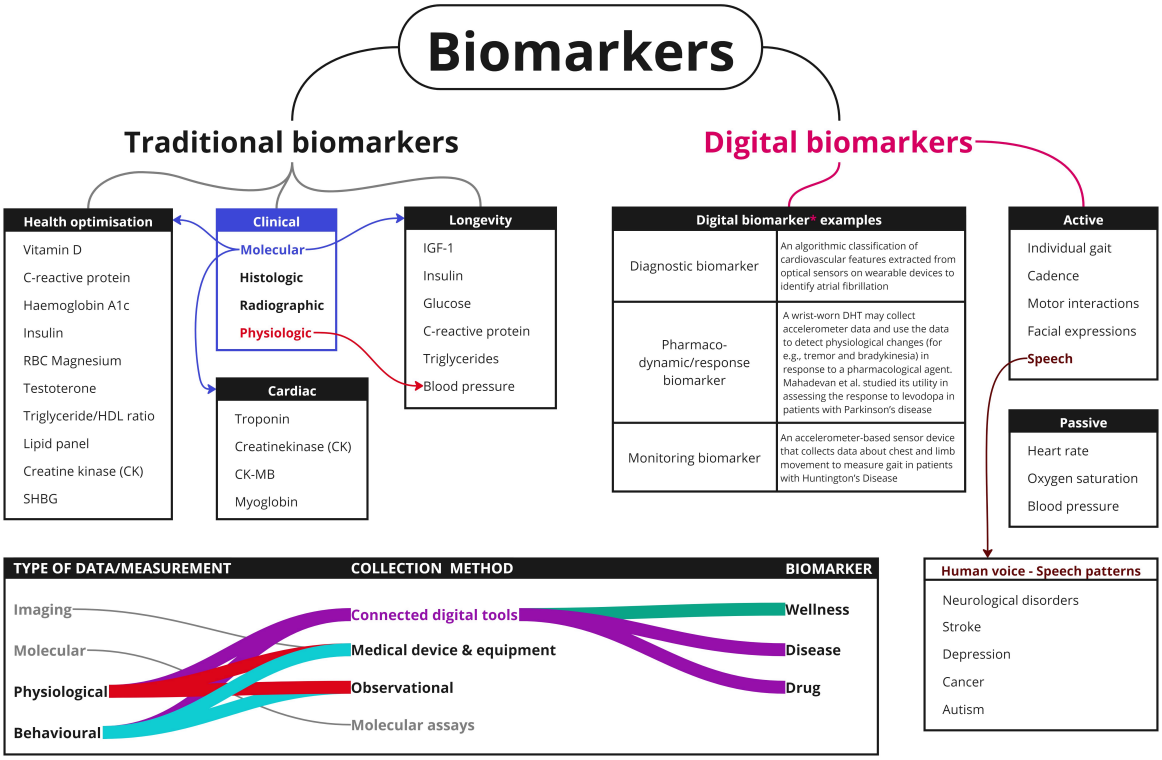


Figure 1.12 Traditional versus digital biomarkers.
A summary and comparison of the most frequently tested biomarkers for disease prevention, diagnosis, and treatment, compared with data obtained from machines (imaging, accelerometer, photoplethysmography, near infrared, etc.) grouped as digital biomarkers.

1.1.6.7 Future of digital health interventions

The future of digital health interventions is highly promising for cardiovascular health, with significant advancements aimed at promoting physical activity, stress reduction, and healthy eating. Modern digital tools, including sophisticated fitness trackers and custom mobile apps, are set to transform exercise routines by providing personalised workout plans based on heart rate and effort, improving heart health, and reducing risk factors.[201] Additionally, new stress management technologies like mindfulness apps, virtual reality relaxation, and biofeedback are emerging as effective ways to lower stress, enhance mental health, and indirectly benefit heart health.[202] Digital solutions are also revolutionising dietary management by tracking nutrition and offering tailored dietary advice, crucial for preventing heart-related issues.[203] Moreover, the use of micro-randomised trials in these digital solutions allows for the real-time fine-tuning of health strategies, greatly improving the personalisation and effectiveness of interventions for individuals.[190] The introduction of gamification in health apps, through points, levels, and rewards, presents an innovative method to engage users and encourage lasting changes in behaviour that support cardiovascular health.[182, 204, 205] In conclusion, the future trajectory of digital health interventions (**Figure 1.13**) in cardiovascular care is marked by a transition towards more personalised, engaging, and adaptive solutions. These interventions are not merely technological feats but are pivotal in shaping health behaviours and preferences, thereby ushering in a new era of cardiovascular health management.

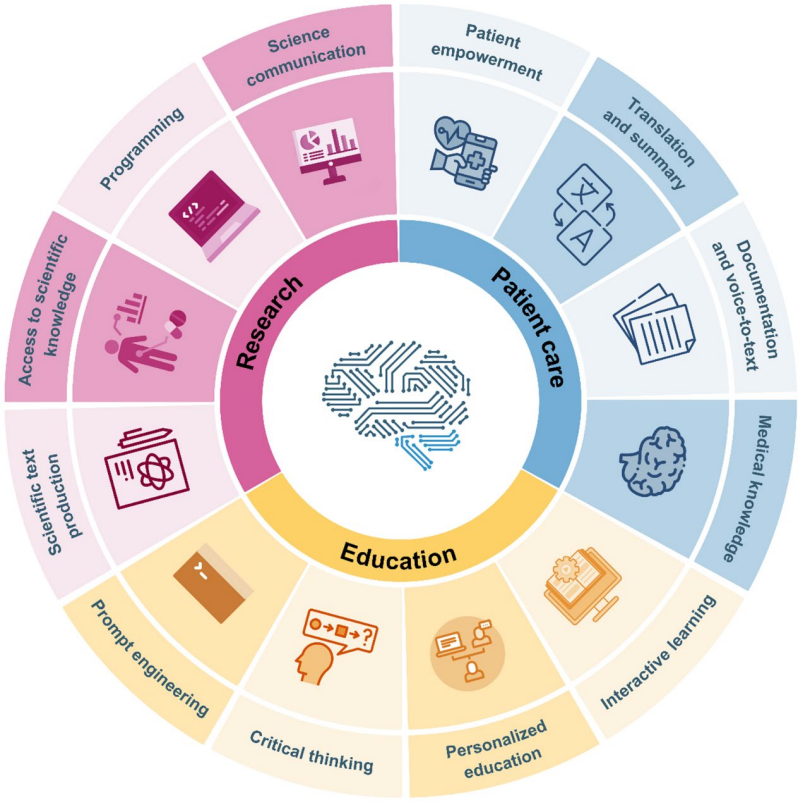


Figure 1.13 The future of digital health interventions in enhancing patient care and biomedical scientific discovery.
Figure adapted from Clusmann *et al.,* Commun Med (2023).[206]

1.2 Summary of introduction

The prevalence of coronary heart disease (CHD) is a growing global concern. CHD remains one of the leading causes of death and disability worldwide. This increase is closely linked to unhealthy lifestyle choices, including poor diet and lack of physical activity, which are major contributors to the development of CHD. One of the features of CHD is impaired vascular health. Vascular disease involves the narrowing or blockage of blood vessels, which can lead to serious cardiovascular events such as heart attacks and strokes. Maintaining vascular health is essential for overall cardiovascular function, and its deterioration significantly increases the risk of cardiometabolic diseases, including type 2 diabetes.

Unhealthy lifestyles are one of the main contributors to poor vascular health and CHD. Unhealthy diets and inactivity play a significant role in the onset of these conditions. Diets high in processed foods, sugar, and saturated fats contribute to vascular disease, while a lack of physical activity exacerbates the problem. Other harmful habits, such as smoking and excessive alcohol consumption, further degrade cardiovascular health, increasing the risk of CHD and related complications. Managing stress is also crucial, as chronic stress is associated with higher risks of heart disease and conditions like obesity and diabetes. Adopting lifestyle modifications, such as quitting smoking and reducing alcohol intake, benefits both heart health and general well-being.[207]

Digital health interventions play an important role in the prevention and management of cardiometabolic diseases, including CHD. In recent years, digital health tools such as mobile apps and wearable devices have shown promise in promoting healthy ageing and disease prevention.[208] These interventions help individuals track their diet, physical activity, and stress levels, providing personalised feedback and support for healthier lifestyle changes.[209] Real-time monitoring of cardiovascular markers like heart rate and blood pressure enables early detection and timely treatment of potential health issues.[209, 210] Additionally, digital health interventions facilitate the implementation of evidence-based recommendations for diet and physical activity, offering access to educational resources that encourage positive lifestyle changes.[211] By combining healthy eating with regular exercise, these tools support vascular health, reduce disease risk, and promote longevity. Ongoing research is needed to further understand the complex relationships between vascular health, lifestyle factors, and digital health technologies, and to develop effective strategies for enhancing heart health and ageing well.

1.3 Research gap

Despite substantial progress in understanding coronary heart disease and cardiometabolic health, several critical research gaps remain. While there is a general understanding of the importance of vascular health indicators, there is a notable gap in the focused examination of the predictive value of specific markers for major adverse cardiovascular events. Current literature has not adequately investigated the potential of CIMT and a composite biomarker index in predicting cardiovascular risks. Existing association studies offer valuable correlations between lifestyle factors and vascular function but do not establish causality, representing a significant gap in literature. The use of randomised controlled trials, such as LIVEPLUS, to rigorously examine the causal effects of lifestyle interventions, including a 5:2 pescatarian diet, on vascular function remains underexplored. This includes

physiological metrics such as FMD, CIMT, PWA, AIx, and PWV in individuals with low attenuation plaques.

Although the theoretical benefits of gamification in health interventions are acknowledged in the literature, empirical evidence on its practical application and effectiveness is limited. There is a significant lack of research exploring the impact of gamification in smartphone applications on cardiometabolic risk factors such as body weight, BMI, systolic blood pressure (SBP), LDL cholesterol, and glycated haemoglobin (HbA1c). Comparisons between gamified app-based education, standard app-based education, and standard care without an app are particularly scarce. The absence of empirical evidence on the outcomes of gamified health interventions presents a critical gap. Research on how specific gamification strategies within apps influence user engagement and effectiveness is lacking. Evaluations of game attributes (assessment, rules, action language, fiction) and elements (progress, feedback, challenge, goal setting) that affect health outcomes are needed to provide robust evidence on the effectiveness of these strategies. Comprehensive evaluation of the overall quality and efficacy of health apps, especially those using gamification strategies, is necessary. Current literature lacks thorough assessments using tools such as the Mobile Apps Rating Scale (MARS) to determine the performance and practical utility of these gamified solutions in a healthcare context. The effect of motivational messages delivered via mobile apps on physical activity in adults with heart disease is underexplored. There is a need for studies leveraging micro-randomised trials to assess the impact of motivational messages sent at different times of the day on physical activity, aiming to identify effective strategies for enhancing physical activity in this population.

1.4 Aims of thesis

This thesis will explore the role of digital health augmented lifestyle interventions and on cardiometabolic outcomes, and the role of vascular health on overall cardiovascular outcomes. The specific aims are:

1. To investigate the association between CIMT and atherosclerotic cardiovascular disease by risk factor burden.
2. To examine the impact of digital health and varied dietary interventions on CHD patients, specifically focusing on the effects of a six-month lifestyle intervention on vascular function.
3. To systematically review the impact of digital health interventions on cardiometabolic risk factors in adults with at least one cardiometabolic risk factors.
4. To investigate the efficacy of personalised, timely technological interventions in promoting increased physical activity, thereby potentially impacting cardiometabolic health and public health at large.

1.5 Specific hypotheses

1. The influence of lifestyle factors on cardiometabolic health indicators varies by age and sex, which will be demonstrated through the correlation between carotid intima-media thickness (CIMT) and a combined biomarker score.
2. Digital health and dietary interventions will improve vascular function after 6 months in patients with coronary artery disease (CHD).

3. Digital health interventions will positively impact cardiometabolic risk factors in adults who have at least one such risk factor, based on a systematic review of their effects.
4. Nudges sent as timely interventions will successfully promote increased physical activity, thereby benefiting cardiometabolic health.

1.6 Significance of this research

Cardiometabolic health remains a key public health concern worldwide. While inpatient medications and surgical interventions can manage end-stage disease management, this thesis delves into the synergistic effects of digital health interventions and lifestyle modifications on cardiometabolic outcomes, thereby addressing a crucial area in the prevention and management of cardiovascular diseases (CVDs), a primary cause of global mortality.

The investigation into the age and sex-specific dynamics between lifestyle factors and cardiometabolic indicators, as described in **Chapter 2**, will uncover the specific predictive value of CIMT and a composite biomarker index for major adverse cardiovascular events. By analysing data from the UK Biobank cohort, it seeks to fill the existing gap in literature regarding the predictive capabilities of these biomarkers. Consequently, in **Chapter 4**, the analysis of digital health and dietary interventions on vascular function in coronary artery disease (CHD) patients offers evidence of the potential benefits of technologically supported lifestyle modifications in halting or slowing CHD progression. This is particularly relevant given the rising trends in sedentary behaviour and poor dietary habits. The systematic review (**Chapter 5**) of the effects of digital health interventions on cardiometabolic risk factors in adults aims to consolidate existing knowledge and highlight research voids, thereby shaping future research directions and clinical practices to bolster preventive strategies. Additionally, exploring tech-driven prompts (**Chapter 7**) to increase physical activity tackles a significant public health issue: the widespread non-compliance with physical activity guidelines. Utilising technology to facilitate lifestyle adjustments could lead to scalable, cost-effective solutions that improve cardiometabolic health and mitigate CVD risk.

In summary, the data from this thesis has the potential to provide valuable insights into the effectiveness of digital health in enhancing cardiometabolic health and vascular function. This could impact policy, clinical guidelines, and public health initiatives, promoting better health outcomes and reducing the healthcare burden associated with cardiometabolic conditions.

Chapter 1 provided an overview of the global burden of cardiovascular CVDs and introduced the critical role of lifestyle factors and digital health interventions in mitigating vascular ageing and improving cardiometabolic health. The chapter emphasised the interplay between sedentary behaviours, poor dietary patterns, and demographic trends, highlighting their combined influence on the rising prevalence of conditions such as hypertension, diabetes, and atherosclerosis. Within this context, the chapter established a compelling need for empirical research to unravel how these modifiable behaviours influence vascular health, and the effectiveness of interventions aimed at fostering long-term behavioural change.

Building upon this foundation, Chapter 2 transitions to an in-depth investigation of these relationships at a population level, using the UK Biobank dataset as a comprehensive resource. By focusing on CIMT, a validated surrogate marker of vascular health, this chapter seeks to identify associations between lifestyle behaviours, cardiometabolic risk factors, and vascular ageing. The analysis examines a broad spectrum of lifestyle variables, including diet, physical activity, and smoking, providing a multidimensional perspective on how these factors contribute to the development and progression of atherosclerosis.

The findings from this chapter are instrumental in setting the stage for the experimental research that follows. While cross-sectional studies are limited in establishing causality, they offer critical insights into potential relationships and areas of focus for targeted interventions. The observed associations between lifestyle behaviours and CIMT provide a valuable basis for designing controlled trials, as discussed in Chapter 3, that can test causal mechanisms and intervention efficacy. This transition underscores the importance of integrating epidemiological and interventional research to inform public health strategies and clinical guidelines.

2 Chapter 2: Carotid intima-media thickness, atherosclerotic cardiovascular disease and risk factor burden in 30,000 adults in the UK Biobank

The relevance of this study lies in its foundational insights into the relationship between lifestyle behaviours and vascular health, providing a basis for designing effective interventions. Using data from the UK Biobank, this chapter examines how modifiable lifestyle factors, such as diet, physical activity, and smoking, contribute to vascular ageing and cardiometabolic risk. Although the data were collected between 2006 and 2010, before digital health tools became widespread, the behavioural targets identified remain highly pertinent to contemporary intervention strategies. The findings offer a comprehensive understanding of population-level risk factors, which is invaluable for informing the development and implementation of digital lifestyle interventions.

This study bridges the gap between traditional epidemiological research and modern digital health approaches. By pinpointing specific lifestyle factors that influence vascular health, it establishes clear priorities for the design of personalised digital tools aimed at encouraging behavioural change. For example, the associations identified in this chapter highlight the importance of interventions focusing on dietary improvements, increased physical activity, and smoking cessation. These findings directly inform the subsequent chapters, which explore how emerging digital technologies can transform these evidence-based targets into scalable and accessible solutions for diverse populations. Despite the temporal gap in data collection, the underlying behavioural targets remain relevant and critical for addressing current challenges in preventive healthcare.

Within the context of this thesis, this study acts as a foundational precursor to the exploration of digital health innovations. It not only provides empirical evidence of key behaviours to be addressed but also emphasises the enduring challenges of fostering long-term adherence, a key issue that digital tools are well-positioned to tackle. By establishing these connections, this chapter underscores how its findings contribute to shaping the future of cardiovascular prevention through innovative and effective digital health platforms.

2.1 Abstract

2.1.1 Background

Carotid intima-media thickness (CIMT) is increasingly used as a surrogate marker for future cardiovascular disease events. The aim of this study was to evaluate independent associations of optimal cardiometabolic health with CIMT and cardiovascular risk.

2.1.2 Methods

We conducted a prospective analysis using data from the UK Biobank cohort to investigate the predictive value of CIMT and cardiometabolic-risk biomarker index (CRBI) for major adverse cardiovascular events. The study included 29,292 participants free from cardiovascular disease at baseline, with comprehensive assessments of CIMT, CRBI, and lifestyle factors.

2.1.3 Results/Findings

During a median follow-up of 4.3 years, 1000 μm CIMT levels was significantly associated with increased risks of coronary heart disease (CHD; HR: 3.15, 95% CI: 1.57, 6.35), myocardial infarction (MI; HR: 3.46, 95% CI: 1.31, 9.15), and heart failure (HF; HR: 3.06, 95% CI: 1.13-8.27), compared to <500 μm CIMT. The CRBI score, reflecting cumulative cardiometabolic risk, showed a linear association with elevated CIMT and increased risks of CHD (HR: 2.70, 95% CI: 1.49-4.91) and MI (HR: 10.43, 95% CI: 3.18-34.24). Lifestyle factors such as smoking and self-reported physical activity also independently influenced CIMT levels.

2.1.4 Discussion/Interpretation

Our findings demonstrate the importance of early detection and management of subclinical atherosclerosis and cardiometabolic risk factors to mitigate future cardiovascular risks. Continued research in diverse populations is warranted to refine risk prediction models and enhance preventive strategies against atherosclerotic cardiovascular disease.

2.1.5 Keywords

atherosclerosis, carotid intima-media thickness, coronary artery disease, myocardial infarction, heart failure

2.2 Introduction

Atherosclerotic cardiovascular disease (CVD) is the leading cause of morbidity, disability and mortality worldwide.[212] In recent decades, a demographic and epidemiological transition has occurred not only in industrialised countries but also in developing nations adopting unhealthy Western diets and lifestyles, leading to a higher cumulative prevalence of atherosclerosis and its main complications, including myocardial infarction, ischemic stroke, heart failure, peripheral arterial disease and vascular dementia.[213, 214] Improving screening tools for the early detection of atherosclerotic CVD is crucial for predicting and preventing major adverse cardiovascular events (MACE). Currently, risk assessment in asymptomatic individuals can be performed using various CVD risk scores, such as the Framingham Risk Score,[215] as well as by non-invasively measuring the intima-media thickness of the common carotid artery (CIMT), a marker of subclinical atherosclerosis.[216, 217]

Accumulating evidence suggest that individual traditional CVD risk factors account for only a small proportion of the variance in CIMT, especially when measured in plaque-free locations.[218] However, since major risk factors are additive in predictive power, assessing their cumulative burden may be more sensitive in capturing CIMT variance and the associated risk of developing MACE.[219] Moreover, the impact of various lifestyle factors, including diet, physical activity, smoking, and sleep, on CIMT, independently of traditional cardiovascular risk factors, is not fully understood, particularly in men and women free of CVD.[220] For example, studies have shown that adherence to a Mediterranean diet, characterised by high consumption of fruits, vegetables, and healthy fats, is associated with reduced CIMT progression only among people with a high initial atherosclerotic burden.[221]

The UK Biobank Study, with its well-defined cohorts of carefully characterised middle-aged men and women, including high-quality CIMT measurements and extensive socio-demographic, lifestyle, and health metrics, provides a unique opportunity to examine factors that may modify CIMT and related cardiovascular risk. In this study, we aimed to investigate the association between carotid intima-media thickness and atherosclerotic cardiovascular disease by risk factor burden among 14,720 men and 14,572 women from the UK Biobank who were free from CVD at baseline. First, we evaluated the prospective association between CIMT values and the risk of MACE. Second, we explored the association between a composite cardiometabolic-risk biomarker index ─ comprising HbA1c, total cholesterol:HDL-cholesterol ratio (TC:HDLr), and blood pressure ─ and CIMT values. Finally, we assessed the prospective association between the composite cardiometabolic-risk biomarker index and the risk of MACE.

2.3 Methods

2.3.1 Study design and population

Details about the UK Biobank cohort have been previously published.[222] Briefly, the UK Biobank cohort comprises 502,632 adults aged 40 to 69 who were assessed at 22 UK centres between March 2006 and December 2010, with a response rate of 5.5%. Participants provided electronic consent and completed a touch-screen questionnaire covering socio-demographic, lifestyle, and health-related information. They also underwent a brief computer-assisted interview and provided physical measurements (height, weight, waist circumference, blood pressure) and biological samples. Ethical

approval was granted by the NHS Research Ethics Committee (Ref. 11/NW/0382) for UK Biobank research. The current analysis, conducted under project 62594, was approved by the UK Biobank research committee and adhered to STROBE reporting guidelines (**Supplementary Table 2.1**).

2.3.2 Lifestyle factors and diet score

Full details of the study design and data extraction for each lifestyle factor collected at baseline (2006-10) are described in the Supplementary Materials (**Supplementary Table 2.2** for definitions and **Supplementary Figure 2.5** for the DAG). As previously described,[223] a continuous diet score was developed based on the consumption of individual food categories recorded in the food frequency questionnaire, with detailed information provided in **Supplementary Tables 2.3 to 2.5**.[224, 225] Alcohol consumption was derived by categorising participants as "Never drinkers" or, for current drinkers, estimating the weekly units of alcohol intake by summing the consumption across different beverage types. Physical activity was categorised as "Low," "Moderate," or "High" based on the International Physical Activity Questionnaire (IPAQ) categorical score, which uses self-reported data on the number of days per week and the duration of walking, moderate, and vigorous activities.[226] Sleep was classified into three groups: less than 7 hours per day, 7 to 9 hours per day (optimal), and more than 9 hours per day.[227, 228] Smoking status was categorised as "Current," "Former," or "Never" smokers. All biochemical markers were measured from blood samples collected at recruitment, and participants who regularly took cholesterol-lowering medications provided this information to an interviewer.

2.3.3 Cardiometabolic-risk biomarker index and score

We developed a simple integrated cardiometabolic-risk biomarker index (CRBI) as a proxy for optimal cardiometabolic health, incorporating three primary metabolic (non-behavioural) cardiovascular risk factors: HbA1c, TC:HDLr, and systolic (SBP) and diastolic (DBP) blood pressure. Following current international guidelines, HbA1c <5.7% without antidiabetic medications was categorised as optimal, between 5.7% and 6.4% or <5.7% but with antidiabetic medications as intermediate, and >6.4% as poor.[229] The TC:HDLr was considered optimal if <3.5 without taking lipid lowering medications, intermediate if between 3.5 and 5 or <3.5 with lipid lowering medications, and poor if >5.[230] SBP was classified as optimal when <120 mmHg without taking antihypertensive medications, intermediate if between 120 and 139 mmHg or <120 mmHg with antihypertensive medications, and poor when >139 mmHg; DBP was optimal if <80 mmHg without taking antihypertensive medications, intermediate if between 80 and 89 mmHg <80 mmHg with antihypertensive medications, and poor if ≥90 mmHg.[231] Detailed definitions and categorisations of this index are outlined in **Supplementary Table 2.6**. For the HbA1c and TC:HDLr variables, a study participant could either score 0 (optimal), 1 (intermediate), or 2 (poor) points. Blood pressure readings were evaluated separately: SBP and DBP were each assigned 0 points for optimal, 0.5 points for intermediate, and 1 point for poor. Therefore, the CRBI score ranged from 0 (optimal) to 6 (poor) (**Supplementary Table 2.7**). Finally, we stratified participants a priori into mutually exclusive categories based on whether they had all optimal risk factor levels (score 0), low risk (scores >0 and ≤1), moderate risk (scores >1 and ≤2), high risk (scores >2 and ≤3), and very high risk (score >3), as detailed in **Supplementary Table 2.7**. For instance, a participant with optimal scores for all biomarkers—HbA1c <5.7%, TC:HDLr <3.5, and BP <120/80 mmHg—would have a CRBI score of

0, indicating optimal cardiometabolic risk. This approach allows for a comprehensive assessment of an individual's overall cardiometabolic health by integrating continuously distributed biological biomarkers into a single index.

2.3.4 Carotid Intima-Media Thickness

Carotid intima-media thickness measurements, collected at imaging visits in 2014, were measured using a CardioHealth Station (Panasonic Biomedical Sales Europe BV, Leicestershire, UK) with participants laying down with their heads elevated at a 45° angle. Automated CIMT measurements were obtained from 2-dimensional carotid scans on both the transverse (short axis) and longitudinal (long axis) planes. Four CIMT readings were taken at specific angles: 120° and 150° for the right carotid artery, and 210° and 240° for the left carotid artery. For each angle, the minimum, mean, and maximum values were recorded.[232] The CIMT values for the four angles were averaged, considering the minimum, mean, and maximum values for our analysis. Quality control of CIMT measurements was performed by the UK Biobank, with validation both internally and externally using predefined criteria.[232, 233] CIMT measurements that failed quality control, either due to values of zero or flagged inconsistencies, were excluded from the analysis.[234] At the time of our study, CIMT measurements were available for 49,112 participants who had completed the second follow-up visit for the UK Biobank. To maximise the sample size, we included participants with available CIMT data and covariate information from the first follow-up (n=29,292).[235]

2.3.5 Cause-specific incidence and CVD mortality

Cardiovascular diagnoses were derived from linked Hospital Episode Statistics using the International Classification of Diseases, 10th Revision (ICD-10) code 'G20' (**Supplementary Table 2.8**). Participants were linked to mortality registries through the UK National Health Service Central Registry, and underlying causes of death were extracted from death certificate data, coded according to ICD-10. The outcomes examined in this study included coronary heart disease (CHD) (ICD-10 code I25), myocardial infarction (MI) (I21, I22, I23), heart failure (HF) (I50), aortic aneurysm (I71), peripheral vascular disease (I73), stroke (I63), and all-cause dementia (A81.0, F00, F01, F02, F03, F05, G30, G31.0, G31.1, G31.8, and I67.3). Participants with records of these conditions at baseline were excluded from the analysis for that specific outcome.

2.3.6 Statistical Analysis

Cohort characteristics were compared using mean (standard deviation [SD]) or median (interquartile range [IQR]) for continuous variables, and percentages for categorical variables. Time-to-event dose-response associations of CIMT with seven disease outcomes (both incident and mortality combined) were investigated. Hazard ratios (HRs) were calculated using Fine-Gray sub-distribution models to account for competing risks from non-disease-specific deaths.[236] Due to the skewed distribution of primary exposures, knots were placed at equally distributed frequencies (10^{th}, 33^{rd}, and 67^{th} percentiles) in areas of higher data density.[237] Departure from linearity was assessed by a Wald test. Proportional hazard assumptions were tested using Schoenfeld Residuals, with no violations observed (all $p>0.05$).

Core models included adjustments for age, sex, ethnicity, C-reactive protein, Townsend deprivation index, sleep duration, physical activity (derived from IPAQ), dietary consumption, CIMT, smoking, alcohol consumption, and body weight. Both adjusted and unadjusted models were reported. Additionally, the same model was repeated with further adjustment for the CRBI score to assess its effect. A linear regression model was fitted to evaluate the association between CIMT (as a continuous outcome) and CRBI score, adjusting for lifestyle factors and other confounders. Multicollinearity was tested via variance inflation factors (VIF). β coefficients and 95% confidence intervals were reported along with p-values. Effect modification by sex was also investigated to determine if lifestyle factors influenced males and females differently. In all models, the reference points for CRBI score and CIMT were optimal (0) and the lowest value (476.8 μm), respectively. The same model was fitted for individual components of the score (blood pressure, TC:HDLr, and HbA1c) to compare the effects across markers and CRBI on CIMT. To minimise the influence of sparse data and preserve sample size, the range of CIMT values was truncated at the 99th percentile. To reduce the risk of reverse causation through undiagnosed diseases, individuals with an event within the first year of follow-up and those with prevalent outcome-specific diseases at the CIMT baseline were excluded. Full details regarding CVD analyses are provided in the Supplementary Material. All statistical analyses were conducted using R (version 4.4.0).

2.4 Results

2.4.1 Baseline characteristics

The analysis included a total of 29,292 participants after excluding those with a history of CHD (n = 1483), MI (n = 745), and HF (n = 285) at baseline and all study covariates were available (**Supplementary Figure 2.1**). The mean age was 64±7.8 years, 48% were women, and 93.8% reported White ethnicity (**Table 2.1**). Participants with higher CIMT were older, had higher BMI, waist circumference, total cholesterol, LDL-cholesterol, triglycerides, blood pressure, HbA1c, C-reactive protein and use of antihypertensive medication and statins (**Table 2.1**).

2.4.2 Carotid IMT as a predictor of major adverse cardiovascular events

We observed an association between CIMT and the incidence of coronary heart disease, myocardial infarction, and heart failure (**Table 2.2**; **Figure 1** in the Supplement), but not with stroke, dementia, peripheral vascular disease, and aortic aneurysm (**Supplementary Figure 2.2**). During a median follow-up of 4.3 years, there were 345, 203 and 232 new cases of CHD, MI, and HF, respectively. We observed a near-linear dose response association between CIMT and event of CHD and MI in the adjusted dose response plots (**Figure *2.1***). The hazard ratio (HR) for CHD was twofold (HR: 2.15, 95% CI: 1.07, 4.31) at 800 μm and threefold (HR: 3.15, 95% CI: 1.57, 6.35) at 1000 μm. HR for myocardial infarction (MI) was 2.46 (95% CI: 0.93, 6.53) at 800 μm, and 3.46 (95% CI: 1.31, 9.15) at 1000 μm. Similar less pronounced pattern was observed for heart failure (HF) (HR: 2.74 at 800 μm and HR: 3.06 at 1000 μm) (**Table 2.2**).

2.4.3 Cumulative burden of cardiometabolic risk factors as predictor of CIMT

The cumulative burden of cardiometabolic risk factors, as assessed by the CRBI score, correlates with higher CIMT (**Figure 2.3**). When participants were stratified by their CRBI score, the magnitude of CIMT increase rose steeply from those with optimal risk factor levels to those with very high CRBI ($p<0.001$). Compared to individuals with optimal cardiometabolic health (representing 2% of men and 14% of women in our sample; **Supplementary Figure 2.3**), those categorised as having a 'very high risk' CRBI score (12% of men and 5% of women) exhibited a significant higher CIMT (β=44.38 μm; 95% CI: 38.25 to 50.51; $p<0.001$). The correlation between CIMT and the CRBI score was more pronounced than with any individual biomarker component (**Supplementary Table 2.10**).

2.4.4 CRBI score as predictor of future cardiovascular events

The CRBI score, reflecting the cumulative burden of cardiometabolic risk factors, predicts a higher likelihood of developing CHD and MI, but not HF (**Table 2.3**). The risk of MI rises linearly from individuals with optimal risk factor levels to those with a very high CRBI score. Compared to those with optimal cardiometabolic health, individuals categorised as having a 'very high CRBI risk' had a sharp increase in MI risk (HR = 10.43, 95% CI: 3.18 to 34.24) after adjusting for multiple confounders. Similar but less pronounced effect was observed for CHD (HR = 2.70, 95% CI: 1.49 to 4.91). Adjustment for CRBI score did not greatly attenuate the magnitude of the associations between CIMT and CVD event risk, as well as their statistical significance (**Figure 2.2**).

2.4.5 Associations between lifestyle factors and CIMT

Risk estimates of CIMT for lifestyle factors are summarised in **Table 2.4**. After adjusting for multiple confounding factors, smoking was associated with higher CIMT, with both former (β=10.16 μm; 95%CI, 7.44 to 12.89) and current smokers (β=14.71 μm; 95%CI, 7.74 to 21.70) having a higher CIMT compared to those who never smoked. Additionally, the analyses revealed a non-linear detrimental role for physical activity as assessed by IPAQ. Compared to participants with low levels of physical activity, those who engaged in high physical activity had a 12.01 μm (95% CI: 8.43 to 15.59) higher CIMT. Sex based stratification is shown in **Table 2.5**, showed that the detrimental effect of physical activity was present in males but not in females. Furthermore, sleep and diet quality were not correlated with changes in CIMT.

2.5 Discussion

Findings from this large prospective study of over 29,000 participants, all free of cardiovascular diseases at baseline and with ultrasound measurements of common carotid artery intima-media thickness, provide the most comprehensive perspective to date on the relationship between CIMT, cardiometabolic risk factors, and major adverse cardiovascular events. We found that higher CIMT is associated with increased risk of incident CHD, MI, and HF, but not stroke or dementia, peripheral vascular disease, or aortic aneurysm. The near-linear dose-response relationship for CHD and MI underscores CIMT's potential as a predictive marker for these outcomes, especially when combined with the CRBI score measuring cumulative cardiometabolic risk. Importantly, in this study, CRBI was a stronger predictor of increased CIMT and the risk of developing CHD and MI than individual risk factors

alone. These results further emphasise the importance of maintaining optimal cardiometabolic risk factor levels to reduce CIMT and subsequent cardiovascular risk.

The most striking findings in this analysis are the substantial differences in atherosclerosis, as assessed by CIMT, and cardiovascular risk between participants with optimal risk factor levels and those with major abnormal risk factors. The CRBI score's strong association with CIMT and cardiovascular events echoes the findings of studies that emphasise the importance of cumulative risk assessment over individual risk factors. The growing emphasis on maintaining optimal or very low levels of traditional risk factors to reduce CVD morbidity and mortality, and to extend health span and lifespan, highlights the impact of favourable cumulative risk profiles on cardiovascular biology and the reduced risk of developing CHD and MI.[238] Moderate calorie restriction, with adequate intake of vitamins and minerals, markedly improves multiple key cardiometabolic risk factors well below conventional risk thresholds used in clinical practice, with endurance exercise training providing additional independent benefits for HDL-cholesterol and glucose metabolism.[239-241]

Our findings align with previous research identifying CIMT as a predictor of cardiovascular events,[242, 243] although we could not observe an association between CIMT and stroke likely due to the low event number. The Rotterdam Elderly Study, with 3,996 participants and a 6.1-year follow-up, identified CIMT as a significant independent predictor for both CHD and stroke.[244] Similarly, a study involving 4,476 subjects 65 years of age or older over a median follow-up period of 6.2 years demonstrated that both common and internal CIMT measurements predicted CHD and stroke.[245] More studies are needed to confirm these associations and further elucidate the mechanisms underlying the relationship between CIMT and cardiovascular events, particularly stroke. Indeed, accumulating data suggest that increased IMT in the common and internal carotid arteries might reflect different underlying pathophysiological mechanisms and therefore be differently associated with CHD and stroke risk.[246]

In examining lifestyle factors, our analysis suggests that smoking, rather than diet quality, alcohol intake, or sleep, is likely associated with increased CIMT. Both former and current smokers tended to have higher CIMT levels compared to those who had never smoked, aligning with previous studies indicating a negative vascular impact of smoking.[242, 247] Notably, dietary intake was measured using a food frequency questionnaire by food groups, which did not consider macronutrient ratios (carbohydrate, protein, and fat), types (saturated, unsaturated, etc.), and energy intake. Although we did not find an association between dietary intake and CIMT, there was a notable association between worsening plasma lipids and increasing CIMT.

Our study uncovered a nonlinear relationship between physical activity and CIMT, with higher activity levels associated with increased CIMT, particularly among males. This aligns with recent observations that lifelong endurance athletes may have more coronary plaques, including non-calcified ones.[248,249, 250] Preclinical data suggest that long-term intensive training, unlike moderate training, can impair arterial structural and functional properties via the renin-angiotensin-aldosterone system.[251] It is possible that In certain individuals, overactivation of the sympathetic and angiotensin systems might lead to abnormal plaque modelling at higher exercise levels. However, our analysis was limited by the use of self-reported

physical activity, which lacks precision. Future research using accelerometers to capture detailed activity types and intensities is needed for a more comprehensive understanding.

This study has several strengths, including a large sample size, comprehensive assessment of cardiometabolic risk factors and CIMT, and the exclusion of individuals who experienced an event within the first year to minimise the risk of reverse causation. However, the results of our analysis must be interpreted within its limitations. First, our study, even if prospective, was observational therefore having inherent limitations compared to intervention trials precluding causal inferences. Secondly, it is important to note that the quality of measurement for predictors self-reported questionnaire-based lifestyle is suboptimal. Moreover, variables were assessed at baseline only, failing to account for changes that may have occurred at follow-up. Thirdly, the relatively brief follow-up period may limit the generalisability of the findings to long-term cardiovascular risk and suggest that future studies with extended follow-up durations are necessary to confirm the observed associations. Fourthly, it was conducted in a single country, in predominantly white individuals, with the limitation of not accounting for unmeasured environmental, genetic, and cultural confounders.

In summary, our extensive prospective study involving around 30,000 initially cardiovascular disease-free participants indicates the association of CIMT with major adverse cardiovascular events, particularly CHD, MI, and HF. We found that higher CIMT levels are strongly correlated with increased cumulative cardiometabolic risk, emphasising the importance of comprehensive assessment of cardiometabolic risk factors, as quantified by the CRBI score, in predicting cardiovascular outcomes. While acknowledging limitations in observational design and potential confounders, these findings suggest the critical need for effective lifestyle and/or pharmacological strategies to optimise cardiovascular health through multi-target risk factor management. Future research should further investigate these correlations and apply composite cardiometabolic biomarker indices across diverse populations to refine preventive approaches and enhance predictive accuracy.

Table 2.1 Participant descriptive characteristics by CIMT quartiles

	Baseline characteristics*	Overall	470-600 µm	>600-670 µm	>670-750 µm	>750 µm	P-value
Anthropometrics	Total population	29292	7323	7323	7323	7323	
	Age (in years)	63.99 (7.77)	59.47 (7.02)	62.85 (7.29)	65.63 (7.22)	68.02 (6.81)	<0.001
	Female N (%)	14572 (48)					
	Ethnicity N (%)						
	White	27420 (93.84)	6791 (92.90)	6855 (93.80)	6889 (94.40)	6885 (94.30)	0.001
	Body weight (kg)	76.28 (15.00)	73.94 (14.68)	75.31 (14.82)	76.46 (14.97)	79.43 (14.98)	<0.001
	BMI	26.46 (4.31)	25.99 (4.35)	26.33 (4.35)	26.56 (4.29)	26.98 (4.21)	<0.001
	BMI# N (%)						<0.001
	Underweight	211 (0.74)	68 (1.00)	67 (0.90)	52 (0.70)	24 (0.30)	
	Healthy weight	11388 (39.98)	3253 (45.60)	3001 (42.00)	2751 (38.80)	2383 (33.50)	
	Overweight	11834 (41.54)	2737 (38.40)	2843 (39.70)	2991 (42.20)	3263 (45.90)	
	Obese	5053 (17.74)	1077 (15.10)	1242 (17.40)	1297 (18.30)	1437 (20.20)	
	Waist circumference (cm)	88.39 (12.53)	85.99 (12.28)	87.35 (12.49)	88.78 (12.51)	91.46 (12.17)	<0.001
	Townsend deprivation index	-1.86 (2.73)					
Major cardiovascular risk factors	Total cholesterol (mmol/L)	5.71 (1.07)	5.58 (1.04)	5.69 (1.06)	5.75 (1.06)	5.82 (1.12)	<0.001
	LDL (mmol/L))	3.57 (0.82)	3.46 (0.80)	3.54 (0.81)	3.60 (0.81)	3.69 (0.85)	<0.001
	HDL (mmol/L)	1.47 (0.37)	1.50 (0.37)	1.50 (0.38)	1.48 (0.38)	1.41 (0.36)	<0.001
	Mean TC/HDL ratio	4.07 (1.09)					
	Triglycerides (mmol/L)	1.65 (0.96)	1.53 (0.93)	1.59 (0.93)	1.66 (0.93)	1.81 (1.02)	<0.001
	Blood pressure						
	SBP	138.49 (18.67)	131.01 (16.44)	136.44 (17.79)	140.67 (18.01)	145.89 (19.07)	<0.001
	DBP	79.05 (10.04)	78.31 (9.72)	79.11 (10.02)	79.33 (10.09)	79.44 (10.27)	<0.001
	HbA1c (mmol/mol)	34.90 (5.02)	34.06 (4.44)	34.70 (4.80)	35.11 (4.87)	35.72 (5.74)	<0.001
	C-reactive protein (mg/L)	2.04 (3.56)	1.93 (3.68)	1.98 (3.52)	2.08 (3.47)	2.15 (3.57)	0.001
	CRBI score categories N (%)						
	Optimal	2253 (7.69)	1013 (13.83)	658 (8.99)	387 (5.28)	195 (2.66)	
	Low	5661 (19.33)	1885 (25.74)	1590 (21.71)	1349 (18.42)	837 (11.43)	
	Moderate	8699 (29.70)	2173 (29.67)	2221 (30.33)	2290 (31.27)	2015 (27.52)	
	High	8416 (28.73)	1587 (21.67)	1946 (26.57)	2229 (30.44)	2654 (36.24)	
	Very high	4263 (14.55)	665 (9.08)	908 (12.40)	1068 (14.58)	1622 (22.15)	
Lifestyle risk factors	Smoking status (%)						<0.001
	Never	18166 (62.20)	4934 (67.50)	4679 (64.00)	4488 (61.50)	4065 (55.70)	
	Former	1010 (3.50)	279 (3.80	259 (3.50)	214 (2.90)	258 (3.50)	
	Current	10041 (34.40)	2099 (28.70)	2373 (32.50)	2599 (35.60)	2970 (40.70)	
	Diet score (%) in quartiles						<0.001
	Optimal	3284 (11.20)	765 (10.50)	824 (11.30)	829 (11.30)	866 (11.90)	
	Healthy	10434 (35.70)	2539 (34.80)	2561 (35.10)	2666 (36.50)	2668 (36.60)	
	Fair	10712 (36.70)	2695 (36.90)	2754 (37.70)	2621 (35.90)	2642 (36.20)	
	Poor	4780 (16.40)	1306 (17.90)	1161 (15.90)	1192 (16.30)	1121 (15.40)	
	Alcohol intake (%)						
	Never	1849 (6.30)	474 (6.50)	462 (6.30)	461 (6.30)	452 (6.20)	
	Daily or almost daily	5054 (17.30)	1082 (14.80)	1228 (16.80)	1286 (17.60)	1458 (19.90)	
	Three or four times a week	8374 (28.60)	2034 (27.80)	2079 (28.40)	2130 (29.10)	2131 (29.10)	
	Once or twice a week	7761 (26.50)	2048 (28.00)	1968 (26.90)	1936 (26.40)	1809 (24.70)	
	Less often	6254 (21.40)	1685 (23.00)	1586 (21.70)	1510 (20.60)	1473 (20.10)	

	Baseline characteristics*	Overall	470-600 µm	>600-670 µm	>670-750 µm	>750 µm	P-value
	Never	1849 (6.30)	474 (6.50)	462 (6.30)	461 (6.30)	452 (6.20)	
	IPAQ (%)						<0.001
	Low	5393 (18.40)	1408 (19.20)	1393 (19.00)	1342 (18.30)	1250 (17.10)	
	Moderate	12403 (42.30)	3153 (43.10)	3113 (42.50)	3078 (42.00)	3059 (41.80)	
	High	11496 (39.20)	2762 (37.70)	2817 (38.50)	2903 (39.60)	3014 (41.20)	
	Sleep category (%)						0.003
	<5-7hr	7015 (23.90)	1826 (24.90)	1788 (24.40)	1744 (23.80)	1657 (22.60)	
	7-9hr	21912 (74.80)	5427 (74.10)	5442 (74.30)	5488 (74.90)	5555 (75.90)	
	>9hr	365 (1.20)	70 (1.00)	93 (1.30)	91 (1.20)	111 (1.50)	
Medication intake	Medication (Males) (%)						<0.001
	Blood pressure medication	1168 (7.90)	175 (5.70)	259 (8.00)	295 (8.00)	439 (9.30)	
	Cholesterol lowering medication	2421 (16.40)	337 (11.00)	463 (14.20)	656 (17.80)	965 (20.40)	
	Do not know	64 (0.40)	17 (0.60)	9 (0.30)	13 (0.40)	25 (0.50)	
	Insulin	17 (0.10)	5 (0.20)	4 (0.10)	3 (0.10)	5 (0.10)	
	None of the above	11046 (75.00)	2517 (82.50)	2514 (77.30)	2712 (73.70)	3303 (69.70)	
	Prefer not to answer	4 (0.00)	0 (0.00)	2 (0.10)	1 (0.00)	1 (0.00)	
	Medication (Females) (%)						<0.001
	Blood pressure medication	952 (6.50)	160 (3.70)	223 (5.50)	303 (8.30)	266 (10.30)	
	Cholesterol lowering medication	934 (6.40)	157 (3.70)	249 (6.10)	273 (7.50)	255 (9.90)	
	Do not know	33 (0.20)	14 (0.30)	6 (0.10)	7 (0.20)	6 (0.20)	
	Hormone replacement therapy	1010 (6.90)	252 (5.90)	280 (6.90)	284 (7.80)	194 (7.50)	
	Insulin	12 (0.10)	2 (0.00)	1 (0.00)	5 (0.10)	4 (0.20)	
	None of the above	11204 (76.90)	3470 (81.20)	3196 (78.50)	2698 (74.10)	1840 (71.20)	
	Oral contraceptive pill or minipill	422 (2.90)	215 (5.00)	116 (2.80)	73 (2.00)	18 (0.70)	
	Prefer not to answer	3 (0.00)	1 (0.00)	0 (0.00)	0 (0.00)	2 (0.10)	

* Study population data is from baseline (2006-2010), CIMT values are from Imaging visit 1 (2014+). Values are Mean (SD) unless otherwise stated.
#BMI: Underweight (<18.50), Healthy weight (18.50 to 25.00), Overweight (25.00 to 30.00), Obese (>30.00).
CRBI score, cardiometabolic risk biomarker index score; IPAQ, International Physical Activity Questionnaire.
CRBI scores of 0, >0 & ≤1, >1 & ≤2, >2 & ≤3, >3 correspond to optimal, low risk, moderate risk, high risk, and very high risk.

Table 2.2 Point estimates of dose response association between CIMT and MACE, where CIMT reference point is 476.8 μm.

CIMT (μm)	**Hazard ratios** (95% CI)		
	CHD	**MI**	**HF**
476.8 (reference)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
500	1.07 (0.95, 1.20)	1.10 (0.93, 1.29)	1.15 (0.97, 1.36)
600	1.42 (0.79, 2.55)	1.62 (0.71, 3.68)	2.04 (0.88, 4.75)
700	1.78 (0.86, 3.66)	2.07 (0.75, 5.72)	2.59 (0.91, 7.35)
800	2.15 (1.07, 4.31)	2.46 (0.93, 6.53)	2.74 (1.00, 7.50)
900	2.61 (1.31, 5.18)	2.92 (1.11, 7.63)	2.89 (1.07, 7.78)
1000	3.15 (1.57, 6.35)	3.46 (1.31, 9.15)	3.06 (1.13, 8.27)

CHD, coronary heart disease; MI, myocardial infarction; HF, heart failure.
Analyses adjusted for age, sex, ethnicity, C-reactive protein, Townsend deprivation index, sleep duration, physical activity derived from IPAQ, dietary consumption, composite biomarker score (HbA1c, total cholesterol to HDL ratio, and blood pressure), smoking, alcohol consumption, and body weight.

Table 2.3 Point estimates of dose response association between CRBI score and MACE, where CRBI score reference point is optimal (HbA1c < 5.7%, TC:HDLr <3.5, BP <120/80).

CRBI score	**Hazard ratios** (95% CI)		
	CHD (Event=345)	**MI** (Event=203)	**HF** (Event=232)
Optimal (reference)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Low	1.33 (0.90, 1.97)	2.98 (1.37, 6.50)	1.00 (0.63, 1.58)
Moderate	1.72 (0.93, 3.20)	6.50 (1.86, 22.64)	1.02 (0.50, 2.11)
High	2.16 (1.20, 3.92)	8.33 (2.48, 28.04)	1.10 (0.56, 2.20)
Very high	2.70 (1.49, 4.91)	10.43 (3.18, 34.24)	1.19 (0.60, 2.39)

CRBI score, cardiometabolic risk biomarker index score.
CRBI scores of 0, ≥0 & ≤1, >1 & ≤2, >2 & ≤3, >3 correspond to optimal, low risk, moderate risk, high risk, and very high risk.
CHD, coronary heart disease; MI, myocardial infarction; HF, heart failure.
Analyses adjusted for age, sex, ethnicity, C-reactive protein, Townsend deprivation index, sleep duration, physical activity derived from IPAQ, dietary consumption, CIMT, smoking, alcohol consumption, and body weight.

Table 2.4 Association between CIMT and covariates (N=29292)

		Adjusted model	
		β (95% CI)	**P-value**
Anthropometrics	**Age (in years)**	5.92 (5.74, 6.09)	<0.001
	Sex		
	Females	ref	
	Males	12.67 (9.63, 15.70)	<0.001
	Ethnicity N (%)		
	White	-7.61 (-12.96, -2.27)	<0.01
	Weight (kg)	0.84 (0.74, 0.94)	<0.001
	Townsend	-0.33 (-0.80, 0.14)	0.170
	CRP (Inflammation)	-0.21 (-0.57, 0.15)	0.245
	CRBI score categories		
	Optimal	ref	
	Low	10.37 (4.99, 15.74)	<0.001
	Moderate	19.89 (14.63, 25.15)	<0.001
	High	32.47 (26.68, 37.96)	<0.001
	Very high	44.38 (38.25, 50.51)	<0.001
Lifestyle risk factors	**Smoking status (%)**		
	Never	ref	
	Previous	10.16 (7.44, 12.89)	<0.001
	Current	14.71 (7.74, 21.70)	<0.01
	Diet score (%)		
	Poor	ref	
	Fair	1.82 (-1.91, 5.56)	0.338
	Healthy	0.54 (-3.24, 4.33)	0.780
	Optimal	1.90 (-3.02, 6.82)	0.449
	Alcohol intake (%)		
	Never	ref	
	~Daily	3.25 (-2.68, 9.17)	0.283
	Less often	1.20 (-4.49, 6.90)	0.677
	1-2/week	5.00 (-0.60, 10.59)	0.080
	3-4/week	3.68(-1.91, 9.26)	0.197
	IPAQ (%)		
	Low	ref	
	Moderate	5.11 (1.60, 8.62)	<0.01
	High	12.01 (8.43, 15.59)	<0.001
	Sleep category (%)		
	<7hr	ref	
	7-9hr	0.68 (-2.28, 3.63)	0.653
	>9hr	6.23 (-5.35, 17.81)	0.292

CRP, C-reactive protein (mg/L); CRBI score, cardiometabolic risk biomarker index score; IPAQ, International Physical Activity Questionnaire.
CRBI scores of 0, >0 & ≤1, >1 & ≤2, >2 & ≤3, >3 correspond to optimal, low risk, moderate risk, high risk, and very high risk.
Analyses adjusted for age, sex, ethnicity, C-reactive protein, Townsend deprivation index, sleep duration, physical activity derived from IPAQ, dietary consumption, CIMT, smoking, alcohol consumption, and body weight.

Table 2.5 Results from the adjusted model stratified by sex. (N=29292)

		Female		Male	
		β (95% CI)	P-value	β (95% CI)	P-value
Anthropo -metrics	**Age**	5.90 (5.67, 6.12)	<0.001	5.90 (5.67, 6.17)	<0.001
	Ethnicity	-6.12 (-12.48, 0.26)	0.006	-9.72 (-18.55, -0.89)	<0.05
	Weight	0.74 (0.61, 0.87)	<0.001	0.95 (0.80, 1.11)	<0.001
	Townsend	0.35 (-0.24, 0.95)	0.245	-0.94 (-1.68, -0.20)	<0.05
CVD risk factors	**CRP (Inflammation)**	-0.62 (-1.06, -0.18)	<0.01	0.36 (-0.22, 0.93)	0.228
	CRBI score categories	-	-	-	-
	Optimal	ref		ref	
	Low risk	26.19 (18.94, 33.44)	<0.001	5.68 (-9.45, 20.81)	0.462
	Moderate risk	52.75 (40.63, 64.88)	<0.001	17.03 (2.55, 31.51)	<0.05
	High risk	83.81 (65.68, 101.93)	<0.001	29.17 (14.71, 43.63)	<0.001
	Very high risk	111.44 (85.89, 137.00)	<0.001	42.86 (28.05, 57.67)	<0.001
Lifestyle risk factors	**Smoking**	-	-	-	-
	Never	ref		ref	
	Previous	6.95 (3.47, 10.44)	<0.001	12.96 (8.78, 17.13)	<0.001
	Current	3.09 (-6.45, 12.62)	0.526	23.32 (13.22, 33.41)	<0.001
	Diet score	-	-	-	-
	Poor	ref		ref	
	Fair	1.59 (-3.46, 6.64)	0.537	1.88 (-3.56, 7.32)	0.499
	Healthy	0.10 (-4.92, 5.13)	0.968	1.03 (-4.59, 6.66)	0.719
	Optimal	1.60 (-4.61, 7.81)	0.613	2.61 (-5.12, 10.35)	0.508
	Alcohol intake	-	-	-	-
	Never	ref		ref	
	~Daily	0.11 (-7.24, 7.46)	0.977	4.58 (-5.01, 14.08)	0.351
	Less often	1.76 (-4.85, 8.37)	0.601	0.26 (-9.48, 10.00)	0.958
	1-2/week	6.45 (-0.17, 13.07)	0.056	2.77 (-6.57, 12.11)	0.560
	3-4/week	2.55 (-4.15, 9.26)	0.455	3.69 (-5.51, 12.90)	0.432
	IPAQ	-	-	-	-
	Low	ref		ref	
	Moderate	0.83 (-3.62, 5.27)	0.715	8.85 (3.44, 14.27)	<0.01
	High	3.26 (-1.32, 7.84)	0.163	20.01 (14.55, 25.47)	<0.001
	Sleep	-	-	-	-
	<7hr	ref		ref	
	7-9hr	1.83 (-1.81, 5.47)	0.324	-0.87 (-5.55, 3.82)	0.717
	>9hr	-6.99 (-22.24, 8.26)	0.369	16.28 (-0.97, 33.54)	0.064

CRP, C-reactive protein (mg/L); CRBI score, cardiometabolic risk biomarker index score; IPAQ, International Physical Activity Questionnaire.
CRBI scores of 0, >0 & ≤1, >1 & ≤2, >2 & ≤3, >3 correspond to optimal, low risk, moderate risk, high risk, and very high risk.
Analyses adjusted for age, ethnicity, C-reactive protein, Townsend deprivation index, sleep duration, physical activity derived from IPAQ, dietary consumption, CIMT, smoking, alcohol consumption, and body weight.

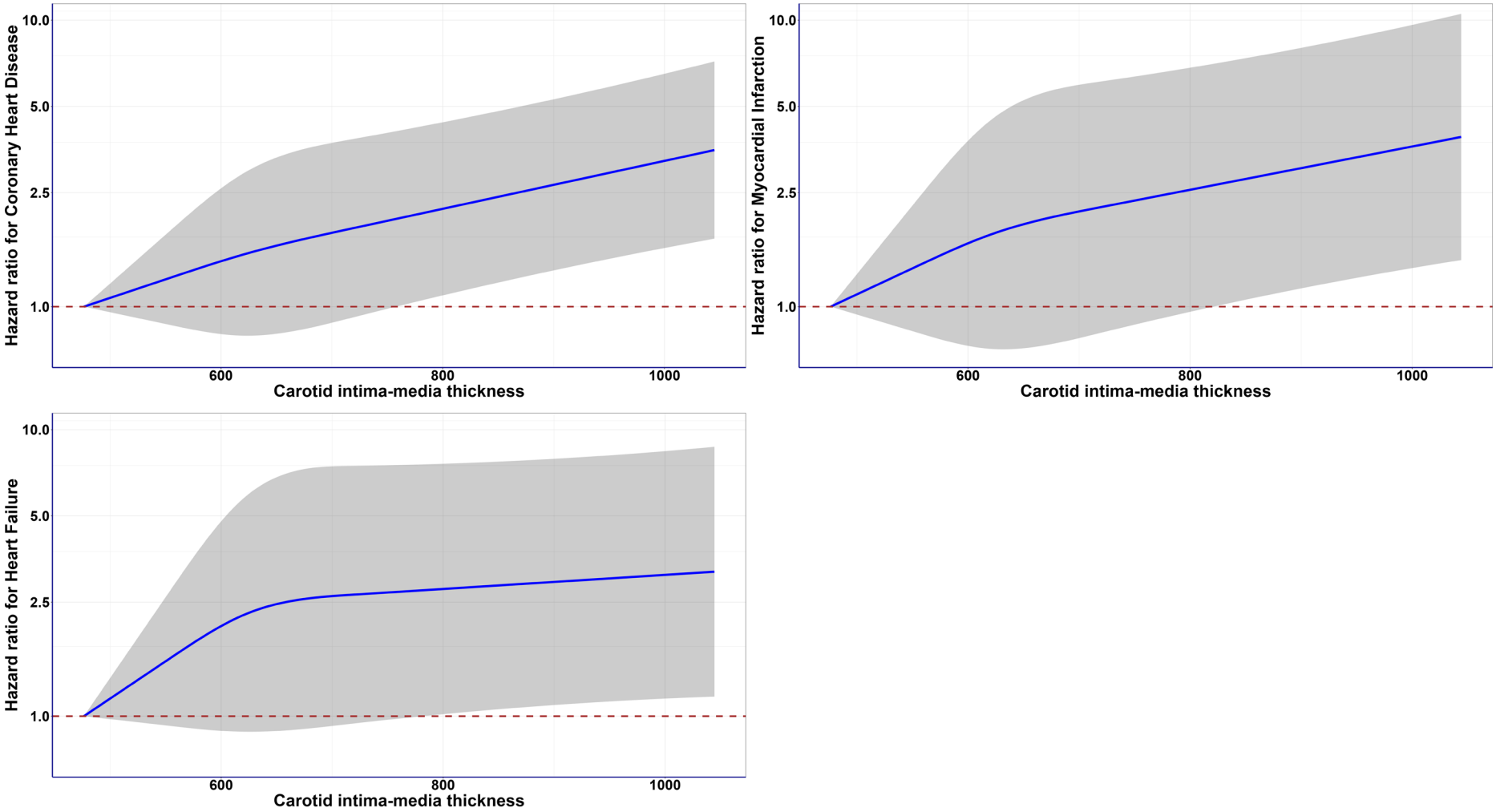


Figure 2.1 Association of carotid intima media thickness and CVD incidence (coronary heart disease, myocardial infarction, and heart failure).
Legend: Analyses were adjusted for age, sex, ethnicity, C-reactive protein, Townsend deprivation index, sleep duration, physical activity (derived from IPAQ), dietary consumption, cardiometabolic risk biomarker index (CRBI) score, smoking, alcohol consumption, and body weight. All analyses excluded participants who had an event in the first year of follow-up and those with prevalent outcome-specific diseases at the CIMT baseline were excluded. Reference for CIMT was set at minimum (476.8 μm). The shaded region indicates the 95% confidence interval (CI). Within this shaded area, the solid line in blue represents the hazard ratio (HR).

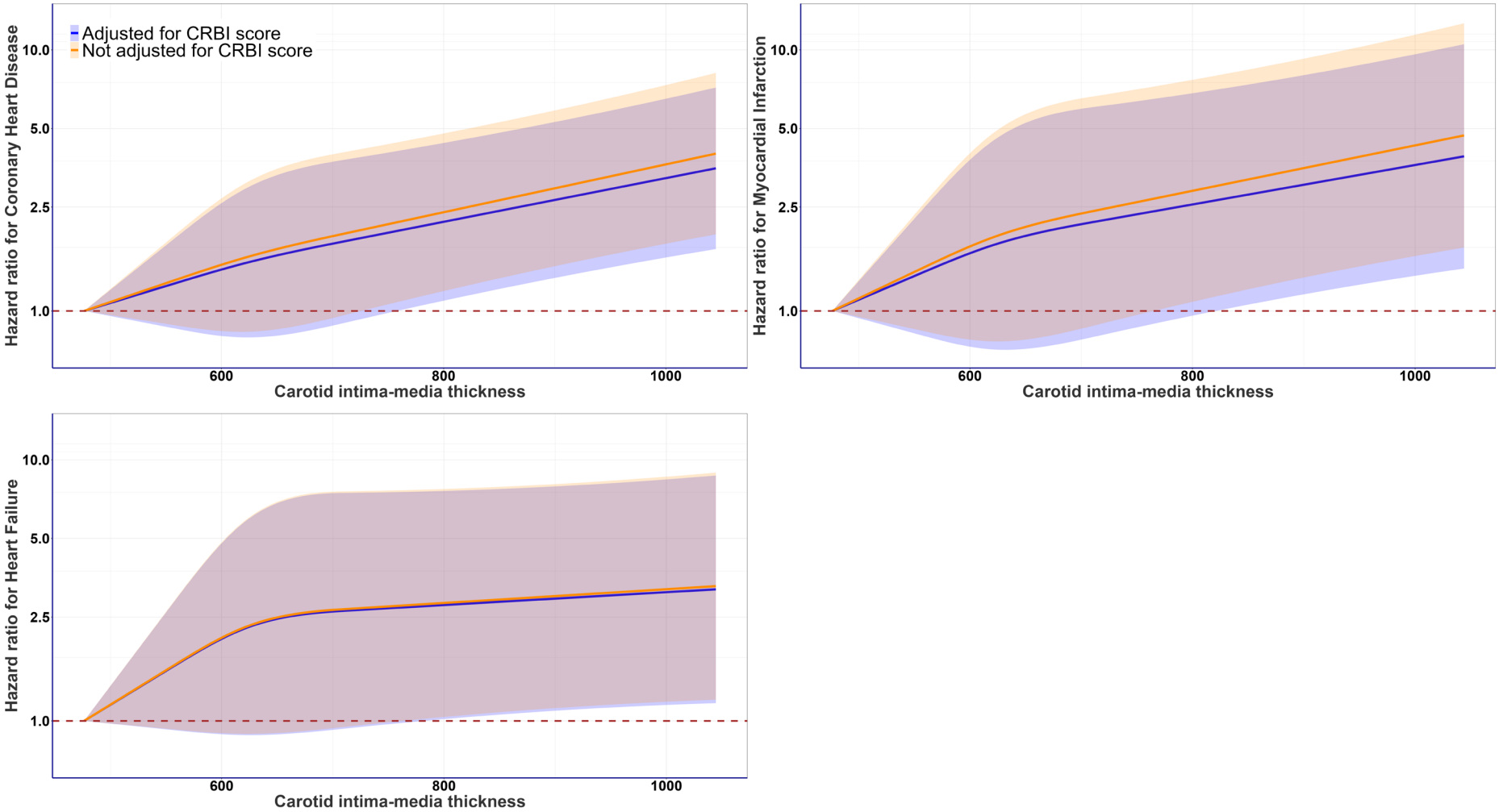


Figure 2.2 Adjustment for the CRBI score attenuated the magnitude of the associations between CIMT and CVD event risk.

Legend: Analyses were adjusted for age, sex, ethnicity, C-reactive protein, Townsend deprivation index, sleep duration, physical activity (derived from IPAQ), dietary consumption, smoking, alcohol consumption, and body weight. All analyses excluded participants who had an event in the first year of follow-up and those with prevalent outcome-specific diseases at the CIMT baseline were excluded. Reference for CIMT was set at minimum (476.8 μm). The shaded region indicates the 95% confidence interval (CI). Within this shaded area, the solid line in blue represents the hazard ratio (HR).

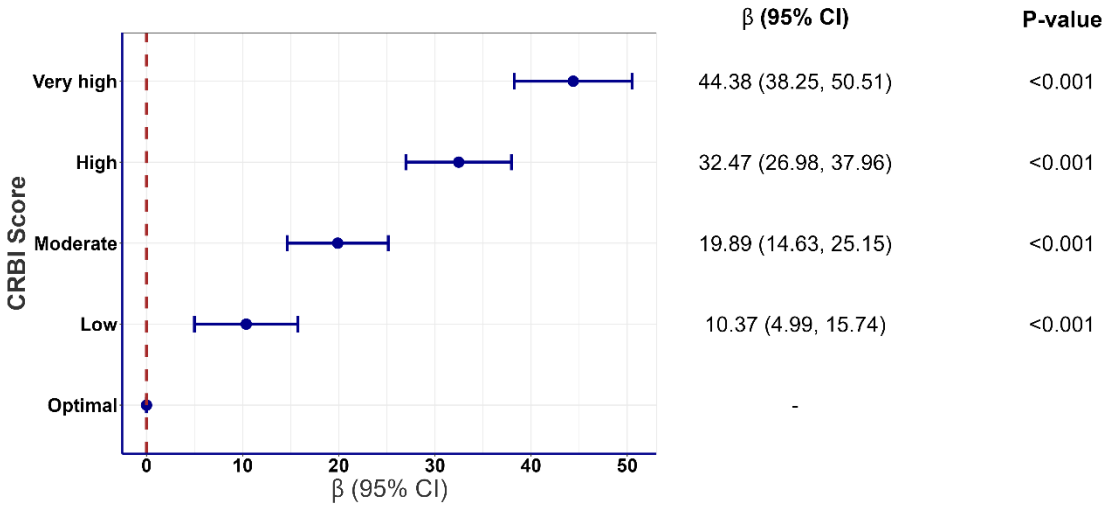


Figure 2.3 Association between cardiometabolic risk biomarker index (CRBI) score and carotid intima-media thickness (cIMT).

CRBI score, cardiometabolic risk biomarker index score. Data are presented as hazard ratios with 95% confidence intervals.
CRBI scores of 0, ≥0 & ≤1, >1 & ≤2, >2 & ≤3, >3 correspond to optimal, low risk, moderate risk, high risk, and very high risk.
Analyses adjusted for age, sex, ethnicity, C-reactive protein, Townsend deprivation index, sleep duration, physical activity derived from IPAQ, dietary consumption, CIMT, smoking, alcohol consumption, and body weight. We removed participants with a previous history of CHD, MI, or HF.
All analyses excluded participants who had an event in the first year of follow-up.

The cross-sectional analysis in Chapter 2 offered compelling evidence of associations between lifestyle behaviours and vascular health markers, particularly CIMT. These findings underscore the role of modifiable lifestyle factors in shaping cardiometabolic risk profiles and the potential of addressing these factors to mitigate vascular ageing. However, the limitations of observational studies, such as their inability to establish causality or control for unmeasured confounders, necessitate a more robust methodological approach to validate these findings.

In response, Chapter 3 introduces the LIVEPLUS Protocol, a rigorously designed randomised controlled trial aimed at testing the causal effects of lifestyle interventions on vascular health. This chapter outlines the study's framework, including its focus on dietary and physical activity interventions, its inclusion of both primary and secondary outcomes, and its robust randomisation and blinding procedures. The protocol addresses key gaps identified in Chapter 2 by providing a controlled environment to evaluate the efficacy of lifestyle modifications over time, thus ensuring a higher level of evidence for clinical practice.

Furthermore, the LIVEPLUS Protocol is designed to capture the nuanced interplay between various lifestyle components and vascular health, including how these interventions influence both structural markers such as CIMT and functional measures such as flow-mediated dilation. This transition from observational to experimental research marks a critical progression in my thesis, moving from association to causation and setting the foundation for understanding the potential of lifestyle interventions in reversing or halting vascular ageing.

3 Chapter 3: LIVEPLUS Protocol

3.1 Chapter 3 published in peer-reviewed form

Cassidy S, Kroeger CM, Wang T, **Mitra S**, Liu C, Ribeiro R, Dai A, Lau J, Huang R, Masedunkas A, Jose S Liu N, Avery L, Yang J, McGrady M, Lo S, George J, Cistulli P, Khor L, Kozor R, Ugander M, Wilcox I, Hunyor I, Fontana L.

Impact of an intensive lifestyle program on low attenuation plaque and myocardial perfusion in coronary heart disease: A randomised clinical trial protocol

Nutrition and Healthy Aging. 2022 Jan 1;7(1-2):9-22
doi: 10.3233/NHA-210146

This abstract for this protocol was presented at the International Behavioural Trials Network Conference, Montreal, Canada, 16 – 18 May 2024.

The author contribution statement can be found in **Appendix H**.

The following pages are as this manuscript appears in its published form.

Nutrition and Healthy Aging 7 (2022) 9–22
DOI 10.3233/NHA-210146
IOS Press

Impact of an intensive lifestyle program on low attenuation plaque and myocardial perfusion in coronary heart disease: A randomised clinical trial protocol

Sophie Cassidy[a,b], Cynthia M. Kroeger[a,b], Tian Wang[a,b], Sayan Mitra[a,b], Chen Liu[a,b], Rosilene V. Ribeiro[a,b,c], Aimee Dai[a,b], Jonathan Lau[a,b], Robin Huang[d], Andrius Masedunkas[a,b], Shane Jose[a], Na Liu[e], Leah Avery[f], Jessica Yang[g], Michele McGrady[b,h,i], Serigne N. Lo[j], Jacob George[k], Peter A. Cistulli[a,b,l,m], Lynn Khor[n], Rebecca Kozor[n], Martin Ugander[n,o], Ian Wilcox[b,h,i], Imre Hunyor[b,h,i] and Luigi Fontana[a,b,p,q,*]

[a]*Charles Perkins Centre, University of Sydney, Sydney, Australia*
[b]*Faculty of Medicine and Health, University of Sydney, Sydney, Australia*
[c]*School of Life and Environmental Science, University of Sydney, Sydney Australia*
[d]*School of Computer Science, University of Sydney, Sydney, Australia*
[e]*The University of Sydney Business School, University of Sydney, Sydney, Australia*
[f]*Centre for Rehabilitation, School of Health & Life Sciences, Teesside University, UK*
[g]*Department of Radiology, Concord Repatriation General Hospital, Sydney, Australia*
[h]*Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia*
[i]*Central Sydney Cardiology, Royal Prince Alfred Medical Centre, Sydney, Australia*
[j]*Melanoma Institute Australia, University of Sydney, Sydney, Australia*
[k]*Storr Liver Centre, The Westmead Institute for Medical Research, Westmead Hospital and University of Sydney, Sydney, Australia*
[l]*Northern Clinical School, Faculty of Medicine and Health, University of Sydney, Australia*
[m]*Centre for Sleep Health & Research, Department of Respiratory Medicine, Royal North Shore Hospital, Australia*
[n]*Kolling Institute, Royal North Shore Hospital, and University of Sydney, Sydney, Australia*
[o]*Department of Clinical Physiology, Karolinska University Hospital, and Karolinska Institute, Stockholm, Sweden*
[p]*Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, Australia*
[q]*Department of Clinical and Experimental Sciences, Brescia University, Brescia, Italy*

Received 23 November 2021
Accepted 17 June 2022
Pre-press 7 July 2022
Published 6 October 2022

Abstract.
IMPORTANCE: The evidence that maintaining a healthy body weight in conjunction with healthier eating patterns, exercise training, and reduced stress can improve clinical outcomes in patients with atherosclerotic cardiovascular disease is substantial. However, little is known about the magnitude and temporal effects of a comprehensive lifestyle treatment on coronary artery anatomy, myocardial inflammation, and fibrosis in people affected by coronary heart disease.

*Corresponding author: Professor Luigi Fontana, Level 5 West, Charles Perkins Centre, Camperdown, University of Sydney, NSW, 2006, Australia. Tel.: +61 2 8627 7499; E-mail: luigi.fontana@sydney.edu.au.

ISSN 2451-9480 © 2022 – The authors. Published by IOS Press. This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (CC BY-NC 4.0).

OBJECTIVE: To conduct a randomised clinical trial to determine the impact of a 12-month intense lifestyle intervention delivered via an mHealth platform (in the form of a mobile App) versus standard clinical care on low attenuation plaque volume and structure, stress myocardial perfusion, and diastolic function.
DESIGN: A single centre, parallel-group, randomised controlled trial. The co-primary endpoints are: 1-Low Attenuation Plaque (LAP) volume (mm^3) using coronary computed tomography angiography (CCTA) at 12 months, and 2-Adenosine stress myocardial blood flow (stress MBF, mL/min/g) using cardiovascular magnetic resonance imaging (MRI) at 12 months. Other key measurements include liver steatosis by MRI, subclinical abnormalities detected by advanced electrocardiography, arterial stiffness, endothelial function, genomic, metabolomic, and gut microbiome-related adaptations to these structural changes. An intention-to-treat principle will be used for all analyses.
SETTING: Participants will be recruited from a large academic cardiology office practice (Central Sydney Cardiology) and Royal Prince Alfred Hospital (RPAH) Departments of Cardiology and Radiology. All clinical investigations will be undertaken within the Charles Perkins Centre-RPAH clinic.
PARTICIPANTS: Individuals ($n = 150$) with stable coronary heart disease who have low attenuation plaque based on a CCTA within the past 3 months, will be randomised to a lifestyle intervention program comprising a 5:2 pesco-vegetarian diet, exercise training, and mindfulness-based stress reduction ($n = 75$) or usual care ($n = 75$).
DISCUSSION: This trial will represent the single most detailed and integrated analysis of the effects of a comprehensive lifestyle intervention targeting multiple metabolic pathways, delivered via a customized m-Health App on smart devices, on coronary macro- and microcirculation, heart physiology, and cardiometabolic risk. It will provide a new framework for allowing clinicians and individuals to optimise metabolic health for the prevention and management of atherosclerotic cardiovascular diseases that is epidemic in modern society.

Trial registration: Australian New Zealand Clinical Trials Registry (ANZCTR). ACTRN12620001151921. https://www.anzctr.org.au/ACTRN12620001151921.aspx

1. Introduction

Cardiovascular disease (CVD) is becoming the primary cause of morbidity, disability and premature death not only in Western countries but also in the developing world [1]. Lifetime risk of a first CVD event at age 50 is ~65% in men [2], and is increasingly affecting younger women and men, especially in some ethnic groups that for genetic and epigenetic reasons poorly tolerate the caloric surplus and the build-up of excess abdominal fat [3]. Some accumulation of cellular and tissue damage within the cardiovascular system is an inevitable part of advancing age. However, persistent exposure to traditional and emerging risk factors (including insulin resistance, triglyceride-rich lipoproteins, trimethylamine N-oxide, and accelerated clonal haematopoiesis) associated with unhealthy lifestyle behaviours play a substantial role in the initiation and development of CVD [4, 5] (Fig. 1). Approximately 25% of patients who develop a myocardial infarction have extensive coronary atherosclerosis in the absence of any traditional modifiable cardiovascular risk factors [6].

A growing body of data from animal, epidemiological and clinical studies have demonstrated that calorie excess, poor nutrition, physical inactivity, sleep disturbances, smoking, and mental stress by acting on multiple metabolic and molecular pathways play major roles in the pathogenesis of

Classical	Novel
Age	Insulin resistance
Gender	Triglyceride-rich lipoproteins
Total cholesterol	Trimethylamine N-oxide
HDL cholesterol	
Diabetes	Clonal hematopoiesis
Smoking	Microbiome
Systolic blood pressure	Inflammation

as the risk increased to 69% in those with 2 or more abnormal cardiometabolic risk factors [10].

Data from nutritional secondary prevention trials in patients with hypertension [11], type 2 diabetes [8], diabetic nephropathy [12], fatty liver disease [13], and high cardio-metabolic risk [14] also showed spectacular improvements in metabolic outcomes and a reduction in major cardiovascular events. The Lyon and Indo-Mediterranean Diet Heart trials have demonstrated a striking protective effect of a Mediterranean-style diet against coronary recurrence rate and sudden cardiac death in those who already suffered from a prior myocardial infarction [12, 15]. Modifications of meal timing, diet quality and the gut microbiome [4, 16] together with regular physical activity [17–19], improved sleep patterns [20, 21] and a reduction in mental stress [3, 22, 23] have also been shown to improve cardiovascular outcomes in those at risk.

1.1. Current challenges

Despite substantial evidence supporting lifestyle behaviour change, there are three major challenges to address. Firstly, there is a need for more mechanistic studies to elucidate the impact of lifestyle on macro- and microvascular structure and function, and advancements in imaging techniques will facilitate this. Coronary computed tomography angiography (CCTA) technology has advanced significantly over recent years and can now identify the volume and structure of low attenuation non-calcified plaques (LAP). LAP is characterised by inflammation, microcalcification, a thin fibrous cap and large lipid-rich necrotic core [24], and in a recent study was the strongest predictor of subsequent myocardial infarction compared to classical risk predictors in individuals with stable Coronary heart disease (CHD). Indeed, those with LAP burden >4% were almost 5 times more likely to have subsequent myocardial infarction [25]. Early evidence suggests that lifestyle intervention may yield LAP changes observable as early as 12 months [26], however there is a dearth of evidence in this area.

Quantification of myocardial blood flow during hyperaemic stress is now possible via automated inline perfusion mapping by cardiovascular magnetic resonance imaging (MRI). Non-invasive myocardial and hemodynamic phenotyping by comprehensive and state-of-the-art cardiac stress MRI can provide quantitative characterisation not only of myocardial blood flow measured during adenosine stress, but also of the volumes and function of heart chambers, left ventricular hypertrophy and diastolic dysfunction, focal and global myocardial inflammation, myocardial infarction or non-ischemic scarring, diffuse myocardial fibrosis, coronary microvascular function including coronary spasm measured with the cold pressor test, and pulmonary congestion at rest and at peak supine ergometer exercise stress [27, 28].

Secondly, current lifestyle interventions are limited in their ability to be scaled up and rolled out across the clinical setting in an affordable way. However, over the past decade there has been an exponential rise in smartphone and wearable use [29], and this type of digital platform may address some of these barriers. Thirdly, the greatest limitation to initiating, engaging and sustaining effective lifestyle change, is adherence. Digital health approaches using an ecosystem which uses a smart phone to deliver these programs have been shown to have superior effectiveness. Smartphone delivery of cardiac rehabilitation was delivered much more effectively than traditional face-to-face cardiac rehabilitation, with enhanced engagement (94% vs. 68% $p<0.05$) and program completion (80% vs. 47%, $p<0.05$) being significantly higher with digital health programs delivered by smartphone [30]. Some advantages of smartphone technology are that it can be initiated rapidly, updated easily, and delivered at anytime from anywhere.

1.2. Aims of LIVEPLUS

The primary aim of the LIVEPLUS study is to assess the effectiveness of a 12-month intensive lifestyle intervention which combines a 5:2 pesco-vegetarian diet, physical activity and stress reduction training, on macrovascular coronary disease (CCTA assessed LAP volume) and microvascular disease (MRI measured stress myocardial perfusion). Secondary aims are to identify changes in other cardiovascular and metabolic/molecular adaptations to this lifestyle intervention. At the centre of the LIVEPLUS study program is digital health ecosystem delivered via a smartphone app (Fig. 2) [31]. Such a digital solution, if proven to be effective, is readily scalable and translatable for incorporation into clinical practice across diverse health care systems at a cost these systems can sustain.

2. Methods

2.1. Study design

LIVEPLUS is a parallel-group, randomised controlled trial (RCT) with a total sample of 150

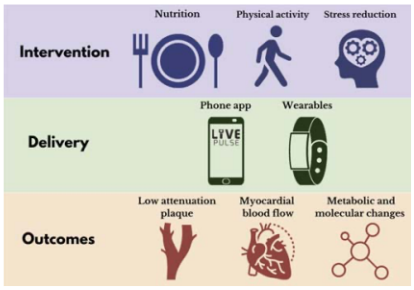


Fig. 2. LIVEPLUS randomised clinical trial.

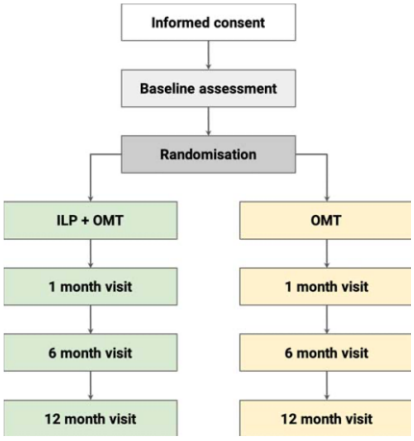


Fig. 3. Study flow. ILP, intensive lifestyle program; OMT, optimal medical therapy.

participants. A 1:1 allocation ratio will be applied to either the intervention group (ILP + OMT) or control group (OMT). Participants in both arms will be followed up over a period of 12 months. A comprehensive set of outcome assessments will be performed prior to initiating the intervention, with follow-up assessments at month 1, 6 and 12 (Fig. 3). This study has been approved by the Sydney Local Health District Ethics committee (2020/ETH01273). Study visits will take place at the Charles Perkins Centre-Royal Prince Alfred Hospital (CPC-RPA) clinic, Royal Prince Alfred Hospital Department of Radiology, and the North Shore Radiology and Nuclear Medicine (NSRNM) facility, Sydney.

2.2. Eligibility criteria

Inclusion criteria are; (1) Presence of LAP on CCTA; (2) 18–80 years of age; (3) BMI >22.0 kg/m^2; (4) Able to provide full informed consent; (5) Considered capable of undergoing all study assessments and adhering to the rigors of the ILP intervention. Exclusion criteria are (1) Non-MRI-compatible implanted devices; (2) Estimated glomerular filtration rate (eGFR) <30 mL/kg/1.73 m^2; (3) Inability to exercise via supine ergometer; (4) Contraindications for adenosine or glyceryl trinitrate; (5) Previous severe allergic reaction to iodinated contrast media; (6) Pregnancy or breastfeeding; and (7) History of any chronic disease process that could interfere with the interpretation of results.

2.3. Recruitment

Participants who have undergone a clinically indicated CCTA within the past 3 months will be recruited if they have quantifiable LAP (plaque within –30 to 150 HU range). At least two experienced CCTA reporters will evaluate the coronary tree for the presence of such plaque. In the general cardiology outpatient population, we expect approximately 20–40% of patients to have LAP. The predominant source of referral for clinically indicated CCTA at RPA for this study will be from a single large academic clinical practice (Central Sydney Cardiology, RPAH Medical Centre) and from patients who have attended the RPA Radiology Department for a clinically indicated CCTA.

2.4. Pre-screening and consent

Following a pre-screening telephone call, an initial video call will take place with eligible, potential participants. During this video call, the research team will deliver a short presentation to the participant to explain the rationale, implications and constraints of the protocol, known side effects and any risks involved in taking part. There will be an opportunity for participants to ask questions and discuss any details of the study. Willing participants will be invited to the CPC-RPA clinic to obtain electronic informed consent through REDCap. Any participant judged by the research team to not possess the capacity for fully informed consent will be excluded from the study, as per the study exclusion criteria.

2.5. Baseline visits

Following consent, participants will be enrolled into the study and undergo a number of clinical baseline assessments. The exact timing of these assessments will be flexible (e.g., due to participant or equipment availability) and can be spread over a number of days, however a potential schedule is shown in Table 1.

2.6. Randomisation and blinding

Enrolled participants will be randomised using random permuted blocks with randomly selected block sizes, via a web-based randomisation system in REDCap, and stratified by age, sex, and BMI. The allocation sequence was generated using blocked size of 2, 4, 6, and 8 from the R package, *blockrand* [32]. An uneven block was included in the middle of the sequence to guard against guessing the group assignment [33]. Investigators and participants will be blinded to the group allocation until all baseline measures have been completed, as the REDCap support statistician is the only individual with access to the upcoming treatment allocations within the randomisation list. After the final baseline measurement, the research co-ordinator will use REDCap to randomise the participant, revealing the group assignment to the study team and participant simultaneously. Due to the nature of the intervention, investigators and participants cannot be blinded during the study, however those performing CCTA, MRI and statistical analysis will be blinded to group allocation.

2.7. Follow-up visits

Table 1 provides an overview of the follow up visits and testing procedures which are planned for months 1, 6, and 12.

2.8. Intervention

The ILP+OMT group will continue to receive standard of care treatment, as well as three main lifestyle intervention components over the 12-month study period. These will target nutrition, physical activity and stress reduction. In the context of each target behaviour, participants will be asked to use the LIVEPULSE app (see section 2.10.1. LIVEPULSE phone app for details) to read 12 education modules (1 per month), and complete multichoice questions at the end of each module to assess learning and provide automatic feedback. The content of the 12 education modules (Table 2) is informed by evidence-based, peer-reviewed research carefully rewritten into lay language, making them accessible and engaging, particularly to those who are new to such lifestyle practices. Participants will also be given online coaching sessions with a dietitian, physical activity coach, and stress reduction coach (Table 3). Each coaching session will be tailored to an individual's progress and needs, using evidence-informed behaviour change techniques [34]. Each coach will receive training in delivery of specific behaviour change techniques to effectively promote change in relation to each target lifestyle behaviour (i.e. nutrition, physical activity and stress reduction). The training will be delivered by a UK-registered practitioner health psychologist with expertise in health behaviour change, and will include use of behaviour change counselling skills as well as behaviour change techniques. Additional online coaching calls may be scheduled to improve adherence to the intervention if considered necessary by the study team.

2.8.1. Nutrition

Several interventional studies have clearly shown that individuals who consume diets rich in fish and nutrient-dense minimally processed plant foods have a lower risk of developing CHD than people who consume energy dense low-fibre Western diets high in saturated and trans fatty acids, animal protein and salt [35–37]. In the LIVEPLUS trial, participants will be asked to follow a 5:2 pesco-vegetarian diet for 12 months. This diet involves a combination of a 5:2 diet and a pesco-vegetarian diet. The aim of a pesco-vegetarian diet will be to substitute meat with fish and processed and refined foods with a range of minimally processed plant-based foods. Red meats, including beef, pork, lamb and other red meat products, and poultry including chicken, duck, goose, and other poultry products are prohibited with this diet. In addition, individual participants will be asked to practice a 5:2 diet, which consists of fasting on 2 non-consecutive days of the week with energy restriction of around 2000 kJ per day for women and around 2500 kJ for men.

During the first 4 weeks of the intervention, participants will receive fresh ingredients and recipes from *Marley Spoon* (a commercial meal delivery service that provides pre-portioned ingredients and recipes to designated addresses for meal preparation), which

Table 1
Schedule of visits and testing procedures at the CPC-RPA clinic. The MRI scan will take place at the North Shore Radiology and Nuclear Medicine facility

	Baseline assessment			1 month	6 month		12 month			
Visit	1	2	3	4	5	6	7	8	9	
Notes	*These visits are flexible and tests can be moved around.*					*These visits are flexible and tests can be moved around but all should be undertaken within 1 week of end-intervention.*				
Informed consent	1									
Full body examination (including BP, weight, waist/hip cm, vital signs)	1			1	1	1			1	
Medical and family history questionnaires	1									
OGTT	1					1				
Psychosocial questionnaires	1					1				
Physical activity assessment (Fitbit & 7-Day PAR)	1					1				
Food diary assessment	1			1	1	1				
Sleep assessment (questionnaires and home sleep study)	1					1				
Urine and Faeces Sample	1			1	1	1				
MRI		1						1		
Randomisation	1									
Fasting blood sample (Biochemistry and Haematology)	1			1	1					
DXA			1						1	
Carotid intima-media thickness			1	1	1				1	
Vascular endothelial function			1	1	1				1	
Autonomic function			1	1	1				1	
Pulse Wave Velocity			1	1	1					
6 minute walk test			1						1	
CCTA							1			

BP, blood pressure; CCTA, coronary computed tomography angiography; DXA, Dual-energy X-ray absorptiometry; OGTT, oral glucose tolerance test; MRI, magnetic resonance imaging; PAR, physical activity recall.

Table 2
Education content for diet, physical activity and stress reduction components for the intervention group

Month	Diet	Physical activity	Stress reduction
1	Introduction of Nutritional Intervention	Importance of physical activity	Introduction
2	Pesco-vegetarian diet	FITT principles and safety	Simple Awareness
3	Intermittent fasting	Physical activity and the heart	Attention and the Brain
4	Healthy eating	Physical activity and the blood vessels	Dealing with Thoughts
5	Dietary measurements	Physical activity and obesity	Biological Basis of Stress: Responding vs. Reacting
6	Fats	Physical activity and mental health	Dealing with Difficult Emotions of Physical Pain
7	Carbohydrates	Physical activity and glucose metabolism	Mindfulness and Communication
8	Protein	Physical activity and fat metabolism	Self-Compassion Cultivation
9	Meal planning	Physical activity and skeletal muscle	Social Connectedness
10	Nutritional labelling	Physical activity and inflammation	A Closer Look at Happiness
11	Dietary patterns and cardiovascular health	Physical activity and brain health	On Relationships
12	Review	Physical activity and cardiorespiratory fitness	Conclusion

FITT: frequency, intensity, time, type.

Table 3
Planned schedule of coaching calls, which can be adapted according to participant preference

	Month 1		Month 2		Month 3		Months 4–12
	Week 1	Week 3	Week 5	Week 7	Week 9	Week 11	Monthly
Dietitian	1 hour	30 min	30 min	30 min	30 min	30 min	30 min
Exercise physiologist	1 hour	30 min	30 min	30 min	30 min	30 min	30 min
Mindfulness coach	1 hour	30 min	30 min	30 min	30 min	30 min	30 min

provides lunch and dinner for 5 days per week to assist with their preparation of a pesco-vegetarian diet. The menu selected by the participants will be sent to the study dietitian and the nutritionist of *Marley Spoon* to ensure it complies with a pesco-vegetarian diet. If participants select meal plans with meat, it will be altered to a pesco-vegetarian diet before delivery. Participants will be required to prepare their breakfasts each day and light meals on fasting days, and the study dietitian will provide the recipes for these meals through the LIVEPULSE mobile app. After the first 4 weeks, they will meet with the study dietitian to design their individualised weekly meal plans and menus to facilitate transition into preparing their own food. The goal is to improve diet quality but also to achieve at least 7-8% weight loss, as we have found this is vital to improve inflammatory, metabolic and cardiac markers [38]. Strategies to implement dietary changes, meal planning, healthy recipes and relevant nutritional information for cardiovascular health will be discussed during dietitian appointments. Along with the education modules, other materials related to the 5:2 pesco-vegetarian diet (e.g. recipes for a pesco-vegetarian diet, recipes for fasting days, food sources that are rich in iron) will also be delivered via the LIVEPULSE mobile app.

2.9. Physical activity

There is strong evidence that reducing sedentary behaviour and increasing overall physical activity level is associated with reduced cardiovascular events and mortality [39]. Participants will be given an individualised home-based programme which will be based on the guidelines from the American College of Cardiology Foundation/American Heart Association to manage individuals with stable ischemic heart disease [40]. The principles we will advise include; 1) to perform 30 to 60 minutes of moderate-intensity aerobic physical activity, such as brisk walking, at least 5 days and preferably 7 days per week; 2) increase daily lifestyle physical activity (e.g. walking breaks at work, gardening, household work); and 3) perform resistance training at least 2 days per week. We

do not have one specific training programme for all individuals, but rather these general principles will be individualised based on baseline activity levels and progress throughout the year. To measure baseline activity, participants will wear a *Fitbit* Inspire 2 physical activity tracker for 7 continuous days and will complete a PAR questionnaire. *Fitbit* Inspire 2 is equipped with 3-axis accelerometer and optical heart-rate tracker, however it lacks GPS receiver for accurate distance data. The *Fitbit* device will enable the researchers to access minute by minute step count, heart rate and heart rate variability for all participants, as well as information about duration and timing of sleep, and participants will be asked to wear it for 12 consecutive months. The goal for all participants will be to reach at least 150 minutes of moderate-intensity aerobic physical activity per week within the first 3 months. If participants respond well during the first 3 months of the physical activity intervention, the following 9 months (month 4–12) will aim to vary the prescription in terms of mode, duration, and intensity. Alongside the education modules, the team have also developed a number of exercise circuit videos aimed at a range of intensities to suit a broad range of fitness and confidence levels, which will be available for viewing anytime via the LIVEPULSE app.

2.10. Stress reduction

Chronic stress is an independent risk factor for atherosclerosis [41]. Body-inclusive stress reduction techniques, such as slow breathing [22, 23], gentle yoga [42], and mindfulness [43], have been shown to improve hypertension and autonomic (cardiovagal) function, as well as mental health and quality of life. In the LIVEPLUS trial, the 12-month stress reduction program will draw techniques from Mindfulness Based Stress Reduction (MBSR) and will be supplemented with additional slow and pressurized breathing techniques, gentle yoga, and concepts from positive psychology on evidence-based tips for cultivating happiness and social connectedness. MBSR is a specific mindfulness approach that integrates various mindfulness meditation techniques, as well as gentle hatha yoga, and has been shown clinically and supported by systematic reviews to be beneficial for cardiovascular and mental health [44]. Each month, participants will be introduced to new stress reduction educational content through the app, as well as asked to practice a new breathing (for about 5–10 minutes, 6 days per week) and mindfulness technique (about 20 minutes, once per week). Breathing and yoga videos have been created by our research team to guide participants through their practice. Example breathing and mindfulness practices include slow breathing at six breaths per minute, alternate nostril breathing, sitting meditation, and mindful yoga.

2.10.1. LIVEPULSE mobile app

LivePulse is a health data collection, management and intervention tool consisting of a mobile app for participants and a web dashboard for the research team to use. The app allows participants to create personalised goals, receive reminders, access educational materials, record and share their health data (weight, exercise, diets etc.) with the research team. The app is publicly available both on the Apple App Store and on the Google Play Store in Australia. The underlying technology of the app has been implemented in similar apps created by the developer, Vulsen, for other research studies, some examples include: Success CKD [45], and My Home Hemo [46]. Key features of the app include;

1-**Education:** Each component of the ILP (nutrition, physical activity and stress reduction) has 12 online modules, and each will be released on a monthly basis for participants to read and interact with. Interactive components include multi-choice questions [26] (Table 2). Video content will be updated throughout the study and will include expert interviews, exercise sessions, breathing techniques and yoga sequences.

2-**Monitoring:** Participants themselves and members of the research team will be able to monitor progress through a number of app features, including weekly entry of body weight, upload of food images and logging mindfulness practice. The app will also extract data on physical activity and sleep from the *Fitbit* device, and in response to participant progress, the app has a facility for research team members to send short messages and reminders to participants, individually and as a group [47, 48]. The app includes a multi subject weight change simulator to predict whether participants are on track with reaching their dietary goals as evidenced by their weight loss trajectory. The algorithm is modelled from the participant's entry of age, height, gender, and regular updated body weight inputs, as well as our input of their target calorie deficit required to achieve the desired percentage weight loss of 7–8% after 1 year. If a participant falls outside of their error region at any point throughout the study, they will be given the opportunity to receive enhanced support.

3-Goal setting: Participants will be encouraged to set short- and long-term behavioural and outcome goals (e.g., dietary, physical activity and weight), which will be discussed and adapted over the duration of the intervention with the research team coaches [48].

4-Social networks: Participants will be encouraged to connect with other users of the app using the group messaging function to facilitate social support.

5-Just-in-time adaptive intervention (JITAI): Intervention arm participants will receive personalised messages prompting physical activity using JITAI. JITAIs aim is to optimise delivery of intervention components in terms of the right time and location for patients. Micro-randomised trials (MRT) offer a way to optimise such interventions by enabling modelling of causal effects and time-varying effect moderation for individual intervention components within a JITAI [49]. For this reason, we will perform an MRT within the intervention arm.

2.11. Control

OMT group participants will continue to receive standard of care treatment but will also be given a *Fitbit* device, and offered video-call appointments with a study dietitian every 3 months. In addition, they will be instructed to follow the American Heart Association (AHA) Diet and Lifestyle Recommendations to include physical activity [50] and stress reduction. The study dietitian will summarise the content on healthy lifestyles from the AHA website into 8 modules of educational materials. These materials will be delivered to participants each month via email for the first 8 months of the study. The content will cover general healthy eating, healthy meal planning and preparation, and tips to increase vegetable intake. They will also be offered the stress reduction programme at the end of the study.

3. Outcomes

3.1. Primary

3.1.1. Low-attenuation plaque (LAP) volume (mm^3)

LAP volume will be measured at baseline as part of a clinically indicated CCTA and at 12 months for the purpose of this study. CCTA will be performed at Royal Prince Alfred Hospital on a Siemens SOMATOM Force 2 × 192 slice Dual Source scanner and will take approximately 10 minutes, with a total visit duration of approximately 30 minutes. Coronary images will be transferred to a workstation with the use of plaque- analysis software. This software will produce colour-coded maps overlaid with differentiated plaque categories by Hounsfield Unit (HU) values, and those with LAP (–30 to 150 HU) will be invited into the study. LAP volume has been consistently shown to be the best marker of instability and strongest prognostic predictor of a future adverse CV event. CCTA readers will be blinded to group allocation.

3.1.2. Stress myocardial blood flow (MBF, ml/min/g)

Stress MBF will be measured at baseline and at 12 months follow-up during an MRI examination at North Shore Radiology and Nuclear Medicine (NSRNM). The duration of the research MRI examination will be approximately 1.5 hours, with a total visit duration of approximately 2 hours.

The cardiac MRI examination will include the assessment of LV diastolic function at rest and exercise, as well as myocardial perfusion at rest and during different types of stress.

Graded exercise testing will be performed using a supine ergometer while the participant is lying supine in the MRI scanner. The work rate will be increased gradually with a total exercise duration of approximately 8–12 minutes [51]. Assessment of diastolic function at stress will be performed immediately after supine ergometry.

The study utilises the same intravenous gadolinium-based contrast agent that is used clinically to assess myocardial perfusion. The cardiac MRI myocardial perfusion images will be acquired at rest, and during the following stress protocols.

(i) Adenosine stress

Intravenous adenosine infusion will be administered at 140 μg/kg/min via a peripheral intravenous cannula. This is the same protocol as is used at invasive coronary physiological assessment.

(ii) Cold-pressor testing (CPT)

CPT will be carried out, as previously described, by immersing the hands or feet of the participant in ice water measuring at approximately 0–4°C for a duration of 4 minutes. Continuous blood pressure and heart rate will be recorded at one minute intervals

throughout the scan, thus about 10–20 minutes before (depending on how long it takes to finish the initial scans) and during CPT [52].

(iii) Glyceryl Trinitrate (GTN)

Exogenous nitrate is utilised to vasodilate the coronary arteries and assess for endothelial dysfunction. 300 mcg sublingual GTN will be given just prior to acquisition of cardiac MRI images.

3.2. Secondary outcomes

The secondary outcomes to be conducted are listed below. For detailed information on each one, please see the supplement.

- Perivascular Adipose Tissue
- Myocardial inflammation
- Diastolic dysfunction
- Pulmonary congestion during exercise
- Secondary plaque characteristics, including noncalcified plaque volume, dense calcified plaque volume and total atheroma volume (TAV, mm^3)
- Liver fat fraction (%) by MRI
- Flow-mediated dilatation (FMD) (%)
- Carotid intima-media thickness (cIMT) (mm)
- Pulse wave velocity (PWV) (m/s) and Augmentation Index (AI) (%)
- Heart rate variability (HRV) during wakefulness and sleep: Low Frequency (LF) and High Frequency (HF) (ms^2)
- Heart age by resting electrocardiography
- Sleep parameters (total sleep time, Rapid Eye Movement (REM) and Non-REM (NREM) durations, respiratory disturbances, and oxygen saturation)

3.3. Exploratory

There are a number of exploratory outcomes, which are listed below. For detailed information on each one, please see the supplement.

- Body composition
  - Weight (kg)
  - Height (cm)
  - Waist/Hip ratio (cm)
  - Dual-energy X-ray absorptiometry (DEXA) body composition
- Intermediate risk factors that are predictive of developing atherosclerosis
  - Glucose (mmol/L) and Insulin (pmol/L)
  - Blood pressure (mmHg) including both central and peripheral pressures
  - Blood biomarkers
- Urinary levels of F2-isoprostane levels
- Serum hormones, proteomics, lipidomics, metabolomics, genetic and epigenetic profiling of white blood cells
- 6-minute walk test
- Dietary intake (total daily kJ, macronutrient and micronutrient intake (%))
- Time spent in moderate physical activity
- Psychometrics

3.4. Safety reporting

Adverse Events (AE) and Serious Adverse Events (SAE) will be recorded and reported throughout the study to monitor and ensure participant safety. The following information will be reported: description, data of onset and end date, severity, assessment of relatedness to trial intervention or device, and action taken. A team of physicians, including cardiologists, will use their clinical judgement to decide whether an AE is of sufficient severity to remove the participant from the study. SAE will be reported to the primary investigator within 24 hours of the study team becoming aware of the event. The full course of the SAE, including any therapy given, will be reported to the study sponsor. All significant safety issues will be reported to the local Human Research Ethics Committee and Research Governance Officers.

3.5. Sample size calculation

This is a randomised two-arm study design with 2 continuous co-primary endpoints repeatedly measured at baseline and after 12-month follow-up. A total of 150 participants (75 in each arm) will provide 90% power to demonstrate the efficacy of either outcome. The sample size is based on a 2-by-2 repeated measures design using each of the co-primary outcomes (PASS 13 Power Analysis and Sample Size Software (2014)). The conservative Bonferroni correction was applied to control the type I error rate due to multiplicity test. The significance level (alpha) is 0.025 using a two-sided, two-sample *t*-test. The assumptions specific to each co-primary outcome are defined below:

For Low-attenuation plaque volume, an absolute mean difference between groups of $\geq 9.0\,mm^3$ at

12-month is expected to declare the efficacy of the intervention (ILP + OMT) over the control (OMT). The control group mean (standard deviation) is 39.0 (12) mm^3 and 32.3 (15) mm^3 at baseline and after 12-month follow-up respectively [53]. A correlation of between measurement pairs of 0.50 is assumed.

For Myocardial blood flow, an absolute mean difference between groups of $\geq$0.4 ml/min/g at 12-month is expected to declare the efficacy of the intervention (ILP + OMT) over the control (OMT). The control group mean (standard deviation) is 2.71 (0.61) mL/min/g and 2.55 (0.57) mL/min/g at baseline and after 12-month follow-up respectively [54]. A correlation of between measurement pairs of 0.50 is assumed. The overall sample size allows for a 20% attrition rate. Identifying eligible participants, enrolling them into the study, and maintaining their commitment to this intensive intervention over a period of 12 months can be challenging. However, the enrolment of 150 participants over a period of 34–36 months is thought to be feasible with the resources available based on previous research.

3.6. Statistical analysis plan

This is the first detailed investigation of effects of ILP on coronary CT coronary plaque modification and myocardial blood flow over an extended period of time in human participants. Efficacy analyses will be conducted on an 'intention to treat' basis. The primary analysis will be performed using Analysis of Covariance (ANCOVA), adjusted for baseline values [55]. Group comparisons will be two tailed with a nominal 2.5% significance level to adjust for the multiplicity testing using Bonferroni method. Subgroup analyses will be conducted to assess differences in intervention effects across the pre-specified gender and age subgroups. Tests of intervention effect modification will be performed by fitting intervention group and the relevant subgroup main effects and interaction into the models adjusted for baseline scores. Interpretation of evidence of heterogeneity of intervention effects among subgroups will remain exploratory (hypothesis generating) given the study is not powered to test subgroups.

Many of the secondary endpoints are exploratory in nature and will need to be confirmed by follow-up studies. Type-II error, i.e., failing to detect a significant effect when it exists is important to this study for all secondary and exploratory outcomes. Thus, all tests of significance for between-group comparisons will be performed at the $p = 0.05$ level of significance. The primary analysis strategy will utilise Intention-to-Treat principles. LIVEPLUS is also interested in mechanistic questions concerning the effect of ILP, and to address these issues, the Marginal Structural Model (MSM) of Robins and colleagues [56] will be applied. All major secondary outcomes are observed repeatedly at well-defined time points over participant follow-up, so that statistical methods for longitudinal and repeated measures analysis will be applied. Subgroup analyses will be tested by evaluating the treatment by subgroup interaction. Withdrawal from the intervention, drop-out from the study, or death (if any) will be analysed using the standard techniques for survival data.

3.7. Trial status

Recruitment began Feb 2022.

4. Conclusions

LIVEPLUS will help us to identify how a mechanism-based comprehensive lifestyle intervention can affect the major and minor vessels in the heart, perivascular fat, cardiac structure and function, arterial stiffness, endothelial function, and liver steatosis. The sophisticated clinical, metabolic and molecular (multi-omic) phenotyping to nutritional, physical activity and cognitive inputs will provide a unique platform for cybernetic/systems modelling responses in patients affected by coronary heart disease. The data generated will also populate complex systems-based models and provide insights that drive the discovery of new predictive biomarkers of disease. Additionally, the smartphone app is an exciting digital health and educational tool, which can empower individuals to engage with, and sustain, the lifestyle changes they need as individuals to reduce their future risk of adverse cardiovascular outcomes and to track the changes they achieve in a personalised way in near real time. Such a personalised digital health solution, if proven to be effective, is ultimately translational and scalable to use in clinical practice and as an educational tool for health care professionals.

Author contributions

SC drafted the manuscript and integrated additional text by co-authors. CMK managed manuscript

revisions by co-authors. LF conceived the idea for the study and is the senior author of the manuscript. All authors contributed meaningfully to the design of this study, drafted sections of the manuscript based on their respective expertise, provided editorial assistance with early drafts, and approved the final version of the submitted manuscript.

Conflict of Interest

Luigi Fontana is an Editorial Board Member of this journal, but was not involved in the peer-review process nor had access to any information regarding its peer-review.

Protocol version

v4.0.

Funding statement

This study will be supported by grants from Australian Youth and Health Foundation and the Australian NHMRC Investigator Grant (APP1177797).

The Australian Health and Youth Foundation.

Supplementary data

Supplementary data to this article can be found online at https://dx.doi.org/10.3233/NHA-210146

References

[1] World Health Organization. The top 10 causes of death. 2014. Available at: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Accessed: 23rd August 2021

[2] Stenling A, Haggstrom C, Norberg M, Norstrom F. Lifetime risk predictions for cardiovascular diseases: Competing risks analyses on a population-based cohort in Sweden. Atherosclerosis. 2020;312:90-8.

[3] Despres JP, Lemieux I. Abdominal obesity and metabolic syndrome. Nature. 2006;444(7121):881-7.

[4] Fontana L. Interventions to promote cardiometabolic health and slow cardiovascular ageing. Nat Rev Cardiol. 2018;15(9):566-77.

[5] Libby P. The changing landscape of atherosclerosis. Nature. 2021;592(7855):524-33.

[6] Mazhar J, Figtree G, Vernon ST, Galougahi KK, Carlo J, Nissen SE, Nicholls SJ. Progression of coronary atherosclerosis in patients without standard modifiable risk factors. Am J Prev Cardiol. 2020;4:100116.

[7] Most J, Tosti V, Redman LM, Fontana L. Caloric restriction in humans: An update. Ageing Res Rev. 2017;39:36-45.

[8] Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, Peters C, Zhyzhneuskaya S, Al-Mrabeh A, Hollingsworth KG, Rodrigues AM, Rehackova L, Adamson AJ, Snichotta FF, Mathers JC, Ross HM, McIlvenna Y, Stefanetti R, Trenell M, Welsh P, Kean S, Ford I, McConnachie A, Sattar N, Taylor R. Primary care-led weight management for remission of type 2 diabetes (DiRECT): An open-label, cluster-randomised trial. The Lancet. 2018;391(10120):541-51.

[9] Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term caloric restriction is highly effective in reducing the risk for atherosclerosis in humans. Proc Natl Acad Sci U S A. 2004;101(17):6659-63.

[10] Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, Wolf PA, Levy D. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113(6):791-8.

[11] Sacks FM, Svetkey LP, Vollmer WM, Appel LJ, Bray GA, Harsha D, Obarzanek E, Conlin PR, Miller ER, 3rd, Simons-Morton DG, Karanja N, Lin PH, Group DA-SCR. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. N Engl J Med. 2001;344(1):3-10.

[12] Ruggenenti P, Abbate M, Ruggiero B, Rota S, Trillini M, Aparicio C, Parvanova A, Petrov Iliev I, Pisanu G, Perna A, Russo A, Diadei O, Martinetti D, Cannata A, Carrara F, Ferrari S, Stucchi N, Remuzzi G, Fontana L, Group CRSOS. Renal and systemic effects of caloric restriction in patients with type 2 diabetes with abdominal obesity: A randomized controlled trial. Diabetes. 2017;66(1):75-86.

[13] Franco M, Bilal U, Orduñez P, Benet M, Morejon A, Caballero B, Kennelly JF, Cooper RS. Population-wide weight loss and regain in relation to diabetes burden and cardiovascular mortality in Cuba 1980-2010: Repeated cross sectional surveys and ecological comparison of secular trends. BMJ. 2013;346:f1515.

[14] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Martinez-Gonzalez MA, Investigators PS. Primary prevention of cardiovascular disease with a Mediterranean diet. N Engl J Med. 2013;368(14):1279-90.

[15] Tosti V, Bertozzi B, Fontana L. Health benefits of the mediterranean diet: Metabolic and molecular mechanisms. J Gerontol A Biol Sci Med Sci. 2018;73(3):318-26.

[16] Heianza Y, Ma W, Manson JE, Rexrode KM, Qi L. Gut microbiota metabolites and risk of major adverse cardiovascular disease events and death: A systematic review and meta-analysis of prospective studies. J Am Heart Assoc. 2017;6(7).

[17] Riordan MM, Weiss EP, Meyer TE, Ehsani AA, Racette SB, Villareal DT, Fontana L, Holloszy JO, Kovacs SJ. The effects of caloric restriction- and exercise-induced weight loss on left ventricular diastolic function. Am J Physiol Heart Circ Physiol. 2008;294(3):H1174-82.

[18] Fontana L, Villareal DT, Weiss EP, Racette SB, Steger-May K, Klein S, Holloszy JO, Washington University School of Medicine CG. Caloric restriction or exercise: Effects on coronary heart disease risk factors. A randomized, controlled trial. Am J Physiol Endocrinol Metab. 2007;293(1):E197-202.

[19] Stewart RAH, Held C, Hadziosmanovic N, Armstrong PW, Cannon CP, Granger CB, Hagstrom E, Hochman JS, Koenig W, Lonn E, Nicolau JC, Steg PG, Vedin O, Wallentin L, White HD, Investigators S. Physical activity and mortality in patients with stable coronary heart disease. J Am Coll Cardiol. 2017;70(14):1689-700.

[20] St-Onge MP, Zuraikat FM. Reciprocal roles of sleep and diet in cardiovascular health: A review of recent evidence and a potential mechanism. Curr Atheroscler Rep. 2019;21(3):11.

[21] Khan SU, Duran CA, Rahman H, Lekkala M, Saleem MA, Kaluski E. A meta-analysis of continuous positive airway pressure therapy in prevention of cardiovascular events in patients with obstructive sleep apnoea. Eur Heart J. 2018;39(24):2291-7.

[22] Gerbarg PL, Brown RP, Streeter CC, Katzman M, Vermani M. Breath practices for survivor and caregiver stress, depression, and post-traumatic stress disorder: Connection, Co-regulation, compassion. OBM Integrative and Complementary Medicine. 2019;4(3):1.

[23] Bernardi L, Porta C, Spicuzza L, Bellwon J, Spadacini G, Frey AW, Yeung LY, Sanderson JE, Pedretti R, Tramarin R. Slow breathing increases arterial baroreflex sensitivity in patients with chronic heart failure. Circulation. 2002;105(2):143-5.

[24] Stone GW, Maehara A, Lansky AJ, de Bruyne B, Cristea E, Mintz GS, Mehran R, McPherson J, Farhat N, Marso SP, Parise H, Templin B, White R, Zhang Z, Serruys PW, Investigators P. A prospective natural-history study of coronary atherosclerosis. N Engl J Med. 2011;364(3):226-35.

[25] Williams MC, Kwiecinski J, Doris M, McElhinney P, D'Souza MS, Cadet S, Adamson PD, Moss AJ, Alam S, Hunter A, Shah ASV, Mills NL, Pawade T, Wang C, Weir McCall J, Bonnici-Mallia M, Murrills C, Roditi G, van Beek EJR, Shaw LJ, Nicol ED, Berman DS, Slomka PJ, Newby DE, Dweck MR, Dey D. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction: Results from the multicenter SCOT-HEART Trial (Scottish Computed Tomography of the HEART). Circulation. 2020;141(18):1452-62.

[26] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernandez-Sola J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundstrom J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V, Group G-N-JGBoCDW. Global burden of cardiovascular diseases and risk factors, 1990-2019: Update from the GBD 2019 study. J Am Coll Cardiol. 2020;76(25):2982-3021.

[27] Messroghli DR, Moon JC, Ferreira VM, Grosse-Wortmann L, He T, Kellman P, Mascherbauer J, Nezafat R, Salerno M, Schelbert EB, Taylor AJ, Thompson R, Ugander M, van Heeswijk RB, Friedrich MG. Clinical recommendations for cardiovascular magnetic resonance mapping of T1, T2, T2* and extracellular volume: A consensus statement by the Society for Cardiovascular Magnetic Resonance (SCMR) endorsed by the European Association for Cardiovascular Imaging (EACVI). J Cardiovasc Magn Reson. 2017;19(1):75.

[28] Ramos JG, Fyrdahl A, Wieslander B, Thalen S, Reiter G, Reiter U, Jin N, Maret E, Eriksson M, Caidahl K, Sorensson P, Sigfridsson A, Ugander M. Comprehensive cardiovascular magnetic resonance diastolic dysfunction grading shows very good agreement compared with echocardiography. JACC Cardiovasc Imaging. 2020;13(12):2530-42.

[29] Widmer RJ, Collins NM, Collins CS, West CP, Lerman LO, Lerman A. Digital health interventions for the prevention of cardiovascular disease: A systematic review and meta-analysis. Mayo Clin Proc. 2015;90(4):469-80.

[30] Varnfield M, Karunanithi M, Lee CK, Honeyman E, Arnold D, Ding H, Smith C, Walters DL. Smartphone-based home care model improved use of cardiac rehabilitation in post-myocardial infarction patients: Results from a randomised controlled trial. Heart. 2014;100(22):1770-9.

[31] Cassidy S, Hunyor I, Wilcox I, Fontana L. Changing the conversation from 'chronic disease' to 'chronic health'. Eur Heart J. 2021.

[32] Snow G. blockrand: Randomization for Block Random Clinical Trials. R package version 1.5. https://CRAN.R-project.org/package=blockrand. 2020.

[33] Schulz KF, Grimes DA. Unequal group sizes in randomised trials: Guarding against guessing. The Lancet. 2002;359(9310):966-70.

[34] Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, Eccles MP, Cane J, Wood CE. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: Building an international consensus for the reporting of behavior change interventions. Ann Behav Med. 2013;46(1):81-95.

[35] Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, Rastogi SS, Manor O, Pella D, Berry EM. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): A randomised single-blind trial. The Lancet. 2002;360(9344):1455-61.

[36] de Lorgeril M, Salen P, Martin JL, Monjaud I, Delaye J, Mamelle N. Mediterranean diet, traditional risk factors, and the rate of cardiovascular complications after myocardial infarction: Final report of the Lyon Diet Heart Study. Circulation. 1999;99(6):779-85.

[37] Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, Gomez-Gracia E, Ruiz-Gutierrez V, Fiol M, Lapetra J, Lamuela-Raventos RM, Serra-Majem L, Pinto X, Basora J, Munoz MA, Sorli JV, Martinez JA, Fito M, Gea A, Hernan MA, Martinez-Gonzalez MA, Investigators PS. Primary prevention of cardiovascular disease with a mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med. 2018;378(25):e34.

[38] Kraus WE, Bhapkar M, Huffman KM, Pieper CF, Krupa Das S, Redman LM, Villareal DT, Rochon J, Roberts SB, Ravussin E, Holloszy JO, Fontana L. 2 years of caloric restric-

tion and cardiometabolic risk (CALERIE): Exploratory outcomes of a multicentre, phase 2, randomised controlled trial. The Lancet Diabetes & Endocrinology. 2019;7(9):673-83.

[39] Winzer EB, Woitek F, Linke A. Physical activity in the prevention and treatment of coronary artery disease. J Am Heart Assoc. 2018;7(4).

[40] Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, Douglas PS, Foody JM, Gerber TC, Hinderliter AL, King SB, 3rd, Kligfield PD, Krumholz HM, Kwong RY, Lim MJ, Linderbaum JA, Mack MJ, Munger MA, Prager RL, Sabik JF, Shaw LJ, Sikkema JD, Smith CR Jr, Smith SC Jr, Spertus JA, Williams SV, Anderson JL, American College of Cardiology Foundation/American Heart Association Task F. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation. 2012;126(25):e354-471.

[41] Yao BC, Meng LB, Hao ML, Zhang YM, Gong T, Guo ZG. Chronic stress: A critical risk factor for atherosclerosis. J Int Med Res. 2019;47(4):1429-40.

[42] Bussing A, Michalsen A, Khalsa SB, Telles S, Sherman KJ. Effects of yoga on mental and physical health: A short summary of reviews. Evid Based Complement Alternat Med. 2012;2012:165410.

[43] Reive C. The biological measurements of mindfulness-based stress reduction: A systematic review. Explore (NY). 2019;15(4):295-307.

[44] Praissman S. Mindfulness-based stress reduction: A literature review and clinician's guide. J Am Acad Nurse Pract. 2008;20(4):212-6.

[45] Muscat DM, Lambert K, Shepherd H, McCaffery KJ, Zwi S, Liu N, Sud K, Saunders J, O'Lone E, Kim J, Robbins A, Webster AC. Supporting patients to be involved in decisions about their health and care: Development of a best practice health literacy App for Australian adults living with Chronic Kidney Disease. Health Promot J Austr. 2021;32(Suppl 1):115-27.

[46] Huang R, Liu N, Nicdao MA, Mikaheal M, Baldacchino T, Albeos A, Petoumenos K, Sud K, Kim J. Emotion sharing in remote patient monitoring of patients with chronic kidney disease. J Am Med Inform Assoc. 2020;27(2):185-93.

[47] Shcherbina A, Hershman SG, Lazzeroni L, King AC, O'Sullivan JW, Hekler E, Moayedi Y, Pavlovic A, Waggott D, Sharma A, Yeung A, Christle JW, Wheeler MT, McConnell MV, Harrington RA, Ashley EA. The effect of digital physical activity interventions on daily step count: A randomised controlled crossover substudy of the MyHeart Counts Cardiovascular Health Study. The Lancet Digital Health. 2019;1(7):e344-e52.

[48] Samdal GB, Eide GE, Barth T, Williams G, Meland E. Effective behaviour change techniques for physical activity and healthy eating in overweight and obese adults; systematic review and meta-regression analyses. Int J Behav Nutr Phys Act. 2017;14(1):42.

[49] Klasnja P, Hekler EB, Shiffman S, Boruvka A, Almirall D, Tewari A, Murphy SA. Microrandomized trials: An experimental design for developing just-in-time adaptive interventions. Health Psychol. 2015;34S:1220-8.

[50] The American Heart Associaton Diet and Lifestyle Recommendations. 2021. Available at: https://www.heart.org/en/healthy-living/healthy-eating/eat-smart/nutrition-basics/aha-diet-and-lifestyle-recommendations. Accessed: 1 September 2021.

[51] Mezzani A. Cardiopulmonary exercise testing: Basics of methodology and measurements. Ann Am Thorac Soc. 2017;14(Supplement_1):S3-11.

[52] Hines EA, Brown GE. The cold pressor test for measuring the reactibility of the blood pressure: Data concerning 571 normal and hypertensive subjects. American Heart Journal. 1936;11(1):1-9.

[53] Vaidya K, Arnott C, Martinez GJ, Ng B, McCormack S, Sullivan DR, Celermajer DS, Patel S. Colchicine therapy and plaque stabilization in patients with acute coronary syndrome: A CT coronary angiography study. JACC Cardiovasc Imaging. 2018;11(2 Pt 2):305-16.

[54] Brown LAE, Onciul SC, Broadbent DA, Johnson K, Fent GJ, Foley JRJ, Garg P, Chew PG, Knott K, Dall'Armellina E, Swoboda PP, Xue H, Greenwood JP, Moon JC, Kellman P, Plein S. Fully automated, inline quantification of myocardial blood flow with cardiovascular magnetic resonance: Repeatability of measurements in healthy subjects. J Cardiovasc Magn Reson. 2018;20(1):48.

[55] European Medicines Agency Committee for Medicinal Products for Human Use. Adjustment for baseline covariates in clinical trials | European Medicines Agency. 2015.

[56] Robins JM, Hernan MA, Brumback B. Marginal structural models and causal inference in epidemiology. Epidemiology. 2000;11(5):550-60.

Chapter 3 detailed the LIVEPLUS Protocol, establishing the methodological groundwork for a robust RCT that examines the impact of lifestyle interventions on vascular health. The protocol underscored the significance of integrating dietary changes, physical activity, and regular health monitoring to address key markers of vascular function. With the framework in place, Chapter 4 transitions to presenting the actual outcomes of this six-month intervention, offering a comprehensive analysis of its efficacy in improving vascular and cardiometabolic health.

This chapter delves into both primary and secondary outcomes, with a strong focus on markers such as FMD, PWV, and CIMT, alongside biochemical and body composition indicators. The results reveal the extent to which structured lifestyle changes can influence vascular health, shedding light on physiological mechanisms that underlie these improvements. Additionally, the chapter provides valuable insights into individual variability in response to the intervention, an important consideration for tailoring future clinical approaches.

Beyond the immediate findings, Chapter 4 also reflects on the broader implications of the intervention, including its feasibility and acceptability among participants. These discussions are critical for informing subsequent chapters, particularly those exploring strategies to sustain behavioural changes. The chapter serves as a bridge, connecting the experimental evidence with the need for innovative solutions to enhance adherence and long-term efficacy, a theme that is central to the next chapter.

4 Chapter 4: Impact of a 6-month digital lifestyle intervention on vascular function and arterial stiffness

What is known:

1. Vascular dysfunction and arterial stiffness independently increase the risk of death from cardiovascular diseases (CVD).[252-254]
2. CVD patients with low attenuation plaque (LAP) in coronary arteries are at a greater risk of poor cardiovascular outcomes, yet preliminary findings indicate that changes in lifestyle could lead to alterations in CVD risk, although there is a significant lack of research in this field.[255]
3. More specifically, there are limited studies looking at changes in vascular measures following lifestyle interventions in individuals with LAP.[256] FMD and Carotid IMT are two important measures of atherosclerotic disease, with PWV being the gold standard for predicting arterial stiffness and associated with traditional CVD risk factors such as age, sex, race, smoking, alcohol consumption, habitual endurance exercise, blood pressure, dyslipidaemia, dietary patterns, risk-lowering drug therapy, glycaemia, hyperuricaemia, obesity-related anthropometric parameters, obesity, and obesity-related diseases.[257]
4. Exercise and weight reduction are recognised for enhancing the flexibility of arteries.
5. There is increasing awareness of the benefit of mHealth interventions in clinical care. [258, 259]

What this study adds:

1. Impact of a 6-month lifestyle intervention on vascular measure changes in a LAP population.
2. Augmenting clinical care with a digital intervention via mHealth in a LAP population.
3. Although it is acknowledged that weight loss improves arterial stiffness, and CVD risk, there have been limited studies examining effects of an intensive lifestyle intervention in reducing CVD risk.

Key findings include:

1. 6 months of an intensive lifestyle intervention in individuals with LAP led to significant weight loss and an improvement in PWV.
2. Despite significant weight loss with the intensive lifestyle intervention, the impact on cardiometabolic measures was limited.
3. This intensive lifestyle intervention delivered through a digital platform was achievable in individuals with LAP.

4.1 Introduction

Low attenuation plaque (LAP) is a significant risk factor in the development of cardiovascular diseases (CVD), which itself remains a leading global cause of morbidity and mortality.[260] LAPs are prone to rupture, due to their vulnerable nature, leading to acute coronary syndromes and strokes, and thus, emphasise the critical need for early detection and management to prevent adverse cardiovascular events.[3] Despite growing awareness of its implications, the influence of lifestyle modifications on LAP's progression and stability remain underexplored.[214, 261]

Non-invasive measures of cardiovascular health are essential for the early detection of CVD and the assessment of intervention efficacy, highlighting their importance in the management and study of LAP. These measures include Flow-Mediated Dilation (FMD),[262] Carotid Intima-Media Thickness (IMT),[263] Pulse Wave Velocity (PWV), Pulse Wave Analysis (PWA),[264] Augmentation Index (AIx),[265, 266] and Subendocardial Viability Ratio (SEVR),[267, 268] which offer invaluable insights into arterial stiffness, endothelial function, and overall cardiovascular risk. However, literature on the impact of lifestyle interventions on these vascular health markers in individuals with LAP is sparse. This highlights a significant gap in our understanding of how lifestyle behavioural modifications influence progression of LAP and, by extension, the risk of CVD. Given the escalating global burden of CVD, claiming approximately 17.9 million lives annually and accounting for nearly one-third of all deaths worldwide, the need for comprehensive strategies that include lifestyle modification is more pressing than ever.[260, 269]

Addressing this need, this 6-month clinical trial will investigate the impact of lifestyle interventions on key vascular health markers including FMD, CIMT, PWV, PWA, AIx, and SEVR in individuals with LAP (optimal values for these vascular measures are shown in **Textbox 4.1**). By integrating digital health

tools in our approach, this study augments ILP targeting intrinsic motivation, with the aim to shed light on the potential for lifestyle modifications to mitigate the risks associated with LAP, thereby contributing to the broader efforts to combat CVD.[270]

Textbox 4.1 Optimal values for FMD, CIMT, and PWV.

Parameter	Description	Optimal Values
Flow-Mediated Dilation (FMD)	Measures the dilation of an artery (the brachial artery, for my thesis) in response to increased blood flow, indicating endothelial function.	> 6.5% (varies by methodology and population, indicating healthy endothelial function).[271]
Carotid Intima-Media Thickness (CIMT)	Measurement of the thickness of the two innermost layers of the carotid artery wall, used as a marker for atherosclerosis.	< 0.9 mm (can increase with age, values above, indicate increased risk of cardiovascular events).[272]
Pulse Wave Velocity (PWV)	Assesses arterial stiffness by measuring the velocity of the blood pressure pulse through the arterial tree.	< 10 m/s (values depend on age and blood pressure, higher values suggest increased arterial stiffness).[273]

4.1.1 Aims/objectives

The primary aim of this study was to determine the effects of a 6-month lifestyle intervention on vascular function (FMD, Carotid IMT, PWA, AIx, and PWV) in individuals with LAP. The secondary and exploratory aims were to explore the impact of ILP on biomarkers, SEVR, and medication usage.

4.2 Methods

4.2.1 Design

Longitudinal two arm prospective randomised clinical trial with measurements taken at baseline with a follow up of six months (**Figure 4.1**). This study is a study within the LIfestyle VulnErable PLaqUe Study (LIVEPLUS), the protocol of which is described in **Chapter 3** of this thesis. Briefly, the two groups for this study are intensive lifestyle program, ILP, (including following the 5:2 diet, with access to the study app), and the optimal medical therapy, OMT, (including following the American Heart Association diet, without access to the study app).

4.2.2 Participants

The participants for this study were selected from the LIVEPLUS study (ACTRN12620001151921), the protocol of which is detailed in **Chapter 3** of this thesis. **Figure 4.10** shows the progression of participants in this study who were initially randomised as part of LIVEPLUS[274] and were being followed from baseline to month 6.

4.2.3 Eligibility criteria

Participants eligible for this study would have had to be aged 18 to 80 years, have a presence of low-attenuation plaque (LAP) on coronary computed tomography angiography (CCTA), have a BMI greater than 22.0 kg/m^2, be capable of providing full informed consent, and be deemed capable of undergoing all study assessments and adhering to the rigors of the ILP intervention. Conversely, individuals with non-MRI-compatible implanted devices, an estimated glomerular filtration rate (eGFR) less than 30 mL/kg/1.73 m^2, an inability to exercise via supine ergometer, contraindications for adenosine or glyceryl

trinitrate, a previous severe allergic reaction to iodinated contrast media, pregnancy or breastfeeding status, or a history of any chronic disease process that could interfere with the interpretation of results were excluded from participating in this study.

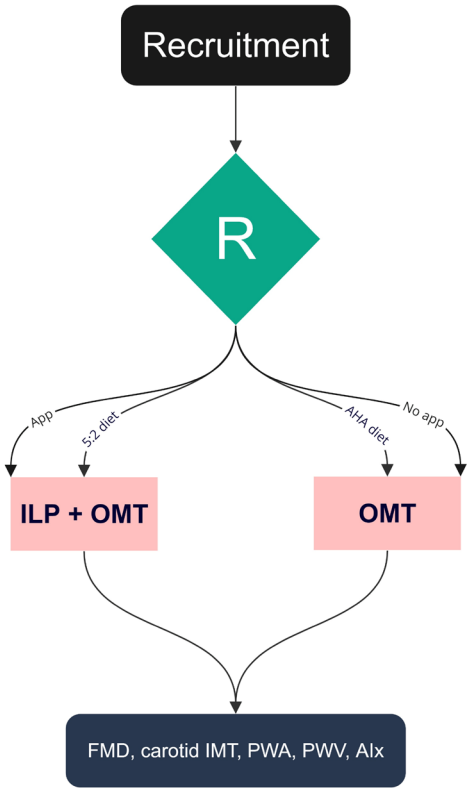


Figure 4.1 Study design flowchart showing the two groups including the primary outcomes measures.
R, randomisation; ILP, intensive lifestyle program; OMT, optimal medical therapy; 5:2 diet, 5 days usual diet and 2 days of reduced calorie fasting; AHA diet, American Heart Association diet guidelines; FMD, flow mediated dilation; carotid IMT, carotid intima media thickness (CIMT); PWA, pulse wave analysis; PWV, pulse wave velocity; AIx, augmentation index.

4.2.4 Recruitment

We recruited participants who had undergone a clinically indicated CCTA and had a quantifiable LAP within the range of -30 to 150 Hounsfield units (HU) (**Figure 4.1**). Presence of plaque in the coronary tree was evaluated by two experienced CCTA reporters (cardiology staff specialists at the hospital). It was estimated that approximately 20-40% of patients in the general cardiology outpatient population would have LAP. The primary source of referral for clinically indicated CCTA at Royal Prince Alfred Hospital (RPA) for this study was from a single large academic clinical practice, Central Sydney Cardiology at RPA Hospital Medical Centre, and from patients who had attended the RPA Radiology Department for a clinically indicated CCTA.

4.2.5 Screening visit

After a pre-screening phone call, eligible potential participants participated in an initial video call. During this call, the research team presented a brief overview of the study protocol, including its rationale, implications, and constraints, as well as any known side effects and risks associated with participation (**Appendix F**). Participants then had the opportunity to ask questions and discuss any details of the

study. Those who were willing to participate were invited to the Charles Perkins Centre-RPA clinic to provide electronic informed consent through REDCap. As determined by the research team, if a potential participant was deemed to lack the capacity for fully informed consent, they were not included in the study.

4.2.6 Intervention

Participants were randomised into two distinct dietary regimen groups: individuals using the study app and adhering to a 5:2 pescatarian diet (ILP+OMT), and those conforming to the conventional American Heart Association dietary guidelines without app access (OMT). Both groups followed the optimal medical therapy, which included ongoing treatments and medications as prescribed by their physicians, with the App group subject to the intensive lifestyle program, which is further described in greater detail in **Chapter 3**.

Following reveal of the group assignment, the participants randomised to the active intervention (OMT+ILP) group were given access to the study app which included educational content for diet, exercise, and mindfulness, and followed the 5:2 pescatarian diet. They also received Marley Spoon's pre-portioned meal kits for the first four weeks. They designed their meal plans with a dietitian, aiming to replace meat with fish and processed foods with plant-based ones. They fasted on two non-consecutive days per week, consuming two vegetable meals with specific energy content. The dietitian guided dietary changes, meal planning, and monitored body weight weekly through the study app. Based on these weights, the dietitian counselled participants on adhering to the 5:2 pescatarian diet and improving diet quality. The OMT group followed the AHA dietary guidelines.[275]

For physical activity, there is strong evidence that reducing sedentary behaviour and increasing physical activity reduces cardiovascular events and mortality.[141] Participants in the ILP+OMT group received an individualised home-based program based on guidelines from the American College of Cardiology Foundation/American Heart Association (AHA)[276] and the European Heart Network's Physical Activity Expert Group.[277] The program aimed for at least 150 minutes of moderate-intensity aerobic physical activity per week, spread evenly throughout the week. All participants wore a Fitbit tracker to measure baseline activity and the ILP+OMT group received an initial consultation with an exercise physiologist to set up a personalised program. The intensity of physical activity was assessed by monitoring the heart rate reserve and the 'talk test'. The absolute risk of exercise-related cardiac events was minimal. The OMT group also wore a Fitbit device and received guidance to adhere to the AHA Diet and Lifestyle Recommendations which encompass physical activity and stress reduction.

Meditation has been shown to have benefits for cardiovascular and mental health. The ILP+OMT group received a Mindfulness-Based Stress Reduction (MBSR) program, which integrated meditation and gentle hatha yoga, both of which are effective and safe methods for alleviating stress.[278] The study implemented this program using the structure and content from the online free course https://palousemindfulness.com/. Sessions were conducted one-on-one, with the first session in person and subsequent sessions electronically to reduce the burden on participants. At the conclusion of the study, the stress reduction program was made available to the OMT group.

The LIVEPLUS protocol[274] was published prior to data collection and analysis for this study, and has been included in this thesis as **Chapter 3**. LIVEPLUS followed participants for twelve months, but this study followed participants for six months due to time limitations.

4.2.7 Outcome measures

With this study being a sub study of LIVEPLUS, we aim to only report outcomes specified for this study (i.e. **Chapter 4** in this thesis) as shown in **Figure 4.2**. All primary and secondary outcomes were obtained while participants were in an overnight fasted state.

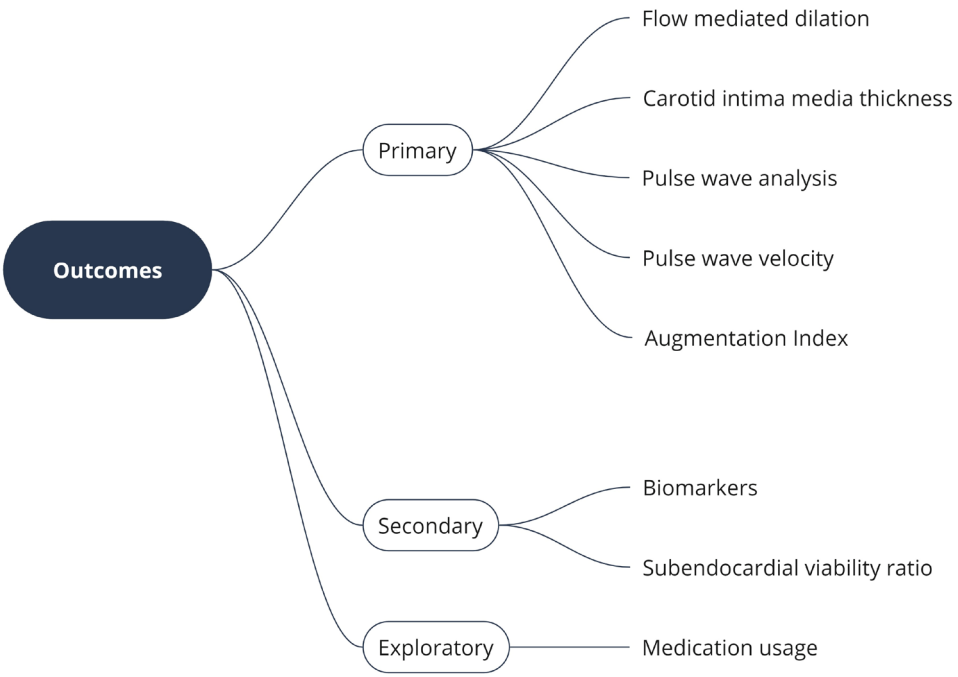


Figure 4.2 Outcome measures

4.2.8 Primary outcomes

The primary outcomes for this chapter are FMD, carotid IMT, PWA, PWV, AIx. All measurements were taken while the participant was in 12 hours fasted state.

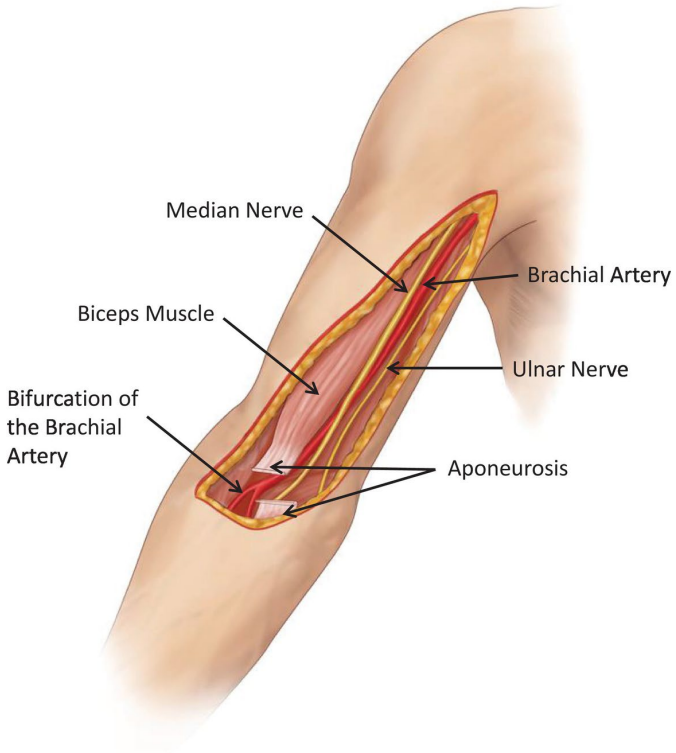


Figure 4.3 Brachial artery anatomical location, anterior aspect.
From Atlas of Surgical Techniques in Trauma (2020).[279]

4.2.8.1 Flow mediated dilation

Fasted brachial artery diameter measurements were obtained while the participant was in a supine position. After 15 minutes of acclimatisation to achieve a haemodynamic steady state, heart rate was continuously monitored using a 3-lead ECG. An automatic cuff (E-20 rapid cuff inflator; D.E. Hokanson Bellevue, WA) was placed around the right forearm distal to the olecranon process in accordance with established FMD guidelines by Corretti *et al.*[280] Image collection, transducer placement, and detailed methods were performed as previously described by Feairheller *et al.*[281] Vascular endothelial function was assessed through FMD using a high-resolution ultrasound device (Philips EPIQ 7 or equivalent) equipped with a 10 MHz linear array transducer and ECG gating. This technique used brief arterial occlusion in the arm, the brachial artery (**Figure 4.3**), for 5 minutes using a cuff, followed by non-invasive ultrasound scanning of the brachial artery proximal to the occlusion site. FMD videos were recorded using the Philips EPIQ 7 ultrasound system (Philips, Netherlands) and stored on our password-protected research data store. Arterial diameters were analysed using edge detection software, Brachial Analyzer for Research 6 (Medical Imaging Applications, Coralville, IA), with varying degrees of complexities (**Figure 4.4**). The highest 10-second interval throughout the 2-minute collection period represented the true peak hyperaemic diameter.

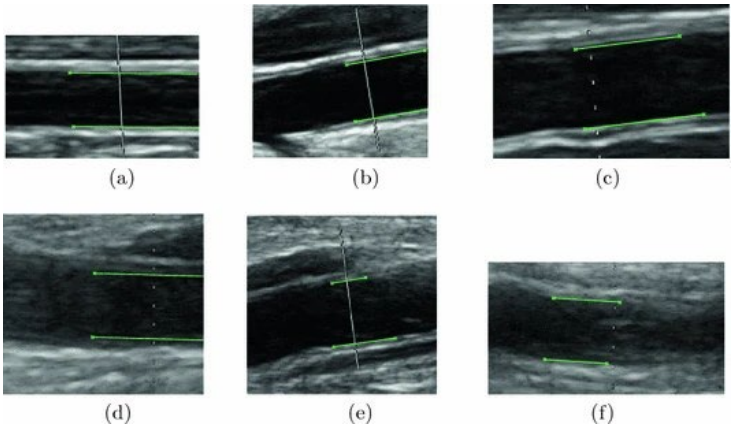


Figure 4.4 Limitations in analysing FMD.
Panels (a, b, and c) being easier to analyse compared to (d, e, and f). From van Oort *et al.*, Hypertension (2020).[39]

4.2.8.2 Carotid intima media thickness

The thickness of the inner and middle layers of the carotid artery wall, known as the intima-media thickness (IMT), can be assessed noninvasively using ultrasound imaging. This measurement serves as an indicator of the early stages of atherosclerosis,[282] and provides additional information about future CVD risk, especially in adults over the age of 40.[283] Carotid IMT measurement was performed involving a bilateral ultrasound examination of the distal common carotid arteries using a high-resolution ultrasound device (Philips EPIQ 7 or equivalent) equipped with a 10 MHz linear array transducer and ECG gating (**Figure 4.6** (1)). The mean IMT of the far wall was determined offline from a section of the vessel located at least 5 mm below the end of the common carotid artery, in accordance with the Mannheim Carotid Intima-Media Thickness and Plaque Consensus,[284] using validated semi-automated edge-detection software (Carotid Analyzer for Research 6) (**Supplementary Figure 4.1**). On the same day as the FMD measurements, CIMT images were recorded. Images were obtained and measurements were made using the Philips EPIQ 7 ultrasound system. Three measurements of the posterior wall of both the right and left common carotid arteries were collected in accordance with established guidelines (Roman et al.[285]).

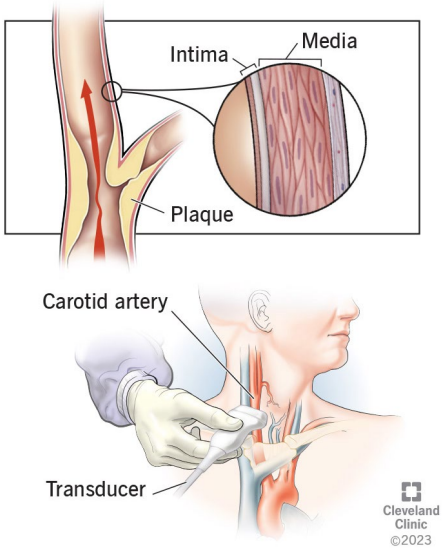


Figure 4.5 Measuring the intima-media thickness of a carotid artery.
Adapted from Cleveland Clinic.[286]

Figure 4.6 (1) Philips EPIQ 7 for ultrasound measurements, (2) SphygmoCor XCEL system for pulse wave analysis, pulse wave velocity, augmentation index, and SEVR.
From Philips EPIQ 7 (2024)[287] and SphygmoCor XCEL Pulse Wave Analysis (PWA) System (2024).[288]

4.2.8.3 Pulse wave analysis

The measurement of PWA is an output from the SphygmoCor device (**Figure 4.6** (2)).[289] A cuff was applied to the participant's arm aligned over the brachial artery. The participant was made to lie in a supine position for 5 minutes before measurements are taken. The software which comes with the device was then used to start cuff inflation for the PWA measurement which is an automatic process. The brachial cuff first inflates to measure the blood pressure, following which, the PWA waveform was captured. The SphygmoCor device while capturing the PWA, also calculated the aortic augmentation pressure and augmentation index (**Figure 4.7**).

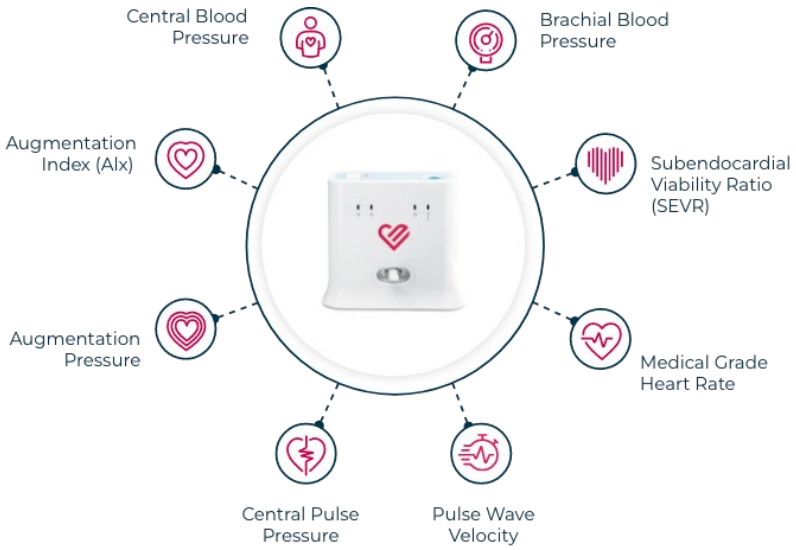


Figure 4.7 SphygmoCor XCEL evaluates a range of digital biomarkers related to vascular health.
From SphygmoCor XCEL Pulse Wave Analysis (PWA) System (2024).[288]

Aortic augmentation refers to the increase in central aortic pressure due to the reflection of pulse waves from the peripheral vasculature back to the heart. It is measured as the difference between the second peak (reflected wave peak) and the first peak (ejection wave peak) of the central aortic pressure waveform. The augmentation index (AIx) is the ratio of aortic augmentation to pulse pressure, expressed as a percentage. Pulse pressure is the difference between systolic and diastolic blood pressure.

$$AIx = \frac{\text{Aortic Augmentation}}{\text{Pulse Pressure}} \times 100$$

4.2.8.4 Pulse wave velocity and Augmentation Index

The measurement of Pulse Wave Velocity (PWV) and Augmentation Index (AIx) was conducted at baseline and at month six. We used the SphygmoCor XCEL system (**Figure 4.6** (2)) for the non-invasive determination of PWV by measuring the blood pressure waveform travelling between two arterial sites (**Figure 4.8**).[290] This was achieved by concurrently recording pressure waveforms at the carotid artery using a tonometer pressure sensor and at the femoral artery using a specialised blood pressure cuff.[291] Additionally, the SphygmoCor XCEL system allows for the assessment of peripheral arterial stiffness through the calculation of AIx as an output. AIx is calculated as (P2-P1) x 100/P1(%), where P1 represents pulse pressure and P2 represents the pressure corresponding to the inflection point on the pulse wave.[292]

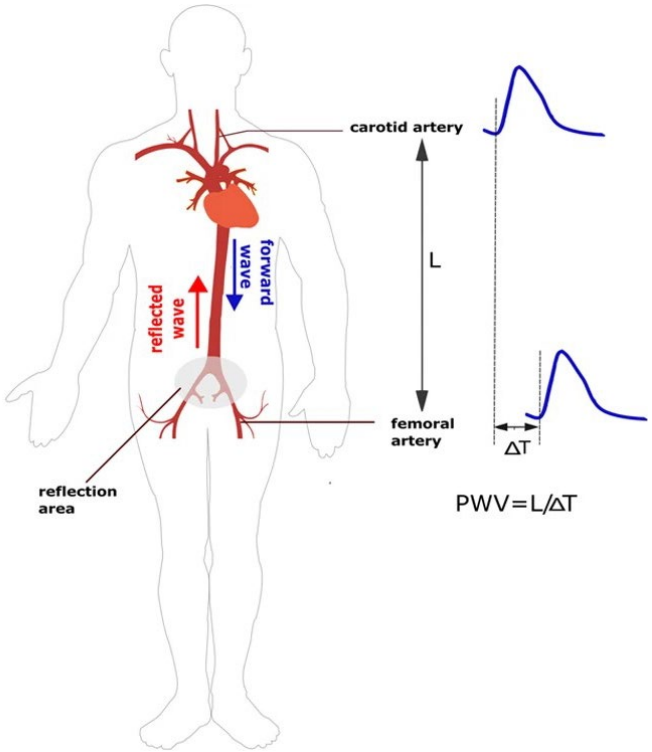


Figure 4.8 Pulse wave velocity (PWV) assessment.
Adapted from Jeroncic *et al*. Scientific Reports (2016).[293]

4.2.9 Secondary outcomes

4.2.9.1 Subendocardial Viability Ratio (SEVR)

The Subendocardial Viability Ratio (SEVR), also known as the Buckberg index,[294] is a non-invasive haemodynamic index used to assess the balance between myocardial oxygen supply and demand, particularly in the subendocardial region of the heart.[295] It was measured using SphygmoCor XCEL system[288] from the pulse wave analysis, specifically using the aortic pressure waveform. It is defined as the ratio of the area under the blood pressure curve during diastole (when coronary perfusion primarily occurs) to the area under the curve during systole (when myocardial oxygen demand is highest).[296] In mathematical terms, SEVR = (DPTI/SPTI) × 100, where DPTI is the diastolic pressure-time index and SPTI is the systolic pressure-time index.[297]

4.2.9.2 Blood biomarkers

Venepuncture was performed while the participant was in an overnight fasted state. Fasting glucose, haemoglobin A1c, Total cholesterol to HDL-C ratio, white cell count, neutrophil, cholesterol, triglyceride, HDL-C, LDL-C, Non-HDL-C. (**Figure 4.9**, and **Appendix B**)

NSW Health Pathology – Royal Prince Alfred Hospital (RPAH)
T: 0436 641 607 / 0417 397 191 |F: 02 9515 7931
Clinical Trials, RPAH, Central Specimen reception
Level 5, Building 77 Missenden Road, Camperdown NSW 2050

Pathology Tests	Collection Instructions	Processing Requirements	Minimum Sample Requirement	Storage Condition	Transport Requirement
FBC	1 x 4ml EDTA (purple top tube) After blood is collected Invert tube a few times to mix additive	Keep whole blood Do not Centrifuge	4ml EDTA whole blood	4°C Must be assayed within 24hrs	Ambient temp, Fridge temp (4°C) if transport is delayed
HbA1c	1 x 4ml EDTA (purple top tube) After blood is collected Invert tube a few times to mix additive	Keep whole blood Do not Centrifuge	0.5ml EDTA whole blood	Whole blood should only be stored for a maximum of 1 day at room temperature (15-35°C) 7 days at fridge temp (4-8°C)	Ambient temp if delivered same day of collection Fridge temp (4°C) if transport is delayed more than 24hrs
EUC, LFT, UA, LDL, Triglycerides, Glucose, HDL, non-HDL Cholesterol	1 x 5ml clotted blood SST (gold top tube)	Keep tube upright at ambient temp for 30mins to allow blood to clot Centrifuge tube at 2100g for 10 mins Transfer serum into false bottom aliquot tube (supplied by NSW HP)	300µl serum	4°C	Fridge temp (4°C)

Figure 4.9 Collection and processing of bloods for respective biomarkers.

4.2.10 Exploratory outcome

4.2.10.1 Medication usage

Medication usage was carefully documented, reflecting both intervention and control cohorts. Self-reported discontinuation or changes in medication regimens including medication adherence and modifications were noted, providing insights into patient-managed treatment plans outside of clinical recommendations.

4.2.11 Data collection and analysis

FMD and CIMT were performed sequentially on the fasted participant soon after phlebotomy during clinic visit. We performed FMD on the participants' right arm because phlebotomy was performed on

the left arm mostly, ensuring the same arm was not used for phlebotomy and FMD. Due to the nature and duration of the test, we collected FMD measurements once per time point. We collected CIMT twice per angle (see **Supplementary Figure 4.2** Meijer's Carotid Arc), per visit, labelling each acquisition for ease of analysis. PWA (AP, AIx, SEVR) and PWV (and pulse transit time) were performed three times per visit, with only the results from "quality control check" approved reports used for analysis. Blood biomarkers were processed by New South Wales Health Pathology at the Royal Prince Alfred Hospital, with the results mailed to our letter box, which were then manually entered in REDCap, and verified by a second member of the research team. Medication usage data was collected during participants' visit, at each time point, and entered in REDCap.

4.2.12 Experimental protocol + randomisation

Participants were randomised using a web-based system in REDCap and stratified according to age, sex, and BMI. The allocation sequence was generated using the R package *blockrand*. Both investigators and participants remained blinded to group allocation till all baseline measurements were completed. Upon completion of the final baseline measurement, participants were randomised in REDCap, revealing their group assignment. Due to the nature of the intervention, blinding during the study was not feasible. However, research personnel responsible for conducting CCTA, MRI, and statistical analysis were blinded to group allocation.

4.2.13 Statistical analysis

We selected those participants who completed up to month 6 in the primary study (LIVEPLUS) to be included in this study. We used R, version 4.3.3, for all analysis. All demographic and clinical characteristics of participants was summarised using mean and standard deviation for continuous variables, and frequency and percentage for categorical variables. Continuous data was tested for normality using the Shapiro-Wilk test. For within-group changes from pre- to post-intervention, normally distributed data was analysed using paired-sample t-tests, whereas the Wilcoxon signed-rank test was applied to data not meeting normality standards. Comparisons between groups were conducted through ANCOVA, incorporating the baseline value as a covariate. Due to the potential co-linearity among variables and our hypothesis-driven approach, we chose not to adjust for multiple comparisons, a decision aimed at minimising the risk of Type II errors, in line with Rothman (1990). This strategy ensured a focused interpretation of results without diluting statistical power. We did not use any data imputation methods to handle missing data, however sensitivity analysis may be carried out for any outliers across our outcomes. Correlation analyses may be conducted using Pearson's correlation for normally distributed data and Spearman's rank for non-normal distributions, to explore relationships between outcome measures. We have set the significance threshold at $P < 0.05$, carefully balancing the risks of Type I and II errors to validate the significance of our findings with confidence. Additionally, we will perform subgroup analyses looking at the impact of weight loss (≤5% & >5%) on outcome measures, body composition and biomarkers.

4.3 Results

4.3.1 Population characteristics

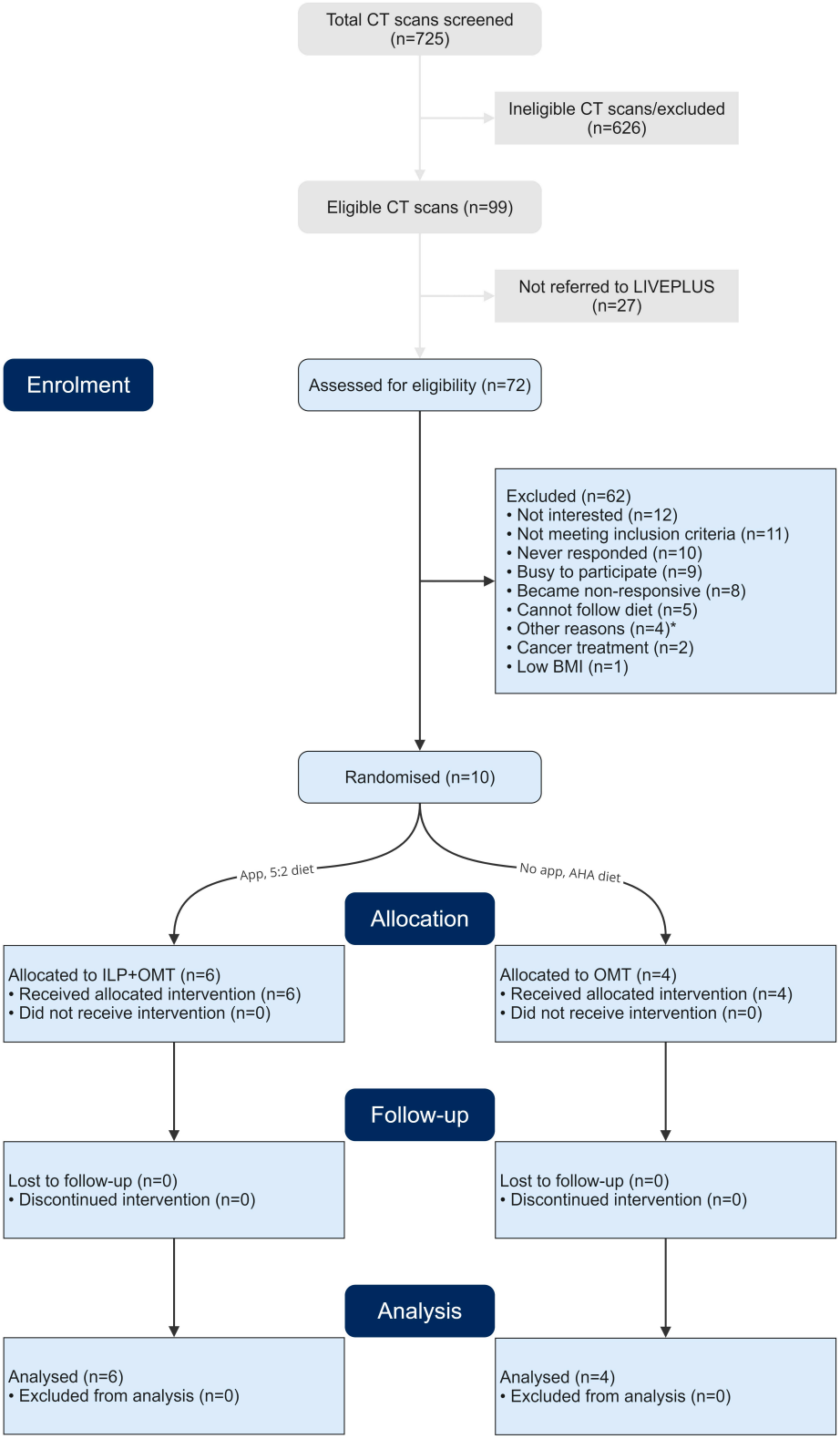


Figure 4.10 CONSORT Flow Diagram

*Other reasons include (n=1 each for) CT scan done at a clinic other than RPA; participant screened but had other health problems and needed to speak to therapist; trouble changing medications to participate; lives too far from our clinic.

Seventy-two individuals were assessed for eligibility (**Figure 4.10**) with 62 screened out, leaving 10 individuals eligible for randomisation. Of these, 6 participants were randomised to the intervention group and 4 to the control group. Although the parent study, LIVEPLUS, recruited 21 participants until December 2023, 11 of these participants were not included in this study as they had not reached 6 months follow up.

Baseline characteristics were similar across groups (**Table 4.1**). Participants in the intervention group (n=6, 60%, with 33% females) and control group (n=4, 40%, with 25% females), had mean ages of 60.17 ± 10.13 years and 60.50 ± 12.12 years, respectively, showing no meaningful difference. Other measures such as height (intervention: 174.42 ± 9.16 cm; control: 173.12 ± 13.14 cm) and weight (intervention: 84.95 ± 20.76 kg; control: 90.80 ± 20.89 kg) were similarly distributed. BMI was 8% lower in the intervention group (27.63 ± 4.56 kg/m^2) compared to the control group (30.02 ± 4.57 kg/m^2), with similar variability for participants (P=0.44). Waist to hip ratios (0.96 ± 0.08 vs. 0.90 ± 0.12, P=0.39) displayed minor variations across groups without substantial differences. Metabolic parameters, including fasting glucose (5.08 ± 0.36 mmol/L for control vs. 5.95 ± 1.11 mmol/L for intervention, P=0.17) and HbA1c levels (5.25 ± 0.30% or 34.25 ± 3.50 mmol/mol for control vs. 5.58 ± 0.26% or 37.67 ± 2.88 mmol/mol for intervention, P=0.10 and P=0.13, respectively), along with lipid profiles (cholesterol 4.90 ± 1.95 mmol/L vs. 3.62 ± 0.32 mmol/L, P=0.14; HDL-C 1.92 ± 0.61 mmol/L vs. 1.42 ± 0.10 mmol/L, P=0.08), showed no significant differences between the groups. Blood pressure and white cell counts, including neutrophil counts, were also similar (SBP: control 118.50 ± 9.92 mmHg, intervention 126.89 ± 31.79 mmHg, P=0.63; DBP: control 73.88 ± 6.33 mmHg, intervention 76.78 ± 8.25 mmHg, P=0.57; white cell count: control 5.15 ± 0.91 x10^9/L, intervention 5.40 ± 1.27 x10^9/L, P=0.75; neutrophil count: control 2.90 ± 0.77 x10^9/L, intervention 3.33 ± 0.89 x10^9/L, P=0.45). Subgroup analyses revealed no significant impact of weight loss (≤5% & >5%) on outcome measures, body composition and biomarkers (**Supplementary Tables 4.1 – 4.3, and Supplementary Figure 4.3**).

4.3.2 Primary outcomes

4.3.2.1 Flow mediated dilation

The FMD index, a measure of endothelial function, increased by 7.9% in the control group (5.71 ± 4.53 to 6.16 ± 8.26) and by 36.8% in the intervention group (6.41 ± 2.72 to 8.77 ± 4.21). Although the intervention group demonstrated a larger relative improvement, the changes within and between groups showed overlapping variability (P=0.59; **Table 4.2**).

4.3.2.2 Carotid intima media thickness

Carotid IMT_{Mean} increased by 18.2% in the control group, and 27.7% in the intervention group. Similar trends were observed for Carotid IMT_{Max}. While both groups showed a greater increase in IMTMax (control: 14.5%; intervention: 22.9%), the between-group differences did not reach statistical significance (P=0.14 and P=0.33, respectively; **Table 4.2**).

4.3.2.3 Pulse wave analysis

Aortic augmentation increased by 30.9% in the control group (5.67 ± 3.97 to 7.42 ± 4.31 mmHg; P=0.04*) and by 8.9% in the intervention group (8.67 ± 5.90 to 9.44 ± 6.55 mmHg; P=0.86). Despite

this difference, there were no meaningful differences between groups (P=0.72). (**Table 4.2**). Augmentation Index values showed similar trends .

4.3.2.4 Pulse wave velocity

Pulse wave velocity increased by 18.9% in the control group (7.35 ± 1.06 to 8.74 ± 0.61 m/s) and decreased by 2% in the intervention group (7.68 ± 0.90 to 7.53 ± 0.89 m/s). The between-group (P=0.04*) suggests a differential response to the intervention (**Table 4.2**).

4.3.3 Secondary outcomes

4.3.3.1 Biomarkers

Weight decreased by 6.3% in the intervention group (from 84.95 ± 20.76 kg to 79.57 ± 18.99 kg) compared to 5.6% in the control group (from 90.80 ± 20.89 kg to 85.76 ± 19.19 kg). BMI reductions mirrored these trends, with an 8.7% reduction in the intervention group and a 5% reduction in the control group. Waist-to-hip ratios declined marginally in both groups without notable differences (**Table 4.3**). Fasting glucose, HbA1c levels, and lipid profiles remained relatively stable, with minor fluctuations across groups. For instance, cholesterol increased by 9.9% in the intervention group but showed a slight decline of 2.7% in the control group.

4.3.3.2 Subendocardial viability ratio

Neither group showed a significant change in SEVR, with the control group experiencing a decrease (p=0.20) and the intervention group showing a slight decrease (p=0.72). There was no significant between-group difference (P=0.59) in SEVR (**Table 4.2**).

4.3.4 Exploratory outcome

4.3.4.1 Medication usage

Medication usage patterns remained largely unchanged in both groups (**Table 4.4**), except for a reduction in antihypertensive medications in the intervention group and the introduction of Aspirin in the control group. Supplements such as calcium and Vitamin D3 were consistently used in the intervention group, while usage of sleep-related medications such as Melatonin remained unchanged across both groups (**Supplementary Table 4.1**).

Table 4.1 Participant characteristics

	Control	Intervention	P value
N	4 (40)	6 (60)	-
Female	1 (25)	2 (33)	-
Age (in years)	60.50 ± 12.12	60.17 ± 10.13	0.96
Height (cm)	173.12 ± 13.14	174.42 ± 9.16	0.86
Weight (kg)	90.80 ± 20.89	84.95 ± 20.76	0.67
BMI (kg/m^2)	30.02 ± 4.57	27.63 ± 4.56	0.44
Waist to Hip ratio	0.96 ± 0.08	0.90 ± 0.12	0.39
Fasting glucose (mmol/L)	5.08 ± 0.36	5.95 ± 1.11	0.17
HbA1c (%)	5.25 ± 0.30	5.58 ± 0.26	0.10
HbA1c (mmol/L)	34.25 ± 3.50	37.67 ± 2.88	0.13
Total Chol to HDL-C ratio	2.65 ± 1.18	2.57 ± 0.31	0.87
SBP (mmHg)	118.50 ± 9.92	126.89 ± 31.79	0.63
DBP (mmHg)	73.88 ± 6.33	76.78 ± 8.25	0.57
White cell count ($x10^9/L$)	5.15 ± 0.91	5.40 ± 1.27	0.75
Neutrophil ($x10^9/L$)	2.90 ± 0.77	3.33 ± 0.89	0.45
Cholesterol (mmol/L)	4.90 ± 1.95	3.62 ± 0.32	0.14
Triglycerides (mmol/L)	1.07 ± 0.32	1.05 ± 0.31	0.91
HDL-C (mmol/L)	1.92 ± 0.61	1.42 ± 0.10	0.08
LDL-C (mmol/L)	2.58 ± 1.71	1.72 ± 0.31	0.25
Non-HDL-C (mmol/L)	3.00 ± 1.89	2.20 ± 0.34	0.33

Values are N (%) or Mean ± SD

Table 4.2 Impact of the intervention on outcome measures

	Control (N=4)			**Intervention** (N=6)			**P value**‡
	Pre	**Post**	***p* value**†	**Pre**	**Post**	***p* value**†	
Flow mediated dilation							
FMD index (%)	5.71 ± 4.53	6.16 ± 8.26	0.86	6.41 ± 2.72	8.77 ± 4.21	0.23	0.59
Carotid IMT							
Carotid IMT_{Mean}	0.55 ± 0.08	0.65 ± 0.14	0.15	0.65 ± 0.29	0.83 ± 0.16	0.06	0.14
Carotid IMT_{Max}	0.76 ± 0.07	0.87 ± 0.20	0.23	0.83 ± 0.40	1.02 ± 0.23	0.16	0.33
Pulse wave analysis							
Aortic augmentation (mmHg)	5.67 ± 3.97	7.42±4.31	0.04*	8.67 ± 5.90	9.44 ± 6.55	0.86	0.72
Augmentation index (%)	12.92 ± 15.41	19.08±10.76	0.29	19.78 ± 10.34	20.17 ± 6.89	0.92	0.64
SEVR	193.45 ± 51.16	179.25 ± 38.66	0.20	167.34 ± 10.85	165.56 ± 16.26	0.72	0.59
Pulse wave velocity (N=8)							
PWV (m/s)	7.35 ± 1.06	8.74 ± 0.61	0.06	7.68 ± 0.90	7.53 ± 0.89	0.63	0.04*
Pulse transit time (ms)	63 ± 11.31	62.78 ± 6.18	0.65	68.78 ± 13.14	72.39 ± 11.51	0.43	0.24

Values are Mean ± SD

† Wilcoxon rank test

‡ Adjusted for baseline value for ANCOVA

* p<0.05

** p<0.01

p value = within group

P value = between group

IMT = intima media thickness; FMD = flow mediated dilation; PWV = pulse wave velocity; SEVR = sub endocardial viability ratio; Carotid IMT reported from Far wall measurements for more accuracy of results as per literature.

Table 4.3 Impact of the intervention on body composition and biomarkers

	Control (N=4)			**Intervention** (N=6)			**P value**‡
	Pre	**Post**	***p* value**†	**Pre**	**Post**	***p* value**†	
Weight (kg)	90.80 ± 20.89	85.76 ± 19.19	0.28	84.95 ± 20.76	79.57 ± 18.99	0.02*	0.78
BMI (kg/m^2)	30.03 ± 4.57	28.53 ± 5.16	0.25	27.63 ± 4.56	20.67 ± 10.66	0.04*	0.28
Waist to Hip ratio	0.97 ± 0.07	0.90 ± 0.08	0.16	0.90 ± 0.10	0.86 ± 0.10	0.29	0.73
Fasting glucose (mmol/L)	5.08 ± 0.36	5.13 ± 0.39	0.50	5.95 ± 1.11	5.78 ± 1.32	1.00	0.51
HbA1c (%)	5.25 ± 0.30	5.23 ± 0.40	1.00	5.58 ± 0.26	5.56 ± 0.33	0.53	0.80
HbA1c (mmol/L)	34.25 ± 3.50	31.50 ± 3.54	0.50	37.67 ± 2.88	37.40 ± 3.58	0.62	0.52
Total Chol to HDL-C ratio	2.65 ± 1.18	2.53 ± 1.10	1.00	2.57 ± 0.31	2.60 ± 0.48	0.92	0.79
SBP (mmHg)	118.50 ± 9.92	121.13 ± 3.97	0.62	126.92 ± 31.86	126.70 ± 28.91	0.71	0.82
DBP (mmHg)	73.88 ± 6.33	78.00 ± 4.42	0.14	77.00 ± 8.61	74.60 ± 7.09	0.53	0.29
White cell count (x10^9/L)	5.15 ± 0.91	4.63 ± 0.74	0.36	5.40 ± 1.27	5.22 ± 1.08	0.67	0.46
Neutrophil (x10^9/L)	2.90 ± 0.77	2.63 ± 0.81	0.42	3.33 ± 0.89	3.24 ± 0.92	0.85	0.51
Cholesterol (mmol/L)	4.90 ± 1.95	4.77 ± 2.36	0.17	3.62 ± 0.32	3.98 ± 0.76	1.00	0.55
Triglycerides (mmol/L)	1.08 ± 0.32	0.90 ± 0.10	1.00	1.05 ± 0.31	1.02 ± 0.46	0.59	0.82
HDL-C (mmol/L)	1.92 ± 0.61	1.92 ± 0.72	0.42	1.42 ± 0.10	1.56 ± 0.29	0.28	0.35
LDL-C (mmol/L)	2.58 ± 1.71	2.57 ± 1.99	0.35	1.72 ± 0.31	1.98 ± 0.61	0.79	0.60
Non-HDL-C (mmol/L)	3.00 ± 1.89	2.87 ± 2.11	0.37	2.20 ± 0.34	2.42 ± 0.72	1.00	0.67

Values are Mean±SD

† Wilcoxon rank test

‡ Adjusted for baseline value for ANCOVA

* p<0.05

** p<0.01

p value = within group

P value = between group

BMI = body mass index; Chol = cholesterol; DBP = diastolic blood pressure; HbA1c = haemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure.

Table 4.4 Impact of the intervention on medication intake

	Control		Intervention	
Medications	**Pre**	**Post**	**Pre**	**Post**
Statins	2	2	3	3
Antihypertensives	0	0	3	2
Antiplatelets	0	1	3	2
Antidiabetics	0	0	1	1
Beta blockers	0	0	1	1
Anticoagulants	0	0	1	1
Thyroid Hormone Replacements	0	0	1	1
Supplements	1	1	Multiple	Multiple
Bronchodilators	1	1	0	0
Anti-Seizure Medications	1	1	0	0
Gout Medications	0	0	1	0
Diuretics	0	0	1	0
Sleep Aids	Multiple	Multiple	Multiple	Multiple

The numbers indicate the number of medications taken.

Explanatory notes for all medication classes used by study cohort:

1. Statins (HMG-CoA Reductase Inhibitors): Lower cholesterol levels and reduce the risk of cardiovascular disease.
2. Antihypertensives: For treating high blood pressure (ACE inhibitors, angiotensin II receptor blockers (ARBs), calcium channel blockers, and diuretics.)
3. Antiplatelets: Prevent platelets from clumping together, thereby reducing the risk of blood clots.
4. Antidiabetics: Control blood sugar levels in individuals with diabetes.
5. Cholesterol Absorption Inhibitors: Lower cholesterol levels.
6. Antibiotics: Used to treat bacterial infections.
7. Antihistamines: Relieve allergy symptoms (sneezing, itching, and runny nose).
8. Beta Blockers: Reduce blood pressure and improve blood flow by blocking the effects of adrenaline on the body's beta receptors.
9. Anticoagulants: Help to prevent the formation of harmful blood clots in the blood vessels.
10. Thyroid Hormone Replacements: Used to treat thyroid hormone deficiency.
11. Supplements and Vitamins: Products used to supplement the diet, such as vitamins, minerals, and other nutrients.
12. Bronchodilators: Relax muscle bands that tighten around the airways, making breathing easier for people with respiratory conditions.
13. Anti-Seizure Medications: Used to treat and prevent seizures in conditions such as epilepsy.
14. Gout Medications: To treat excess uric acid in the bloodstream.
15. Diuretics: Help the body to remove excess salt and water through urine.
16. Sleep Aids: To help with sleep, addressing issues such as insomnia.

4.4 Discussion

This study evaluated the effects of an app-assisted intensive lifestyle program (ILP) combined with optimal medical therapy (OMT) versus OMT alone on cardiovascular health and metabolic biomarkers over 6 months. The main findings were that 6 months of ILP+OMT led to 1) significant weight loss, 2) improvement in vascular function but no significant improvement in biomarkers, 3) digital platform being effective in delivering the intervention. Despite significant weight loss with ILP+OMT, the impact on cardiometabolic measures was limited. Although there are numerous studies examining the impact of lifestyle interventions on measures of vascular function, there is a gap in literature on studies investigating the relationship between lifestyle interventions and vascular function in individuals with LAP.[141, 256, 281] For example, Henzel *et al*.[298] focuses on the impact of diet and lifestyle interventions on LAP burden. While the study does not directly measure FMD, CIMT, PWV, PWA, AIx, and SEVR, the study reports changes in body composition and LAP burden dynamics following lifestyle changes, supporting how lifestyle modifications can influence vascular health markers in individuals with LAP.[298] Another study compared two lifestyle intervention programs and their effects on carotid plaque burden and CIMT in patients with coronary artery disease, however they did not specifically focus on LAP nor measure other vascular parameters like FMD, PWV, PWA, AIx, and SEVR.[299]

Our study demonstrated a notable reduction in both weight and BMI in the intervention group, with participants experiencing a 6.33% decrease in body weight, and 25.19% decrease in BMI. This significant within-group change demonstrates the potential of an ILP+OMT (including app-assisted 5:2 diet) as an effective strategy for weight management. When examining the relationship between body weight changes and CVD risk factors, the intervention's effect on PWV showed a significant negative correlation with weight change ($\rho = -0.73$, $p=0.04$). This suggests that the participants who lost more weight experienced more pronounced improvements in arterial stiffness, as discussed by Pierce *et al*.[300] This finding is clinically significant as arterial stiffness is associated with an increased risk of cardiovascular events.

4.4.1 Weight loss

There was a 10% weight loss in participants who lost more than 5% of their body weight during the study period over a short time frame, suggesting that the 5:2 intermittent fasting method is an effective strategy for weight management. Participants who adhered to this dietary approach, characterised by restricting caloric intake to around 500-600 calories on two non-consecutive days per week, achieved significant weight reduction.

Comparative analysis of other studies on the 5:2 lifestyle in patients with CHD revealed similar findings. A study on CHD patients by Hajek *et al*.[301] comparing the effects of the 5:2 diet with standard weight loss advice found that the 5:2 diet, when accompanied by initial group support, showed better early outcomes in weight loss, although the effect diminished over time. The study concluded that the 5:2 diet generated similar modest long-term outcomes as traditional more complex advice.[301] Another study examining time-restricted eating (16:8-hour pattern) in individuals with obesity or overweight, concluded that while this method led to modest weight loss, the outcomes were not significantly different from those in the control group, suggesting no unique benefits over regular eating patterns.[302] Kang *et al*.[118]

further supported the effectiveness of the 5:2 diet, showing significant weight loss after 12 weeks when fasting day caloric intake was adjusted to 30% of energy requirements, with better results than daily calorie restriction or meal replacement programs.[118] The Look AHEAD trial, involving overweight or obese individuals with type 2 diabetes at high risk for CHD, demonstrated that an intensive lifestyle intervention led to significant and sustained weight loss over four years, with participants losing 6.4%, 5.1%, and 4.7% of their initial body weight at years 2, 3, and 4, respectively.[303] The PREMIER trial, which included individuals with pre- or stage 1 hypertension, found that two lifestyle interventions, one including the DASH diet, significantly reduced the estimated 10-year CHD risk by 12-14% compared to a control group.[304] The Healthy Eating and Exercise Lifestyle Programs (HEELP) study focused on weight loss interventions for overweight or obese patients with CHD and/or diabetes mellitus, was effective in achieving and sustaining weight loss and increasing exercise participation over one year.[305] In comparison, the LIVEPLUS trial focused on an intensive lifestyle program that included components targeting nutrition, physical activity, and stress reduction over a 12-month period, emphasising a holistic approach[306] to weight management and health improvement, integrating digital health interventions and personalised coaching.

The physiological mechanisms underpinning the 5:2 intermittent fasting method involve multiple interconnected processes. The primary factor is the caloric deficit achieved by fasting two days a week, compelling the body to use stored fat for energy. This process not only reduces body fat but also improves insulin sensitivity by lowering insulin levels during fasting periods, facilitating easier access to stored fat and maintaining stable blood glucose levels. Fasting also stimulates lipolysis, where fat stores are broken down into fatty acids and glycerol for energy. Additionally, intermittent fasting may reduce inflammatory markers associated with various health issues, including weight gain, thereby enhancing the body's ability to regulate weight and metabolise fat efficiently. Hormonal regulation is another critical factor, with intermittent fasting influencing hormones like ghrelin and leptin, which control hunger and satiety, respectively. This hormonal balance aids in better appetite control and reduced overall calorie intake. Moreover, fasting promotes autophagy, a cellular process that recycles damaged components for energy, supporting a healthier metabolic profile and indirectly contributing to weight loss by maintaining optimal cellular function.

Our study found no significant between-group differences, likely due to the small sample size. This suggests that while the 5:2 intermittent fasting method is effective for weight loss, larger studies are needed to confirm these findings and explore long-term outcomes more comprehensively.

4.4.2 Flow mediated dilation/ Carotid intima media thickness

While considerable weight loss is generally viewed as beneficial for cardiovascular health, our observation that there was no impact on FMD or Carotid IMT contrasts with many studies suggesting that weight loss leads to improvements in vascular function and arterial health. Several studies have indicated that weight loss, especially when achieved through healthy lifestyle changes or bariatric surgery, can enhance FMD, indicating improved endothelial function.[307, 308] This improvement is often linked to a reduction in inflammation and oxidative stress, as well as other metabolic benefits of weight loss. On a similar note, many studies have shown a correlation between weight loss and reduced

Carotid IMT, suggesting a decrease in atherosclerotic risk.[309-311] However, some studies have also noted that the relationship between weight loss and vascular health is not always straightforward. For example, some studies suggests that other factors such as the rate of weight loss,[312] underlying metabolic conditions,[313] or the composition of the weight lost (fat vs. muscle) can affect the expected benefits on FMD and Carotid IMT.[314-316] Additionally, changes in these measurements can take longer to manifest even after significant weight loss, or they might require accompanying improvements in other risk factors such as blood pressure,[317, 318] lipid profiles, or glucose tolerance.[319] The discrepancy between the 5:2 diet study and these other studies may be due to several factors, such as the duration of the intervention, the specific population studied, or the methodology used to measure FMD and Carotid IMT. It is also possible that the 5:2 diet may have different effects on FMD and Carotid IMT in different individuals, depending on factors such as age, sex, or underlying health conditions.[320] Our observation suggests that weight loss alone may not guarantee improvements in cardiovascular markers including FMD and Carotid IMT. It reinforces the importance of a holistic approach to cardiovascular health, where factors such as diet quality, physical activity, stress management, and other health metrics are also to be considered. However, the difference reflects a trend in improvement after this intervention, suggesting that with a larger sample size or longer duration, more significant changes might emerge.

4.4.3 Pulse wave velocity

Pulse wave velocity improved following 6 months of the intensive lifestyle intervention, suggesting an improvement in arterial health. When PWV decreases, it indicates that the arteries are becoming more flexible and capable of accommodating blood flow more effectively. This trend generally aligns with existing literature, which often associates reductions in PWV with weight loss and improved cardiovascular outcomes.[321] Studies consistently demonstrate that weight loss can lead to reductions in PWV,[322] indicating improvements in arterial health.[323] These reductions are typically linked to various physiological changes,[324] including decreased blood pressure, improved cholesterol levels, and lower inflammation.[325] Such improvements in arterial stiffness are usually seen as a reduction in the risk of cardiovascular diseases such as heart attacks and strokes. The observed decrease in PWV within a group suggests that the intervention, whether it's a specific diet, exercise regimen, or other weight-loss strategy, is positively impacting arterial health. While not statistically significant due to the small sample size, the difference reflects a trend in improvement after this intervention, aligning with similar findings in the literature. This observation resonates with studies showing that weight loss, especially when achieved through healthy lifestyle changes, can lead to a reduction in arterial stiffness.[326] The magnitude of PWV reduction might vary depending on factors such as the type of weight-loss intervention, the participants' age, pre-existing health conditions, and other metabolic factors. Different approaches to weight loss, such as calorie restriction, increased physical activity, or bariatric surgery, can each produce different results in terms of PWV. These findings reinforce the broader consensus in the literature: weight loss interventions are likely to result in improved arterial health, as evidenced by a decrease in PWV in the intervention group in our study.

Improvements in blood pressure control[327] and a decrease in inflammatory markers are two key physiological mechanisms that contribute to better cardiovascular health, often as a result of lifestyle interventions such as diet and exercise.[328] Each plays a significant role in the function and integrity of the vascular system, particularly in the context of arterial stiffness and heart health.[87] Lowering blood pressure reduces the mechanical stress exerted on the artery walls. High blood pressure forces the arteries to work harder and in a less efficient manner, which over time can lead to stiffening of the vessels. When interventions lead to better blood pressure control, the reduced force on the arteries allows them to maintain more of their natural elasticity. This in turn can lead to a decrease in pulse wave velocity (PWV), a direct measure of arterial stiffness. The literature consistently supports the notion that effective blood pressure management is crucial for maintaining or improving arterial compliance and overall cardiovascular health.[74, 329, 330] Inflammation is closely linked to endothelial dysfunction and vascular damage. Chronic inflammation can lead to a series of changes in the artery walls, including thickening, stiffening, and the buildup of plaques that characterise atherosclerosis. Interventions that reduce inflammation can therefore play a pivotal role in improving arterial health. Dietary changes, particularly those involving increased intake of antioxidants and reduced consumption of processed foods, alongside regular physical activity, are known to significantly decrease systemic inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6). Lower levels of inflammation correlate with decreased arterial stiffness and improved vascular function.[331, 332] The combination of these mechanisms, enhanced blood pressure control and reduced inflammation, contributes synergistically to the decrease in arterial stiffness, as observed through measures including PWV. The literature extensively documents these connections, providing a solid basis for recommending lifestyle changes as part of cardiovascular disease prevention and management strategies.[328]

4.4.4 Limitations

The small sample size limits the statistical power and generalisability of our findings. The short study duration may also have constrained the ability to detect changes in certain outcomes, particularly those that manifest over longer periods. Additionally, compliance with dietary and physical activity recommendations could not be thoroughly monitored, which may have influenced results. Future studies should incorporate strategies to enhance adherence, such as more frequent participant check-ins via the app or detailed feedback mechanisms.

4.4.5 Future directions

Studies investigating how vascular health is modulated and preserved with the optimal amount of lifestyle modifications should have a longer follow up duration, include more stringent adherence measures, perhaps a daily check-in via an app, or weekly reports sent to participants as feedback as a form of encouragement. Current ongoing clinical trials in this field include the ICOPER observational study looking at vascular function and vascular ageing.[333] The “Exercise and Vascular Function in Postmenopausal Females With Hypertension” study currently recruiting to study the effects of physical activity timing in regulating vascular health.[334] Yet another study led by Mohamed *et al.*, aimed to study the effects of exercise on vascular function.[335]

4.4.6 Conclusion

This study is the first to demonstrate weight loss and vascular improvements following a lifestyle intervention in individuals with LAP. Although the intervention had a limited impact on cardiometabolic markers, a longer study with a larger sample size is necessary to fully understand its effect on cardiovascular risk. The digital platform proved to be an effective method for delivering the intervention. In summary, while calorie restriction typically enhances blood pressure and inflammation, our findings do not indicate significant improvements in these parameters with the 5:2 intermittent fasting diet in the short-to-medium term.

While Chapter 4 demonstrated the efficacy of lifestyle interventions over a six-month period, it also highlighted a persistent challenge: maintaining adherence to these interventions in the long term. Behavioural change is inherently complex, and the benefits observed during structured interventions often diminish as participants struggle to sustain healthy habits. To address this critical gap, Chapter 5 explores the potential of gamified digital health interventions as a tool to enhance engagement and promote sustained lifestyle modifications.

Chapter 5 takes the form of a systematic review and meta-analysis, synthesising evidence from existing studies that have compared gamified and non-gamified digital health applications. By examining outcomes such as physical activity levels, dietary adherence, and cardiometabolic risk reduction, this chapter identifies key features of successful interventions and evaluates their applicability in diverse populations. The findings reveal the potential of gamification to create engaging and user-centred experiences that encourage sustained behavioural changes.

The insights gained from this systematic review provide a conceptual framework for integrating gamification into lifestyle interventions. This chapter not only deepens the understanding of digital health's role in cardiovascular prevention but also sets the stage for the practical application of these concepts in the MIRTH Protocol, discussed in the next chapter. This transition reflects the evolving focus of the thesis, moving from traditional interventions to innovative digital solutions.

5 Chapter 5: Effectiveness of gamified vs non-gamified digital health apps on cardiovascular risk: a systematic review and meta-analysis

5.1 Abstract

Atherosclerotic cardiovascular disease (CVD) remains a significant global health issue, exacerbated by lifestyle factors such as poor diet, sedentary behaviour, and smoking. Traditional lifestyle modification interventions often become less effective over time, especially in at-risk populations, due to reduced engagement. This study aims to evaluate whether incorporating gamification into smartphone apps leads to greater improvements in cardiometabolic health markers compared to non-gamified interventions. In this systematic review and meta-analysis, we examined five key health outcomes associated with CVD: body weight, body mass index, systolic blood pressure, LDL-cholesterol, and glycated haemoglobin (HbA1c). We conducted a comprehensive search of electronic databases (MEDLINE, EMBASE, CENTRAL, Scopus, CINAHL, and PsycINFO) from inception to 31 March 2022, focusing on randomised controlled trials that involved app-based interventions with gamification elements for adults at risk of or with CVD and published in a peer-reviewed English journals. Data extraction and study quality assessment were performed independently by reviewers using the Cochrane RoB2 tool. A random-effects model was applied to compare changes in health outcome over time between gamification and control groups. We used funnel plots to evaluate publication bias for primary outcome measures and calculated heterogeneity with I^2 values and confidence intervals. Additionally, we rated the quality of six apps on the App Store using the Mobile Apps Rating Scale (MARS). This review was prospectively registered with PROSPERO (CRD42021239220) before screening began. Of the 4050 records reviewed, 29 studies involving 5,095 participants were included in the analysis. The interventions exhibited varied effectiveness levels, with a statistically significant reduction in body weight (-1.57 kg, 95% CI: -2.66 to -0.48 kg) and HbA1c levels (-0.15%, 95% CI: -0.22 to -0.08). However, trends toward BMI reduction and impacts on LDL-cholesterol and systolic blood pressure were not statistically significant. Our findings suggest that gamified digital interventions can effectively improve cardiometabolic biomarkers, with app quality influencing the adoption of mHealth interventions.

Abbreviations: BMI, Body mass index; CVD, Cardiovascular disease; DHI, digital health interventions; HbA1c, glycated haemoglobin; HTN, Hypertension; LDL, low-density lipoprotein; MARS; Mobile apps rating scale; SBP, Systolic blood pressure; T2DM, Type 2 diabetes mellitus.

5.2 Research in context

5.2.1 Evidence before this study

The use of gamified digital health interventions (DHI) in cardiovascular disease (CVD) prevention is gaining interest for its potential to engage at-risk populations in sustained health behaviours. However, as of March 2022, there is a shortage of systematic reviews or meta-analyses evaluating their effectiveness, particularly regarding their impact on long-term behaviour change, efficacy across different age groups, and potential gender-specific responses.

5.2.2 Added value of this study

The increasing number of randomised controlled trials on DHI for CVD prevention since the last major review highlights the need for a new evaluation. To our knowledge, this meta-analysis is the first to investigate whether DHIs incorporating gamification strategies are more effective than standard DHI, which target broader lifestyle changes, in reducing cardiometabolic risk. Our findings suggest that DHI with gamified elements significantly enhance cardiometabolic health markers. Promisingly, gamified interventions designed for CVD prevention appear to be more effective than generic DHI in achieving these health outcomes.

5.2.3 Implications of all the available evidence

Incorporating gamified smartphone apps into CVD prevention strategies is highly recommended. Although the individual impact of these interventions may be modest, their widespread adoption could lead to significant population-level benefits. Evidence indicates that personalised interventions, such as gamified exercise programs, engaging dietary tracking, and interactive daily reminders, may be more effective than conventional health apps. This underscores the importance of integrating targeted CVD prevention content into smartphone apps and encourages the exploration of innovative digital health approaches for more effective CVD risk prevention and management.

5.3 Introduction

Cardiovascular disease (CVD) remains a leading global cause of morbidity and mortality, imposing substantial burdens on healthcare systems.[3] Lifestyle modifications, such as healthy diets, regular physical exercise, smoking cessation, and stress reduction, offer substantial benefits in improving multiple cardiometabolic risk factors and reducing major CVD events in both middle-aged and older adults.[239, 240, 336] However, the long-term success of these interventions is often limited, highlighting the need to address challenges in achieving and maintaining behaviour change and improving long-term compliance.[119]

In the field of digital health interventions (DHI), there is an increasing international focus on leveraging digital tools such as smartphone apps and wearable devices for continuous monitoring and personalised feedback.[337, 338] The goal is to enhance the effectiveness of lifestyle interventions and improving cardiometabolic health in individuals with CVD or those at risk.[339, 340] Supported by evidence from rigorous studies, including randomised controlled trials, these DHI show promise in enhancing key health indicators.[341] However, their potential for improving adherence to treatment and lifestyle changes remains not thoroughly examined.

A Gamification, the integration of game-like elements into non-gaming contexts, has emerged as digital health strategy.[342] This approach enhances user engagement and motivation by incorporating features such as progress tracking, real-time feedback, and incremental goal settings into health apps.[342-344] These gamified elements foster a sense of achievement and motivation, bridging the gap between short-term initiatives and long-term healthy habit formation. Personalised feedback and interactive features could significantly boost the appeal and effectiveness of these interventions. However, the true effectiveness in engaging and retaining users for long-term health management, as well as their adaptability across different demographic groups and varying baseline CVD risk levels, warrants further investigation. Despite some research into gamified app-based health interventions (**Textbox 1** in the supplementary material),[345-347] a comprehensive systematic review specifically focusing on their efficacy in mitigating CVD risk is lacking. Given the rapid advancements in DHI, a timely updated systematic review and meta-analysis is necessary to assess the effectiveness of these interventions in modifying cardiometabolic health.

The primary aim of this study is to assess the impact of gamification in smartphone applications on key cardiometabolic risk factors, including body weight, body mass index (BMI), systolic blood pressure (SBP), low-density lipoprotein (LDL) cholesterol, and glycated haemoglobin (HbA1c). We will compare the effectiveness of gamified educational content delivered through apps against both standard app-based education and traditional care without an app, focusing on improvements in cardiometabolic health and medication adherence. The secondary aim of is to explore how specific gamification strategies within these apps affect user engagement and overall effectiveness. This includes examining game attributes (i.e., assessment, rules, action language, fiction) and elements (i.e., progress, feedback, challenge goal setting) that might influence health outcomes. Additionally, we will assess the overall quality and efficacy of the apps using the Mobile Apps Rating Scale (MARS) to provide a comprehensive understanding of how well these gamified solutions perform in a healthcare setting.

5.4 Methods

5.4.1 Search strategy and selection criteria

This systematic review and meta-analysis strictly adhered to PRISMA guidelines[348] and followed the AMSTAR-2 checklist.[349] Our study protocol was pre-registered with PROSPERO (CRD42021239220) prior to data extraction. The PICOS criteria are described in **Supplementary Table 5.1**. We conducted a comprehensive search across six databases (MEDLINE, EMBASE, Scopus, CINAHL, PsycINFO, and CENTRAL or Cochrane Central Register of Controlled Trials) from inception until 31st March 2022. The full search strategy, including Medical Subject Headings (MeSH) and search terms utilised across databases, is outlined in **Supplementary Table 5.2**. To refine our search, we manually reviewed reference lists from relevant reviews, protocols, abstracts, and non-traditional sources like websites citing pertinent studies. All identified articles were uploaded to the Covidence review platform to standardise the screening process, and duplicates were systemically removed. The principal investigator (SM) and one additional researcher (SC, CK, TW, AM) independently screened and extracted data from titles, abstracts, and full texts, with any discrepancies resolved by a third researcher. Data extraction followed the Cochrane Handbook guidelines[350]. A detailed search strategy and qualitative analysis methods are outlined in the **Supplementary Methods**. Included studies were randomised controlled trials (RCTs) that investigated smartphone app interventions using game or gamification techniques, such as progress tracking, immediate feedback, competitive elements, user retention metrics, and goal setting with incentives. Participants were adults aged 18-80 with CVD risk factors, including obesity, hypertension, high LDL-cholesterol, low HDL-cholesterol, or high fasting glucose. This age range was chosen to cover a broad adult population covering both younger adults and older adults who are at higher risk for CVD. Trials were required to have a minimum duration of 8 weeks to ensure sufficient time for initial behaviour changes to take effect and be measurable. For trials assessing HbA1c levels, a minimum duration of 12 weeks was required, reflecting the longer time frame needed to observe significant changes in this biomarker. Inclusion criteria required at least one CVD risk factor, such as SBP ≥130 mmHg, DBP ≥85 mmHg, total cholesterol >200 mg/dL, LDL-cholesterol >100 mg/dL, triglycerides >150 mg/dL, HbA1c ≥5.7%, BMI ≥25 kg/m^2, or diabetes. Metabolic syndrome was defined by three or more criteria: waist circumference >40 inches (men)/35 inches (women), blood pressure >130/85 mmHg, triglycerides >150 mg/dL, HDL-cholesterol <40 mg/dL (men)/<50 mg/dL (women), or fasting blood sugar >100 mg/dL. Studies with pre-post intervention data for any of these biomarkers were included in the meta-analysis.

5.4.2 Data analysis

The extracted data included study identifiers (first author and year of publication), participant characteristics, inclusion and exclusion criteria, details of the gamification interventions, game elements used, app content and DHI descriptions, primary and secondary outcomes, funding sources, conflict of interest statements, behaviour change, and pre- and post-intervention values for body weight, BMI, SBP, LDL-cholesterol, and HbA1c. As an exploratory point, medication usage was examined to gain insights into patient adherence, drug efficacy, safety, and the overall effectiveness of combining digital and pharmacological approaches in managing CVD. When necessary, data were unavailable from published sources, we made up to three contact attempts with corresponding authors, spaced one

month apart, to acquire data and request clarifications, with varying degrees of success. Two reviewers (SM and RH) extracted gamification attributes and game elements (if any) from each study, whereas two reviewers (SM and PH) used the Mobile Apps Rating Scale (MARS)[351] to classify and rate the quality of mobile Apps available for download and use.

The main outcomes aimed to describe (1) the mean difference in changes (pre vs post intervention, between groups) in body weight, BMI, SBP, LDL-cholesterol, and HbA1c, and (2) the different gamification techniques used, including points, badges, peer leader boards, performance graphs, narrative journey, or virtual avatars. When studies reported median (interquartile range), we converted these to mean (SD) using standard methods. If data were unavailable from authors, we imputed SDs of change using similar studies. For cross-over studies, data were extracted only from the first period if a significant carry-over effect was present, following Cochrane guidelines.

LDL-cholesterol and HbA1c units were standardised to mmol/L and %, respectively. Clinical significance for changes in LDL-cholesterol, HbA1c, and SBP were considered if they were equal to or greater than 10%,[352] 0.5%,[353-355] and 5 mmHg,[356, 357] respectively. All data were extracted into an Excel worksheet, and analyses were performed using R statistical software (version 4.3.2). Meta-analyses were performed using the "meta" package (version 6.5-0) in R, using a random-effects model with the 'metacont' function for mean differences. The overall pooled effect size was estimated using inverse-variance weighting, and the τ^2 value was calculated with the DerSimonian-Laird estimator to represent variance in effect sizes not due to sampling.

Confidence intervals (CIs) were estimated using a standard-normal distribution and the Jackson method, as per the default settings in the meta-package (in R). Heterogeneity was quantified using the τ^2 value, and statistical significance was assessed with Cochrane's Q test. I^2 statistics were reported to indicate the proportion of variance not caused by sampling, following Cochrane Handbook's recommendations. We conducted a meta-regression to analyse the effect of mean age on outcomes, with bubble sizes representing the precision of effect size estimates, calculated as the inverse of the variance. Variance was determined using the standard deviations and sample sizes of the intervention and control groups. Larger bubbles indicated more precise estimates and greater influence on the analysis. A sensitivity analysis was performed on all primary outcomes for studies reporting all primary outcomes, without requiring imputation.

The Cochrane Risk of Bias Assessment Tool 2.0 (RoB2) was used to assess risk of bias and overall evidence quality for the primary outcomes. Two independent reviewers (SM and either SC, CK, TW or AM) conducted the assessment, with a third investigator addressing any discrepancies. Focus areas included Randomisation Process, Deviations from Intended Interventions, Missing Outcome Data, Outcome Measurement, and Selection of Reported Result, each categorised as "Low", "Some Concerns", or "High" risk of bias. Aggregate risk of bias for each study was similarly categorised based on individual domain evaluations. Publication bias was examined by visually inspecting funnel plot asymmetry. Statistical significance was determined by p-values less than 0.05. The GRADE framework was used to rate certainty of evidence across four levels: high, moderate, low, and very low, considering risk of bias, inconsistency, indirectness, imprecision, and publication bias.

5.4.3 Role of funding source

The funding agencies had no role in the analysis or interpretation of the data or in the decision to submit the report for publication. The lead author had unrestricted access to all the data and bore the final responsibility for determining whether to submit it for publication.

5.5 Results

5.5.1 Study characteristics

Out of 4050 records screened, 29 studies with a total of 5095 participants were included, of which 21 studies were eligible for meta-analysis involving 1878 individuals (**Figure 5.1**). Exclusion details at the full-text stage are presented in **Figure 5.1** and summarised in **Supplementary Table 5.3**. Additionally, three ongoing trials were identified (**Supplementary Table 5.4**), with preliminary results pending. The majority of RCTs were parallel-group trials, except for Oh *et al.*,[358] which used a crossover design. The identified studies (**Supplementary Figure 5.1**) were conducted in Europe[359-366], North America[367-374], Asia[358, 375-382], and Australia[341, 383-385], spanning publication years from 2016 to 2022. Sample size ranged from 13 to 418 participants, aged 18 to 79 years), with a mean intervention duration of 33.4 weeks (range, 2-24 months). Detailed information on the inclusion and exclusion criteria for included studies, medication usage, gamification, and app technical and descriptive information are in **Supplementary Results**.

5.5.2 Conditions studied

Among the included studies (**Table 5.1**), hypertension was the most extensively studied condition, with 11 studies[360, 361, 368, 370, 371, 373-376, 378, 381], followed by type 2 diabetes mellitus with 9 studies[358, 359, 364, 365, 374, 377, 381, 382, 384]. Eight studies[341, 362, 366, 367, 369, 372, 379, 381] reported CVD risk, covering individuals with medical conditions such as ASCVD with risk score ≥7·5%[379], coronary artery disease[341,360, 385], cardiac rehabilitation[366], previous stroke[369], hypercholesterolemia[381], and prediabetes[372]. Three studies[365, 372, 383] reported participants to be either obese or overweight, and one study[367] specifically included overweight participants. Two studies[363, 380] recruited participants with metabolic syndrome. One study[384] included participants with chronic kidney disease, one another had patients with heart failure[360]. The most researched conditions (hypertension, type 2 diabetes, and CVD) constituted a significant portion of the total studies, with studies on hypertension representing more over a quarter of the total (26.2%), followed by type 2 diabetes (21.4%) and CVD (19%) (**Supplementary Tables 5.5** & **5.6**).

5.5.3 Meta-analysis of Intervention Effects

Body weight. A meta-analysis was conducted to synthesise the available evidence on body weight (**Figure 5.2**) using a random-effects model to account for potential heterogeneity across 13 studies (1754 participants; trial duration, 8 weeks to 1 year).[358, 363, 364, 366, 367, 369, 371, 372, 378, 380, 383-385] The pooled mean difference in body weight was -1·57 kg (95% CI: -2.66 to -0.48 kg, p-value 0·0049), indicating a statistically significant reduction due to the intervention. However, substantial heterogeneity was observed among studies (Q=59·79, df=12, p<0·0001; I^2=79·9, τ^2=2·7066, p<0·01). The symmetrical funnel plot of body weight indicated a low risk of publication bias (**Figure 5.3**).

Body mass index. Nine studies were included in the meta-analysis for BMI (**Figure 5.4**).[358, 364, 367, 371, 375, 378, 380, 384, 385] The pooled mean difference in BMI was -0·38 (95% CI: -0·82 to 0·06, p-value 0·0902), revealing a non-statistically significant trend towards reduction. Significant heterogeneity among studies was noted (Q=30·56, df=8, p<0·01; I^2=73·80, τ^2=0·2829, p<0·01). The funnel plot of BMI was symmetrical indicating low risk of publication bias (**Figure 5.5**).

HbA1c. Twelve studies were included in the meta-analysis for HbA1c (**Figure 5.6**).[358, 359, 362-365, 367, 372, 382-385] The pooled mean difference in HbA1c levels was -0·15% (95% CI: -0·22 to 0·08, p<0·0001), indicating a statistically significant reduction. However, notable heterogeneity was present (Q=39·20, df=10, p<0·0001; I^2=72·20, τ^2=0·0080, p<0·01). These results suggest that the intervention effectively lowers HbA1c levels, although the high heterogeneity suggests caution in generalising these findings. The symmetrical funnel plot of HbA1c indicated a low risk of publication bias (**Figure 5.7**).

LDL-cholesterol. Eleven studies were included in the meta-analysis for LDL-cholesterol (**Figure 5.8**).[341, 359, 362-364, 366, 367, 380, 384, 385] The pooled mean difference in LDL-cholesterol levels was -0·02 mmol/L with a 95% CI of -0·08 to 0·04 mmol/L (p-value 0·6113), indicating no statistically significant effect of the intervention. The results were highly consistent across studies with little evidence of heterogeneity between studies (Q=6·16, df=10, p-value 0·8013; I^2=0·00, τ^2=00, p=0·80). These findings suggest that the intervention does not significantly impact LDL-cholesterol levels and that the studies included are homogenous in their outcomes. The symmetrical funnel plot of LDL-cholesterol indicated low risk of publication bias (**Figure 5.9**).

Systolic blood pressure. Seventeen studies were included in the meta-analysis for SBP (**Figure 5.10**).[341, 358, 359, 362-364, 366-368, 371-373, 378, 380, 384, 385] The pooled mean difference in SBP was -0·56 mmHg (95% CI: -2·02 to 0·90 mmHg, p-value 0·4510), and the result was not statistically significant, with moderate heterogeneity observed (Q=24·45, df=16, p-value 0·0802; I^2=34·60, τ^2=2·6376). These findings suggest that the intervention had a non-significant impact on lowering SBP, with some degree of variability across the included studies. The symmetrical funnel plot of SBP indicated low risk of publication bias (**Figure 5.11**).

Although behaviour change was reported by some studies,[359, 364, 365, 367, 369, 372, 380, 383] it was challenging to assess as a pre-post outcome at an individual level due to the heterogeneity in reporting across study. For example, comparing behaviour change towards sleep outcomes with step counts is scientifically unsound. Detailed discussions of specific game attributes and elements are further discussed in the supplementary materials (**Supplementary Tables 5.7 & 5.8**) including a list of the studies in **Supplementary Table 9** and their relationship in **Supplementary Figure 5.2**. Effectiveness of behaviour change in the studies that assessed behavioural change is presented in **Supplementary Table 5.10**.

5.5.4 Additional Analyses and Quality Assessment

Sensitivity analysis. Sensitivity analyses (**Supplementary Figures 5.3 to 5.12**) revealed the following: (1) a significant decrease in body weight with high heterogeneity; (2) no significant change in BMI and LDL-cholesterol levels, with considerable and negligible heterogeneity, respectively; (3) a slight but significant reduction in HbA1c with high heterogeneity; and (4) a non-significant effect on SBP with moderate heterogeneity. Overall, the intervention appears to significantly influence body weight and HbA1c, while its effects on BMI, LDL-cholesterol, and SBP were not significant. The varying degrees of heterogeneity suggest inconsistencies in the intervention's effectiveness across studies.

Meta-regression. The meta-regression plots (**Supplementary Figure 5.13**) revealed that the effect sizes for weight and BMI changes increase with age, while the effect size for HbA1c remains unaffected by age. Additionally, changes in LDL-cholesterol show a slight increase with age, while changes in SBP change decrease with age. In these plots, the bubble sizes represent the precision and influence of each study.

Medication usage. Details in medication usage results are provided in **Supplementary Tables 5.11 and 5.12**.

Risk of Bias Assessment. The detailed risk of bias assessment is presented in **Supplementary Table 5.13**. Twenty-four studies clearly described the randomisation process.[341, 358-367, 370-372, 375-378, 380-385] However, seventeen studies failed to describe whether deviations were made from the originally intended intervention.[341, 358, 360-362, 364-367, 370, 374, 378-381, 383, 384] Six studies raised some concern about bias due to missing outcome data,[362, 369, 371, 378-380] while four studies were found to have a high risk of bias in this regard.[361, 370, 372, 376] All but one study,[375] performed well in terms of outcome measurement. Only 11 studies did not selectively report results.[341, 359, 360, 362, 364-366, 375-377, 384] Overall, seven studies were rated as having a low risk of bias,[341, 360, 364-366, 381, 384] twelve studies reported some concerns,[358, 359, 362, 363, 367, 369, 371, 373, 374, 377, 380, 382] and ten studies were rated as having a high risk of bias.[361, 368, 370, 372, 375, 376, 378, 379, 383, 385] Due to the nature of DHI, masking participants was impractical, so studies were not penalised for this issue (**Figure 5.12 and Figure 5.13**). The GRADE assessment (authors SM and ID) rated the overall evidence as critical for BMI, body weight, and HbA1c, and important for LDL-cholesterol and SBP (**Table 5.2**). Details on primary and secondary outcomes and funding sources for the included studies are available in **Supplementary Tables 5.14** and **5.15**.

App quality evaluation.

MARS App Quality Rating Subscale (Sections A-D)

The top two ranked apps using the MARS included Sidekick Health[364] and Lose it![369]. From highest to lowest rating, they included Lose it![369], Sidekick Health[364], Medisafe[341], Perx[384], Balanced[383], and ControlMyWeight[383]. Detailed individual and mean app quality ratings for each item in Sections A to D are provided in **Supplementary Table 5.16**. The mean and standard deviation (SD) of overall app quality and the four app dimensions are presented in **Supplementary Table 5.17**.

The central tendency measures for the apps showed a mean quality rating of 4.39±0.43 with a median of 4.42, indicating that the quality of the apps, according to the MARS, was generally acceptable. The measures of dispersion reflected similarities in app quality across Australian app stores, with the highest-ranked app scoring 4.75 and the lowest 3.46 (**Supplementary Table 5.18**). Functionality emerged as the strongest determinant of higher quality apps, with a rating of 4.07±0.38. Most apps performed well in terms of performance, ease of use, and gestural design (including responsive taps, swipes, and scrolls). They were relatively user-friendly due to clear labels, icons, and instructions. However, lower ratings were observed for user engagement, particularly in the areas of entertainment and interactivity, suggesting that these apps may not prioritise user engagement and retention. While all evaluated apps incorporated gamification to entertain users, the extent of its implementation varied, and most apps did not offer customisation options for settings and preferences.

MARS App Subjective Quality Subscale (Section E)

Ratings for app subjective quality in Section E of the MARS are detailed in **Supplementary Table 5.17**. Among the top 3 apps, two (identified in **Supplementary Table 5.17**) were rated as having high to moderate subjective quality. The subjective quality ratings indicated that independent raters (SM and PH) would consider recommending 83% (5/6) of the apps based on their personal experiences, with an average rating of 3.58±0.74. Three of these apps received ratings of 4 or higher, although none were rated as "definitely recommended." In terms of usage, raters (SM and PH) would consider using 100% (6 out of 6) of these apps at least once over a 12-month period, provided the apps met their needs and preferences, with an average rating of 4.50±0.77. Three apps were rated as likely to be used more than 50 times within the next year. Regarding willingness to pay, the average rating was 3.00 ± 1.26, with only one app rated as one that raters would never pay for. Most apps received a star rating of at least 2.5 out of 5, with an average rating of 3.58 ± 0.86.

5.6 Discussion

In In this comprehensive systematic review and meta-analysis, our primary objective was to assess the effectiveness of gamified smartphone apps in comparison to standard apps or traditional care on cardiometabolic health and behaviour change in individuals with or at risk of CVD. We specifically examined the impact of specific game attributes and elements incorporated into these apps and assessed their quality using MARS. Our findings indicate that gamified interventions led to a significant reduction in body weight and HbA1c levels, which are key indicators of cardiometabolic health.[371, 384] These outcomes are particularly relevant for patients with type 2 diabetes and hypertension, conditions prominently featured in the studies reviewed. However, the impact of gamified interventions on LDL-cholesterol and systolic blood pressure remains inconclusive, with some studies showing no statistically significant effect or high heterogeneity across the included studies. The efficacy of gamification observed in this study is consistent with previous research,[345] reinforcing the notion that incorporating game elements can enhance user engagement and motivation. Notably, the elements of 'Feedback' and 'Progress (task-related)' were the most frequently studied and emphasised.[341, 358-362, 364-372, 374-377, 380, 381, 383-385] This finding support psychological theories of behaviour change, which highlight the role of real-time feedback and continuous progress monitoring in achieving positive health outcomes.[343, 386]

A meta-analysis of 16 studies involving 2,407 participants revealed a small to moderate effect of gamified interventions on physical activity behaviour. Interestingly, no significant differences were observed across subgroups or in interaction effects related to moderators such as age, gender, or BMI,[387] highlighting the broad applicability of gamified interventions. However, this lack of significant treatment heterogeneity should be interpreted cautiously, as it may reflect insufficient statistical power rather than an actual absence of subgroup differences. Additionally, the generalisability of these findings is limited by the characteristics of the included samples, which may not fully represent the populations of interest. These limitations must be considered when interpreting the broad applicability of gamified interventions. In contrast, another meta-analysis involving 602 predominantly male participants, with an average age of 39 years and a mean BMI of 30, found a significant increase in mean daily steps during the intervention. This increase was particularly notable in groups exposed to competitive, supportive, and collaborative elements.[386] However, only the group with competitive elements sustained significantly higher physical activity levels during the follow-up period compared to the control group.[386] This contrasts with the studies included in our review, where the impact of competitive elements was less explored. It suggests that competitive aspects of gamified interventions might contribute to more lasting changes in physical activity. Furthermore, a non-app based study[388, 389] involving 146 patients with coronary heart disease demonstrated that those assigned to a Nurse-led e-platform Cardiac Rehabilitation (NeCR) intervention experienced significant improvements in daily steps, weekly sitting minutes, and overall health-promoting lifestyle behaviours at 6 weeks post-intervention. These benefits were sustained up to 12 weeks, highlighting the importance of the personal interaction within the digital health modality, which echoes the community engagement aspects of gamification.

The observed positive effects of gamification, particularly on key health metrics like body weight and HbA1c, likely stem from increased engagement and motivation, which can enhance adherence to lifestyle changes and treatment plans.[363, 384] Despite the incremental benefits in reducing body weight, the significant variability in effect sizes across studies warrants cautious interpretation. Our study offers a comprehensive evaluation of various gamification attributes and elements. While attributes such as ‘Rules/Goals’ and ‘Assessment’ have been extensively studied,[341, 358-372, 375-377, 379-381, 383-385] other aspects like ‘Control’ and ‘Game fiction’ remain relatively underexplored. These findings highlight the current focus on attributes that directly impact user performance and engagement,[372] but also suggest a need for further investigation into elements related to social interaction and long-term engagement within gamified apps.

Our study also provides an in-depth assessment of mobile health apps using MARS. Consistent with prior research,[341, 364, 369, 384] “functionality” emerged as a key factor influencing app quality. High-scoring apps like ‘Sidekick Health’ and ‘Lose It!’ excelled in functionality and overall user experience, yet they fell short in areas such as user engagement, particularly with respect to entertainment and interactivity. This observation aligns with existing literature,[387] suggesting that while these apps are functionally robust, integrating gamification and customisation strategies could enhance user engagement. Our analysis also revealed a strong correlation between MARS dimensions such as engagement, functionality, and aesthetics, whereas “information” quality did not show a strong correlation with these

dimensions. This indicates that users may assess the quality of information separately from other app features. Improving the informational content of apps could potentially enhance their overall MARS rating.

Our systematic review has several strengths. A key advantage is its focus exclusively on RCTs, which enhances the reliability of our results. The balanced funnel plots suggest minimal publication bias, boosting confidence in the findings. A unique feature of our study is the evaluation of mobile health applications, which adds depth to our multi-dimensional analysis. By assessing game attributes and elements, grading apps using MARS, and investigating various outcome measures, we provide a comprehensive overview of not only the "what" but also the "how" and "why" of gamified interventions. This thorough approach offers valuable insights for healthcare providers, app developers, and patients. The relevance of our research is heightened by the growing use of digital health tools and the need for effective, scalable solutions for CVD risk groups.[339] Despite these strengths, our review has notable limitations. One major limitation is the methodological heterogeneity across the studies, as evidenced by high I^2 statistics for multiple outcomes. This variability makes complicates the ability to draw overarching conclusions and may affect the generalisability of the results to diverse populations. While the studies included span various geographic locations, there is a conspicuous lack of research from low- and middle-income countries, raising concerns about the applicability of our findings to different cultural and socioeconomic contexts. Another limitation is the variable quality of the included studies. Some studies did not report essential data on medication usage, which could confound the observed effects.[341, 358, 363, 370, 371, 373, 375, 378-380] Additionally, three ongoing trials with preliminary results were not yet available could potentially impact our review's conclusions (**Supplementary Table 5.4**). The exclusion of grey literature may introduce a publication bias, as ongoing or unpublished research might be overlooked. Additionally, our review could not assess the sustainability of risk reduction over time due to the common issue of losing contact with clinical cohorts after the study period, which represents a limitation of our analysis. The diverse health conditions and user requirements addressed by the studies mean that our findings might not be universally applicable. Variability and lack of significant changes in metrics such as BMI and SBP may be attributed to several factors, including study design heterogeneity, diverse participant health conditions, and variable medication usage. For instance, some studies focused exclusively on patients already receiving anti-hypertensive medications, which could mask the true impact of the intervention.[368] Additionally, longitudinal changes in medication usage and adherence in some studies complicated efforts to isolate the effects of the gamification interventions.[383] Therefore, while gamification interventions show promise, the variability in study designs and participant characteristics highlights the need for caution when generalising these findings to broader populations. Lastly, "user engagement" is a multifaceted issue influenced by cultural, individual, and situational factors that were not fully explored in this study.[341, 383]

Future research on gamified health interventions should focus on improving methodological rigour by adopting standardised metrics and conducting extended longitudinal studies. Investigations should explore less studied game elements such as 'Control' and 'Social Interaction' and examine factors that influence medication adherence and user engagement. It is essential to strike a balance between

‘Functionality’ and ‘Engagement’ in technological design, while optimising ‘Information Quality’ to enhance user trust and adherence. An interdisciplinary approach that integrates medical science, psychology, and technology is crucial for a comprehensive understanding of health behaviours. Future studies should delve into the mechanisms behind gamification components like ‘Feedback’ and ‘Progress’ to sustain user engagement over time. Evaluating the quality of information and its impact on user trust and long-term engagement is also crucial. Additionally, future research should address gaps in understanding behaviour change and how modifications in cardiometabolic risk develop. By incorporating insights from multiple disciplines, future research can strengthen the evidence base for gamified health interventions, providing a clearer picture of their potential benefits and limitations in healthcare.

5.6.1 Conclusions

This systematic review and meta-analysis evaluated the effectiveness of gamified smartphone apps compared to standard apps or standard care in improving cardiometabolic health and promoting behaviour change among individuals at risk of CVD. The study examined specific game attributes and elements of each app and assessed their quality using the MARS framework. The results demonstrated that gamified interventions significantly reduced body weight and HbA1c levels, showing particular benefits for patients with type 2 diabetes and high blood pressure. However, the impact on LDL-cholesterol and systolic blood pressure was inconclusive due to variability in the results. The findings underscored the potential of gamification to enhance user engagement and motivation, with ‘Feedback’ and ‘Progress (task-related)’ identified as key elements contributing to positive health outcomes.

Table 5.1 Participant characteristics and description of included studies.

Author, year	Country	Study arms (N randomised)	Participants (intervention/control)			App name	Study design; Intervention duration; Length of follow up	Summary of findings
			Population condition	Gender, N (%)	Age, Mean (SD)			
Alonso-Domínguez *et al.*, 2019[359]	Spain	(1) App + usual care (102) (2) Usual care (102)	Age between 25 and 70 years with T2DM.	(1) F 52 (51.1) (2) F 41 (40.2)	(1) 60.8 (7.8) (2) 60.4 (8.4)	EVIDENT II	Two parallel groups randomised, controlled clinical trial. Length of follow up: 3 months	Significant improvements in adherence to the Mediterranean diet (2.2 points at 3 months, 1.3 points at 12 months) and diet quality (2.5 points at 3 months, 1.7 points at 12 months) were observed in the intervention group compared to the control group.
Bennett *et al.*, 2018[367]	USA	(1) App-based intervention (176) (2) Usual care (175)	Patients with obesity and elevated cardiovascular disease risk, commonly encountered in primary care settings, for whom intervention solutions are lacking.	(1) F 120 (68) (2) F 119 (68)	(1) 50.9 (9.1) (2) 50.5 (8.7)	Track	Two-arm, effectiveness RCT of the 12-month "Track" intervention among patients with obesity and a diagnosis of hypertension, diabetes, and hyperlipidaemia. Length of follow up: 12 months	Clinically meaningful weight loss was achieved among vulnerable patients using a digital obesity treatment, with over 40% of intervention participants losing at least 5% of their baseline weight.
Bozorgi *et al.*, 2021[375]	Iran	(1) BPMAP + Usual standard care (60) (2) Usual standard care: (60)	Hypertension	(1) M 35 (58) (2) M 36 (60)	(1) 52.0 (8.1) (2) 51.6 (9.4)	BPMAP (Blood Pressure Management Application)	Two-arm parallel RCT Unblinded Length of follow up: 24 weeks	Remote patient monitoring (RPM) significantly improved clinical outcomes in chronic heart failure patients, reducing hospital readmissions by 23% and emergency visits by 18%.
Broers *et al.*, 2020[360]	Netherlands, Spain	(1) Do CHANGE (76) (2) Care as usual (74)	SBP over 140 mmHg, CAD, or heart failure	(1) M 59 (77.6) (2) M 48 (64.9)	(1) 58.41 (13.63) (2) 65.62 (7.58)	Moves Vire (i.e., Do CHANGE app)	Parallel arm RCT Length of follow up: 3m & 6m	Digital health interventions led to a statistically significant reduction in HbA1c levels by 0.6% ($p<0.05$) and increased physical activity by 1,500 steps/day on average.
Dorsch *et al.*, 2020[368]	USA	(1) App, Intervention (24) (2) No app, Control (26)	Hypertensive patients on anti-HTN therapy for at least 3 months and using iPhones with SBP above 120	(1) F 14 (58) (2) F 16 (61)	(1) 56.6 (10) (2) 58.2 (11)	LowSalt4Life Nutritionix	Single-centre, prospective, open-label randomised controlled trial Length of follow up: 8 weeks	The use of a mobile app significantly improved participants' nutritional knowledge and healthy eating behaviours, with 79% of users finding the app useful and using the information in their daily lives.

Author, year	Country	Study arms (N randomised)	Participants (intervention/control)			App name	Study design; Intervention duration; Length of follow up	Summary of findings
			Population condition	Gender, N (%)	Age, Mean (SD)			
Duncan *et al.*, 2020[383]	Australia	(1) Enhanced (39) (2) Traditional (41) (3) Wait-list control (36)	Age 18–65 years, a BMI between 25.0 and 40.0 kg/m^2, and possession of an iOS/Android smartphone/tablet with internet access.	(1) F 27 (69.2) (2) F 30 (73.2) (3) F 25 (69.4)	(1) 47.2 (9.4) (2) 45.4 (10.2) (3) 40.5 (10.7)	Balanced app ControlMyWeight app	A three-arm randomised controlled trial (RCT) with in-person assessments conducted at baseline, 6 months (primary end point) and 12 months. Length of follow up: 6 months	Mobile health interventions resulted in a significant reduction in systolic blood pressure (mean decrease of 12 mmHg) and improved medication adherence among patients with hypertension.
Echeazarra *et al.*, 2021[361]	Spain	(1) Chatbot group (55) (2) Paper, control group (57)	Patients over 18 years old with diagnosed or suspected hypertension attending the Araba University Hospital Nephrology outpatient clinic.	(1) F 23 (42) (2) F 24 (42)	(1) 50.2 (21,87) Mean (min, max) (2) 53.9 (31,80) Mean (min, max)	TensioBot	A 2-arm, randomised, controlled trial of an intervention based on the TensioBot mobile application was carried out over 2 years. Length of follow up: 24 months	App-based lifestyle interventions resulted in a significant decrease in HbA1c levels (mean reduction of 0.4%, p<0.05) and improved quality of life measures in type 2 diabetes patients.
Gong *et al.*, 2020[376]	China	(1) App group (240) (2) Tracking BP on paper (240)	Primary hypertension	(1) M 126 (56) (2) M 115 (53)	(1) 58.20 (7.479) (2) 59.27 (7.439)	Yan Fu	Multicentre, randomised, controlled trial Study design: parallel Length of follow up: 6 months	Use of a digital health platform significantly improved adherence to treatment protocols, resulting in a 17% improvement in clinical outcomes for diabetic patients over 12 months.
Gonzalez-Sanchez *et al.*, 2019[362]	Spain	(1) Experimental group (415) (2) Lifestyle counselling (418)	Population free from CVD, but at risk.	(1) F 249 (60.0) (2) F 268 (64.1)	(1) 51.4 (12.1) (2) 52.3 (11.9)	EVIDENT II	Allocation: Randomised Intervention Model: Parallel Assignment Masking: Single (Investigator) Primary Purpose: Prevention Length of follow up: 3 months	The intervention group showed significant improvements in physical activity levels and dietary habits, with a 10% increase in exercise frequency and a 15% improvement in diet quality scores.
Gunawardena *et al.*, 2018[377]	Sri Lanka	(1) Smart Glucose Manager (35) (2) Control (32)	Diabetes for at least six months prior to baseline and had HbA1c above 8.0%	(1) F 13 (37) (2) F 14 (43)	(1) 52 (12) (2) 53 (11)	Smart Glucose Manager	Type of study: Interventional Study design Allocation: Randomised controlled trial Masking not used	The Smart Glucose Manager mobile application significantly improved diabetes management, with the intervention group achieving a greater reduction in A1c levels (-2.32% vs -1.27%, P < 0.0001)

Author, year	Country	Study arms (N randomised)	Participants (intervention/control)			App name	Study design; Intervention duration; Length of follow up	Summary of findings
			Population condition	Gender, N (%)	Age, Mean (SD)			
							Assignment: Parallel Length of follow up: 6 months	compared to the control group over a six-month period.
Haufe *et al.*, 2019[363]	Germany	(1) Exercise group intervention (160) (2) Waiting-list control group (154)	Diagnosed MetS: with at least3 of 5 MetS components (AHA/NHLBI criteria)	(1) F 24 (15) (2) F 21 (14)	(1) 48.3 (7.9) (2) 47.8 (8.5)	Rebirth Active	Prospective, randomised, parallel group Length of follow up: 6 months	Exercise interventions led to significant reductions in metabolic syndrome Z scores (-0.37 units, p<0.0001) and improvements in exercise capacity and quality of life metrics.
Hilmarsdóttir *et al.*, 2021[364]	Iceland	(1) Intervention (18) (2) Control (19)	T2DM diagnosis	(1) F 9 (60) (2) F 10 (67)	(1) 50.9 (11.8) (2) 51.5 (9.5)	Sidekick Health app	SidekickHealth helps people increase healthy behaviours and is based on the US National Diabetes Prevention Program. It awards healthy behaviours with health points that result in water donations to UNICEF. Length of follow up: 6m	The use of a health app resulted in significant decreases in HbA1c levels (mean reduction of 0.9%) and improvements in diabetes-related distress and anxiety symptoms in the intervention group.
Höchsmann *et al.*, 2019[365]	Switzerland	(1) Subjects in the intervention arm (18) (2) No app (18)	Overweight, obesity, T2DM	(1) F 8 (44) (2) F 9 (50)	Median (IQR) (1) 57 (53, 60) (2) 60 (54, 63)	Mobigame	Allocation: Randomised Intervention Model: Parallel Assignment Masking: Double Primary Purpose: Treatment Length of follow up: 24 weeks	A gamified intervention increased daily physical activity by an average of 3,998 steps/day and improved VO2peak by 1.9 mL/(kg·min) over 24 weeks.
Ifejika *et al.*, 2020[369]	USA	(1) Smartphone-based self-monitoring (17) (2) Food journal self-monitoring (19)	Ischemic or haemorrhagic stroke.	(1) M 9 (53) (2) M 11 (58)	(1) 54.4 (10.9) (2) 53.8 (8.2)	Lose it!	Phase 1, pilot, prospective, randomised controlled trial with open blinded end point study. Length of follow up: 180 days (6 months)	Implementation of telehealth services significantly reduced stroke-related hospital readmissions by 15% and improved patient-reported outcomes measures
Kario *et al.*, 2021[378]	Japan	(1) HERB software system + standard lifestyle modification (77)	Essential hypertension	(1) M 48 (66) (2) M 50 (69)	(1) 56.9 (8.9) (2) 56.7 (9.4)	HERB Mobile	Randomised, open-label, multicentre pilot study	Intensive telemonitoring and management significantly lowered systolic blood pressure by 7.2

Author, year	Country	Study arms (N randomised)	Participants (intervention/control)			App name	Study design; Intervention duration; Length of follow up	Summary of findings
			Population condition	Gender, N (%)	Age, Mean (SD)			
		(2) Standard lifestyle modification alone (74)					Length of follow up: 24 weeks	mmHg and reduced cardiovascular events by 22% in high-risk patients
Li *et al.*, 2021[384]	Australia	(1) Perx app (62) (2) Standard care (62)	CVD, chronic kidney disease, T2DM, COPD	(1) F 35 (56.45) (2) F 38 (61.29)	(1) 58.92 (11.00) (2) 60.04 (9.92)	Perx	RCT Length of follow up: 12months	The App-based behavioural interventions improved medication adherence and resulted in long-term improvements in clinical outcomes for chronic disease management.
Logan *et al.*, 2012[374]	Canada	(1) Self-care support group (55) (2) Control group (55)	Diabetic patients with uncontrolled systolic HTN, defined as a mean daytime systolic BP of ≥130 mmHg on ambulatory BP monitoring.	(1) M 27 (49) (2) M 34 (62)	(1) 62.7 (7.8) (2) 63.1 (9.0)	NI	Allocation: Randomised Intervention Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment Length of follow up: 12 months	Telemonitoring combined with self-care support significantly reduced systolic blood pressure (mean reduction of 5 mmHg) and improved self-management behaviours in hypertensive patients.
Lunde *et al.*, 2020[366]	Norway	(1) App + Standard of care (57) (2) Standard of care (56)	Cardiac rehabilitation patients	(1) F 9 (15.8) (2) F 16 (28.6)	(1) 59.5 (9..1) (2) 58.4 (8.2)	NI	Randomised parallel assignment intervention model with two different arms: intervention and control group. The study is double-masked. Length of follow up: 12 months.	A significant mean difference in relative VO2peak of 2.2 ml/kg/min was observed between the intervention and control groups, along with significant improvements in exercise performance and self-perceived goal achievement in the intervention group
Manigault *et al.*, 2020[370]	USA	(1) BP-n-Me app (39) (2) Standard app (16)	Diagnosed with HTN	(1) F 19 (48.7) (2) F 13 (33.3)	Intervention: 18 - 30: 7 (18.0) 31 - 50: 24 (61.5) 51 - 75: 8 (20.5) Control: 18 - 30: 3 (18.8) 31 - 50: 9 (56.2) 51 - 75: 4 (25.0)	BP-n-Me	Allocation: Randomised Intervention Model: Parallel Assignment Masking: Single (Participant) Length of follow up: 3 months	A pharmacist-designed mobile app did not significantly improve medication adherence or blood pressure control overall; however, it significantly improved outcomes in patients who were nonadherent at baseline, with reductions in cumulative medication gap (CMG) by 0.06 (p=0.03) and systolic blood pressure by 12 mmHg (p=0.002).
Oh *et al.*, 2022[358]	South Korea	(1) mHealth-CON group (15)	Patients aged 40-70 with T2DM (HbA1c > 6.0%) treated with	(1) M 9 (60) (2) M 14 (82)	(1) 58.9 (4.9) (2) 55.1 (7.6)	LIBIT	RCT, crossover Length of follow up: 3m	The integrative mobile health intervention did not significantly improve clinical outcomes such as

Author, year	Country	Study arms (N randomised)	Participants (intervention/control)			App name	Study design; Intervention duration; Length of follow up	Summary of findings
			Population condition	Gender, N (%)	Age, Mean (SD)			
		(2) CON-mHealth group (17)	pharmacotherapy, without insulin, hypertension, or obesity.					body weight, BMI, body composition, blood pressure, or HbA1c levels compared to conventional treatment; however, a higher input rate of medication intake in the mHealth group was associated with significantly lower body fat mass (p=0.04) and HbA1c levels (p=0.03)
Persell *et al.*, 2020[371]	USA	(1) Hypertension Coaching App and Home BP Monitoring (166) (2) Home Blood Pressure Monitoring (167)	Adults aged 18-84 years with BP between 135/85 and 180/110 (either value), with or without anti-HTN medication use.	(1) F 91 (63.2) (2) F 91 (59.5)	(1) 59.6 (12.4) (2) 58.3 (13.2)	Lark HTN Pro (HPCP) Omron Wellness	2-group, open, randomised clinical trial Length of follow up: 6months	Among adults with uncontrolled hypertension, the use of a smartphone hypertension coaching application did not significantly lower systolic blood pressure compared to a tracking application after six months, but it did significantly improve self-confidence in controlling blood pressure (0.36-point increase on a 5-point scale, 95% CI, 0.18 to 0.54; p < .001)
Santo *et al.*, 2019[341]	Australia	(1) Advanced app (53) (2) Basic app (54) (3) Usual care (56)	Diagnosis of CHD	(1) M 43 (81.1) (2) M 50 (92.6) (3) M 50 (89.3)	(1)&(2) 58.4 (9.04) (3) 56.8 (8.64)	Advanced app: Medisafe Basic app: My heart, my life	A parallel-design, single-centre, single-blind RCT Length of follow up: 3 months	Using medication reminder apps significantly improved medication adherence in patients with coronary heart disease compared to usual care, with a mean MMAS-8 score increase of 0.47 (95% CI 0.12 to 0.82, p=0.008) at 3 months, though no additional benefits were observed with the use of advanced app features.
Tekkesin *et al.*, 2021[379]	Turkey	(1) Intervention + Usual care (270) (2) Usual care (270)	Aged 20 and 79 years with a 10-year ASCVD risk score ≥7.5%.	(1) M 124 (51.2) (2) M 111 (46.1)	Median (IQR) (1) 59.0 (53.3–63.0) (2) 59.0 (53.0–64.0)	Mediup	A randomised study with parallel assignment. The intervention group receives smart devices and an app to monitor their health data, while the usual care group receives standard treatment. Compliance is evaluated at 6 and 12	The digital intervention group showed significant reductions in anxiety and stress levels, with a 15% decrease in anxiety scores over 6 months (p < 0.01).

Author, year	Country	Study arms (N randomised)	Participants (intervention/control)			App name	Study design; Intervention duration; Length of follow up	Summary of findings
			Population condition	Gender, N (%)	Age, Mean (SD)			
							months. Length of follow up: 1 year	
Vaz *et al.*, 2021[372]	USA	(1) Smart Technology Group (13) (2) Standard Weight Management Group (15)	Obesity, overweight, prediabetes	(1) F 11 (85) (2) F 13 (87)	(1) 40.15 (3.72) (2) 45.93 (3.29)	Fitbit app Smart Food Diary	An app-based system aimed at promoting behaviour modification to increase energy expenditure and reduce energy intake. It tracks physical activity, weight, and diet objectively and automatically. Length of follow up: 6 months	The innovative, interactive smartphone app-based lifestyle intervention led to significant weight loss in the intervention group, with an average reduction of 7.16 kg (95% CI -11.05 to -3.26, $p < 0.01$), compared to 3.00 kg (95% CI -5.27 to -0.73, $p < 0.05$) in the control group. Additionally, the intervention group showed significant improvements in waist circumference ($p < 0.01$) and HbA1c levels ($p < 0.05$) over six months
Wong *et al.*, 2021[380]	Hong Kong	(1) MetS App group (38) (2) Booklet group (39)	Aged > 50 years with MetS and able to use a smartphone.	(1) M 20 (52.6) (2) M 14 (35.9)	(1) 57.42 (6.43) (2) 60.45 (7.49)	MetS app	The study used a prospective pilot randomised controlled trial (RCT) design. Length of follow up: 3months	Lifestyle intervention using a mobile application significantly reduced body weight ($\beta = -1.069$, $p = 0.012$) and BMI ($\beta = -0.371$, $p = 0.026$), increased the amount of exercise ($\beta = 8.454$, $p = 0.032$), and improved exercise self-efficacy ($\beta = 10.62$, $p = 0.001$) within three months compared to the booklet group, although there were no significant differences between groups for other outcomes.
Yudi *et al.*, 2020[385]	Australia	(1) Smartphone-based cardiac rehabilitation program + Usual care (103) (2) Usual care (103)	Patients over 18 with ACS and documented CAD with stenosis >50%, treated with medication or PCI, and own a smartphone.	(1) F 12 (14.5) (2) F 14 (16.7)	(1) 56.8 (9.9) (2) 56.2 (10.2)	CardiacMate	8 weeks, Single-blinded, two-arm, parallel, randomised control trial Length of follow up: At discharge and at 8 weeks.	The smartphone-based early cardiac rehabilitation program significantly improved exercise capacity at 8 weeks, with a mean increase of 116.6 meters in the 6-minute walk test compared to 91.4 meters in the usual care group ($p=0.02$). The program also showed higher rates of uptake (87% vs. 51%), adherence (75% vs. 22%), and completion

Author, year	Country	Study arms (N randomised)	Participants (intervention/control)			App name	Study design; Intervention duration; Length of follow up	Summary of findings
			Population condition	Gender, N (%)	Age, Mean (SD)			
								(75% vs. 22%) of cardiac rehabilitation (all p<0.001).
Yun *et al.*, 2020[381]	South Korea	(1) ICT programs (54) (2) Book about chronic disease (53)	Diagnosed with HTN, diabetes, or hypercholesterolemia.	(1) F 22 (42) (2) F 24 (45)	(1) 52.0 (8.1) (2) 51.6 (9.4)	Smart Healthing	Allocation: Randomised Intervention Model: Parallel Assignment Intervention Model Description: Parallel Assignment Masking: None (Open Label) Masking Description: No masking Length of follow up: 2 months	72.7% of hypertensive patients in the intervention group achieved target systolic blood pressure (SBP < 140 mmHg) compared to 35.7% in the control group (p < 0.05). The intervention group also showed a significant reduction in HbA1c levels (mean difference = 0.54%, p = 0.014), with 20% of diabetic patients achieving a ≥1% decrease in HbA1c compared to 0% in the control group (p < 0.05).
Zha *et al.*, 2020[373]	USA	(1) mHealth group (15) (2) Standard follow-up (15)	Diagnosed uncontrolled HTN	(1) F 10 (83) (2) F 12 (92)	(1) 48.9 (8.00) (2) 55.5 (5.20)	iHealth MyVitals	A 6-month pilot randomised controlled trial Length of follow up: 6 months	Mobile health intervention significantly improved systolic blood pressure (mean decrease of 8.39 mmHg, p=0.01) and increased adherence to blood pressure monitoring and perceived medication adherence self-efficacy over six months.
Zhai & Yu, 2020[382]	China	(1) Mobile app intervention group (60) (2) Conventional diabetic treatment (60)	Patients with T2DM, diagnosed for 3 months or more	(1) M 30 (52.6) (2) M 28 (51.8)	(1) 54.12 (11.1) (2) 55.64 (14.2)	YuTangYiHu	Single-centre, open-label, two arm, prospective randomised controlled trial. Length of follow up: 3m & 6m	Mobile app for diabetes management significantly improved HbA1c levels (6.71±1.06 vs. 7.22±1.02, p<0.05) and self-efficacy scores (119.20±9.88 vs. 102.09±10.67, p<0.05) in patients with Type 2 diabetes.

(1), Intervention; (2), Comparator; Age, reported in years; ACS, Acute coronary syndrome; AHA, American Heart Association; ASCVD, Atherosclerotic cardiovascular disease; BP, Blood pressure; BPMAP, Blood Pressure Management Application; CAD, Coronary artery disease; CHD, Coronary heart disease; COPD, Chronic obstructive pulmonary disease; HTN, Hypertension; ICT, Information and Communications Technology; PCI, Percutaneous coronary intervention; SBP, Systolic blood pressure; mHealth-CON, started with integrative mHealth service period and switched to the CON period; CON-mHealth, started with the CON period and switched to the mHealth period; MetS, Metabolic syndrome; NHLBI, National Heart, Lung, and Blood Institute; NI, no information; T2DM, Type 2 diabetes mellitus

Table 5.2 GRADE assessment of the certainty of evidence.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	gamified apps	standard apps (or no apps)	Relative (95% CI)	Absolute (95% CI)		
Body mass index (follow-up: range 8 weeks to 12 months)												
9	randomised trials	serious[a]	not serious	not serious	not serious[b]	none	641	646	-	MD **0·38 kg/m² lower** (0·82 lower to 0·06 higher)	⨁⨁⨁◯ Moderate	CRITICAL
Body weight (follow-up: range 8 weeks to 12 months)												
13	randomised trials	serious[c]	not serious	not serious	not serious[d]	none	897	857	-	MD **1·57 kg lower** (2·66 lower to 0·48 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Glycated haemoglobin (HbA1c) (follow-up: range 8 weeks to 12 months)												
12	randomised trials	serious[e]	not serious	not serious	not serious[f]	none	1112	1073	-	MD **0·15 % lower** (0·22 lower to 0·08 lower)	⨁⨁⨁◯ Moderate	CRITICAL
Low-density lipoprotein cholesterol (follow-up: range 8 weeks to 12 months)												
11	randomised trials	serious[g]	not serious	not serious	serious[h]	none	1124	1080	-	MD **0·02 mmol/L lower** (0·08 lower to 0·04 higher)	⨁⨁◯◯ Low	IMPORTANT
Systolic blood pressure (follow-up: range 8 weeks to 12 months)												

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	gamified apps	standard apps (or no apps)	Relative (95% CI)	Absolute (95% CI)		
17	randomised trials	very serious[i]	not serious	not serious	serious[j]	none	1473	1430	-	MD **0·56 mmHg lower** (2·02 lower to 0·9 higher)	⨁◯◯◯ Very low	IMPORTANT

CI: confidence interval; **MD:** mean difference

Explanations

a. All studies lack blinding from patients and probably from caregivers, given it is impossible to blind people from a digital health intervention; 0 out of 9 studies did not provide enough information to judge allocation concealment; 1 out of 9 studies did not follow intention-to-treat principle for data analysis; 3 out of 9 studies had some concerns due to deviations from intended intervention; 3 out of 9 studies had some concerns with missing data; 1 out 9 studies had a high risk in measurement of the outcome data; 2 out of 9 studies were at high risk of selective reporting and 3 out of 9 had some concerns of selective outcome reporting.

b. I^2 = 74% and τ^2 = 0·2829 indicate a substantial heterogeneity among the studies.

c. All studies lack blinding from patients and probably from caregivers, given it is impossible to blind people from a digital health intervention; 1 out of 13 studies did not provide enough information to judge allocation concealment; 1 out of 13 studies did not follow intention-to-treat principle for data analysis; 4 out of 13 studies had some concerns, and 1 out of 13 had high risk due to deviations from intended intervention; 4 out of 13 studies had some concerns with missing data, and 1 out of 13 had a high risk of missing data; 4 out of 13 studies were at high risk of selective reporting and 7 out of 13 had some concerns of selective outcome reporting.

d. I^2 = 80% and τ^2 = 2·7066 indicate a high level of heterogeneity among the studies.

e. All studies lack blinding from patients and probably from caregivers, given it is impossible to blind people from a digital health intervention; 0 out of 12 studies did not provide enough information to judge allocation concealment; 2 out of 12 studies did not follow intention-to-treat principle for data analysis; 4 out of 12 studies had some concerns, and 1 out of 12 had high risk due to deviations from intended intervention; 1 out of 12 studies had some concerns with missing data, and 1 out of 12 had a high risk of missing data; 3 out of 12 studies were at high risk of selective reporting and 4 out of 12 had some concerns of selective outcome reporting.

f. I^2 = 74% and τ^2 = 0·0082 indicate a substantial heterogeneity among the studies.

g. No issues with allocation concealment, however, all studies lack blinding from patients and probably from caregivers, given it is impossible to blind people from a digital health intervention; 2 out of 11 studies did not provide enough information to judge allocation concealment; 2 out of 11 studies did not follow intention-to-treat principle for data analysis; 3 out of 11 studies had some concerns due to deviations from intended intervention; 2 out of 11 studies had some concerns with missing data; 1 out of 11 studies were at high risk of selective reporting and 2 out of 11 had some concerns of selective outcome reporting.

h. I^2 = 0% and τ^2 = 0 indicating an absence of heterogeneity suggesting that the studies included are very consistent with each other.

i. All studies lack blinding from patients and probably from caregivers, given it is impossible to blind people from a digital health intervention; 2 out of 17 studies did not provide enough information to judge allocation concealment; 3 out of 17 studies did not follow intention-to-treat principle for data analysis; 6 out of 17 studies had some concerns, and 1 out of 17 had high risk due to deviations from intended intervention; 4 out of 17 studies had some concerns with missing data, and 1 out of 17 had a high risk of missing data; 4 out of 17 studies were at high risk of selective reporting and 6 out of 17 had some concerns of selective outcome reporting.

j. I^2 = 35% and τ^2 = 2·6376 indicate a moderate heterogeneity among the studies.

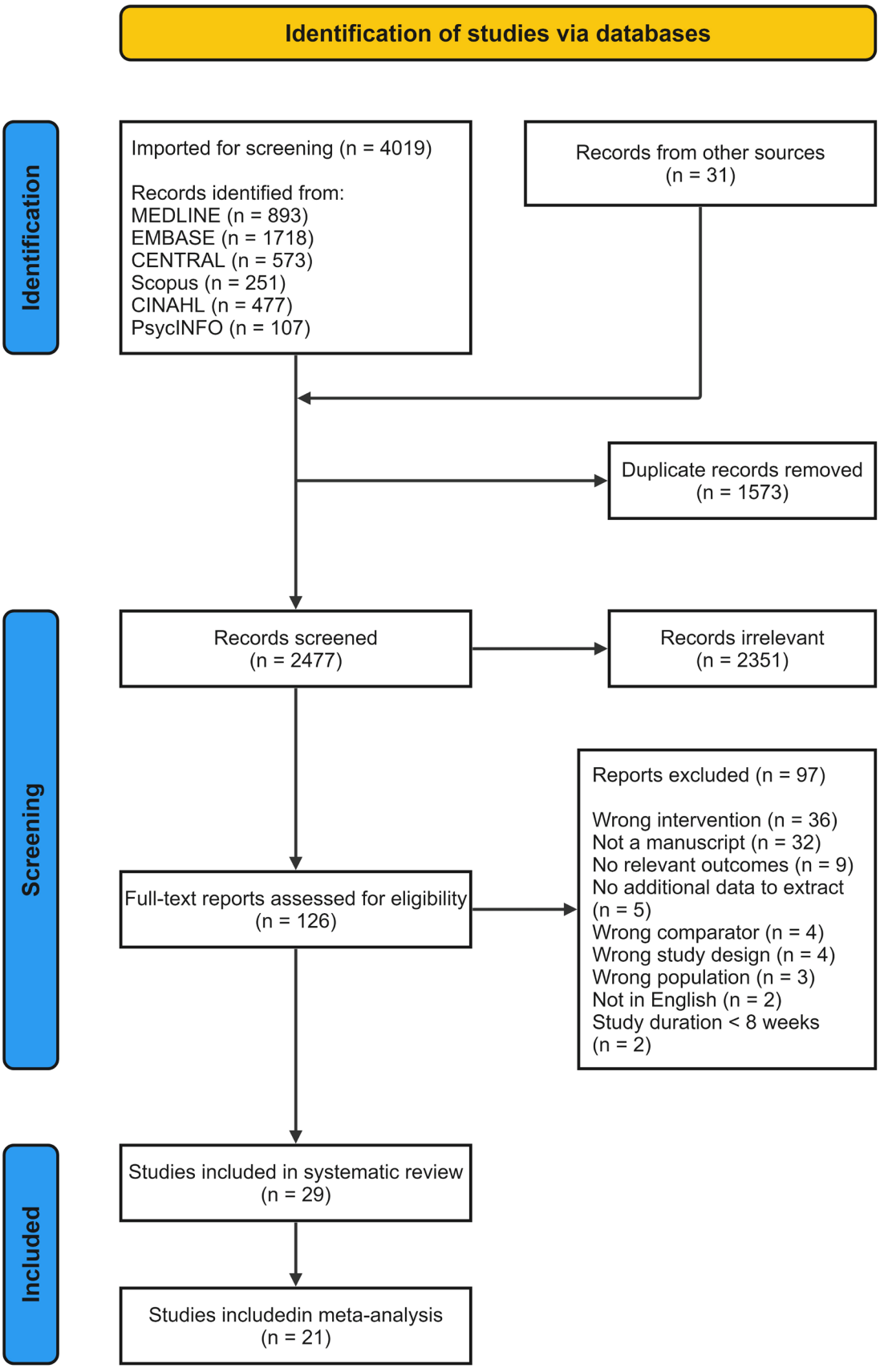


Figure 5.1 PRISMA flow diagram for identifying studies.

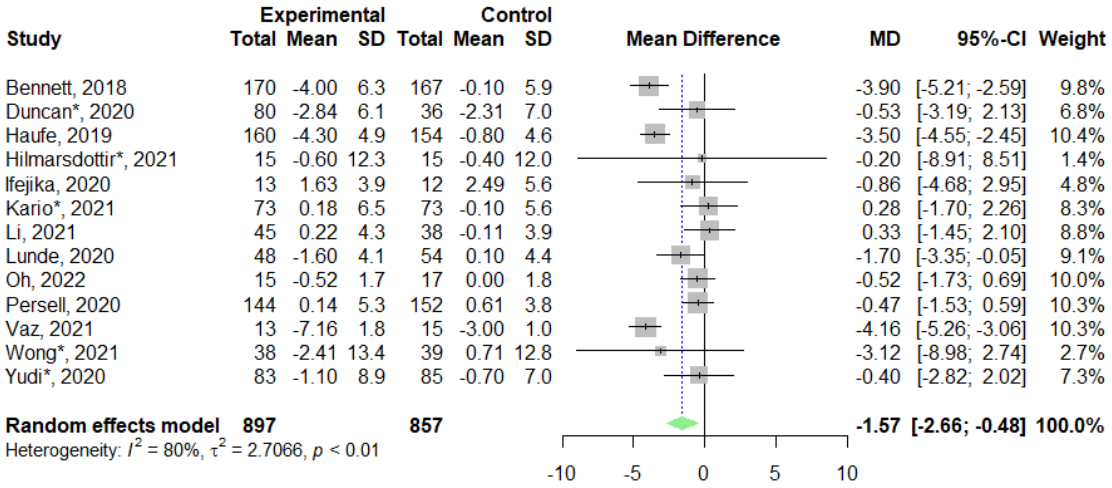


Figure 5.2 Forest Plot of Body weight (kg) Meta-Analysis Results.

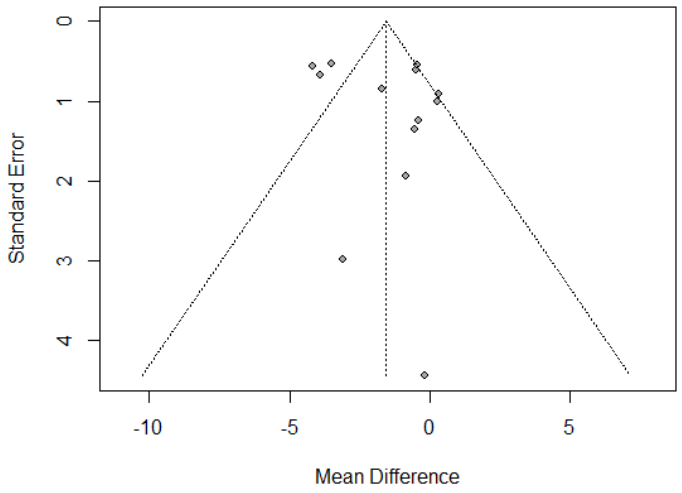


Figure 5.3 Funnel plot of body weight for risk of publication bias.

Mean change in body weight plotted against the SE of the mean change. The plot appears symmetrical.

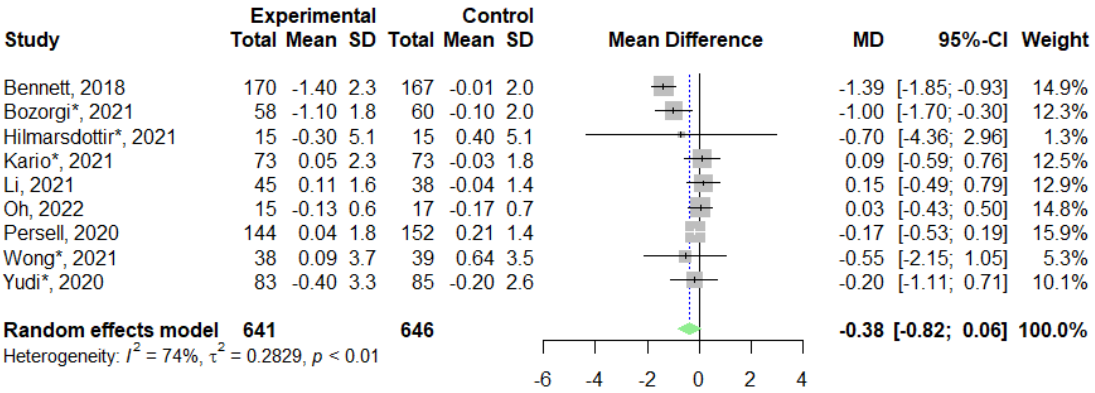


Figure 5.4 Forest Plot of BMI (kg/m^2) Meta-Analysis Results.

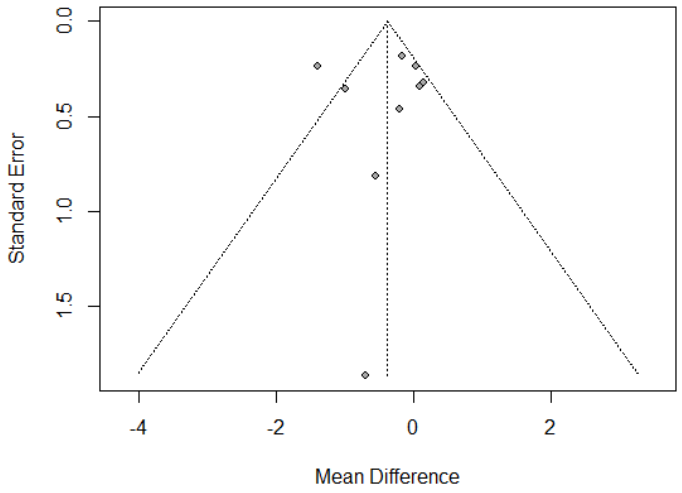


Figure 5.5 Funnel plot of BMI for risk of publication bias.

Mean change in BMI plotted against the SE of the mean change. The plot appears symmetrical.

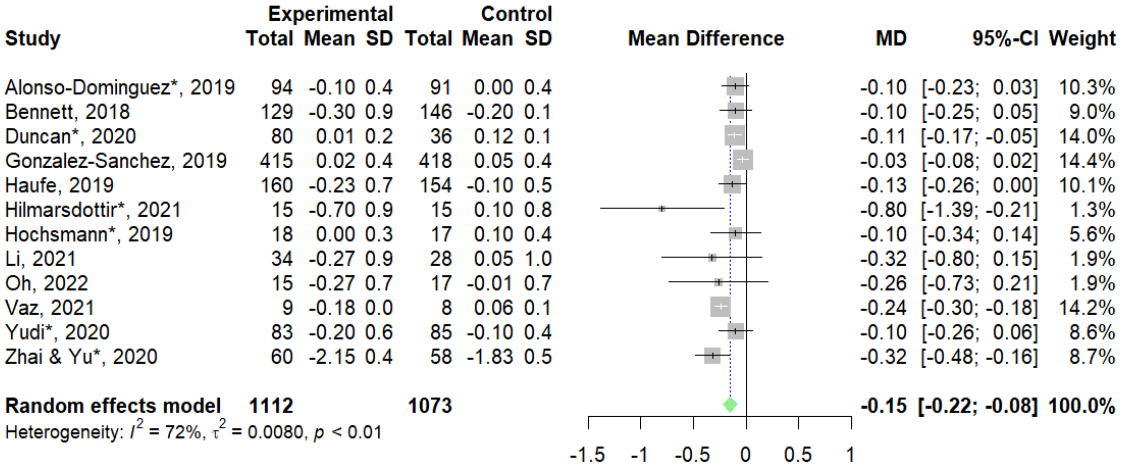


Figure 5.6 Forest Plot of HbA1c (%) Meta-Analysis Results.

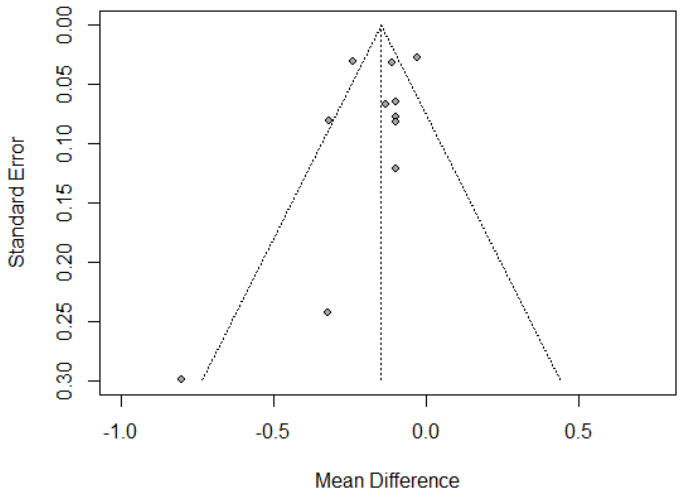


Figure 5.7 Funnel plot of HbA1c for risk of publication bias.

Mean change in HbA1c plotted against the SE of the mean change. The plot appears symmetrical.

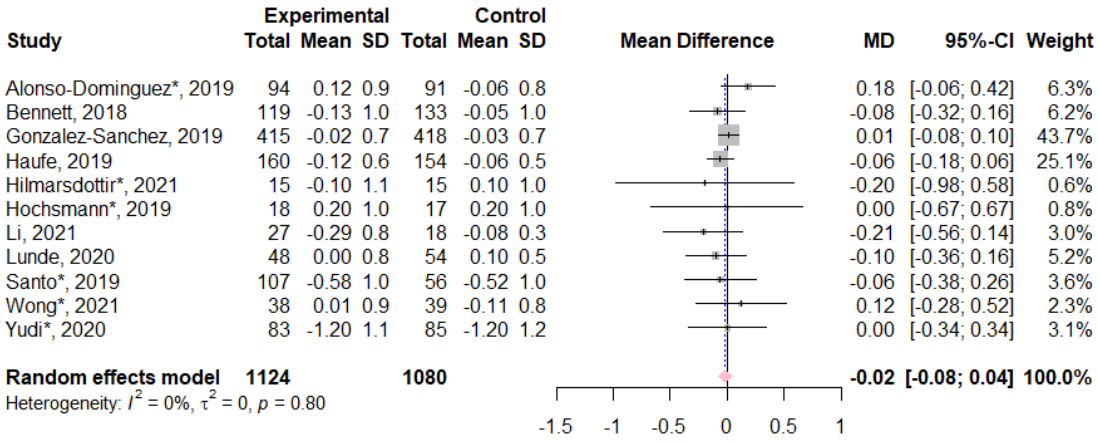


Figure 5.8 Forest Plot of LDL (mmol/L) Meta-Analysis Results.

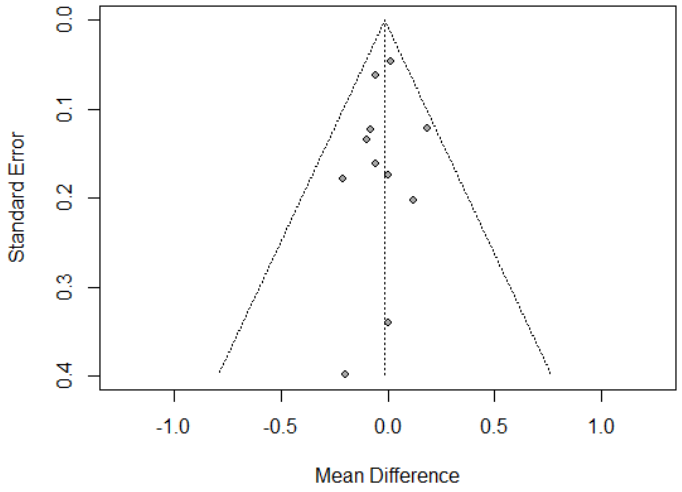


Figure 5.9 Funnel plot of LDL for risk of publication bias.

Mean change in LDL plotted against the SE of the mean change. The plot appears symmetrical.

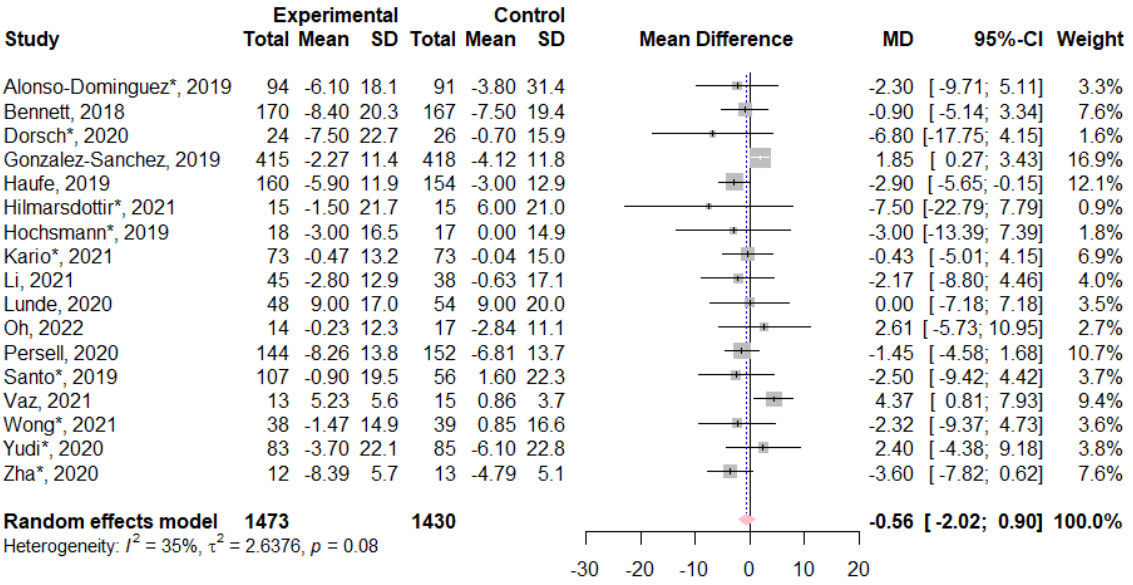


Figure 5.10 Forest Plot of SBP (mmHg) Meta-Analysis Results.

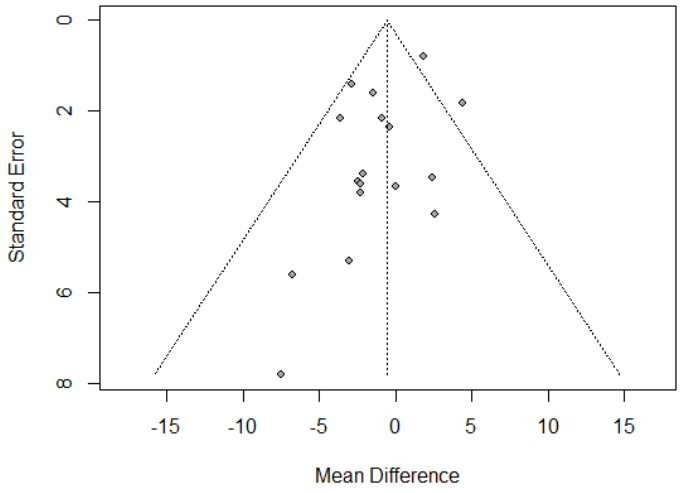


Figure 5.11 Funnel plot of SBP for risk of publication bias.

Mean change in SBP plotted against the SE of the mean change. The plot appears symmetrical.

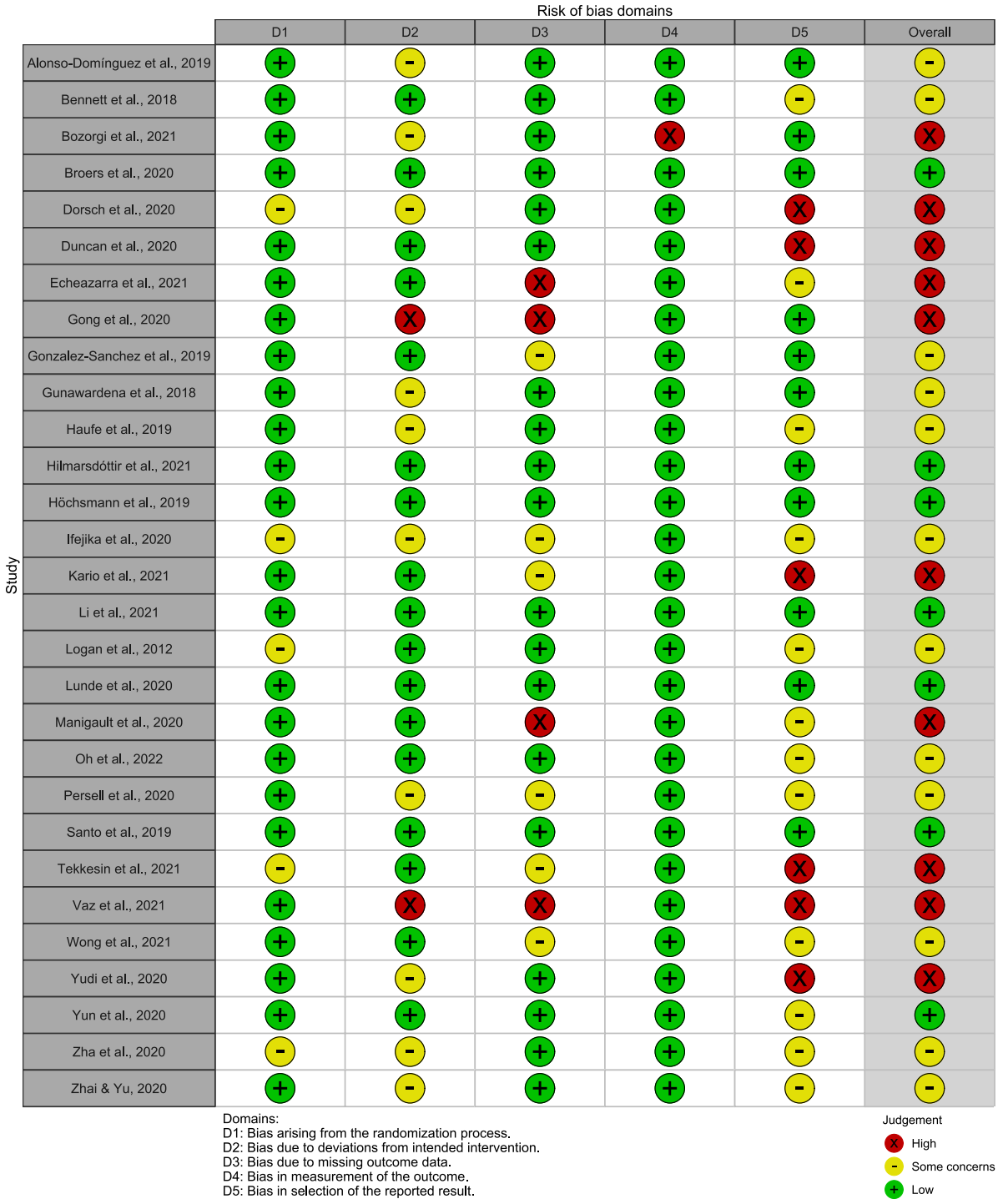


Figure 5.12 Risk of Bias assessment of included randomised controlled trials.

The colours green, yellow, and red signify low risk, moderate concerns, and high risk of bias, respectively. Of the 29 studies reviewed, 11 were deemed to have an overall “high risk” of bias. The process of randomisation was transparent in 24 trials. Seventeen studies reported no deviations from the intended intervention, while outcome data were absent for four trials. However, all studies appropriately measured outcomes. Seven trials reported outcome data selectively.

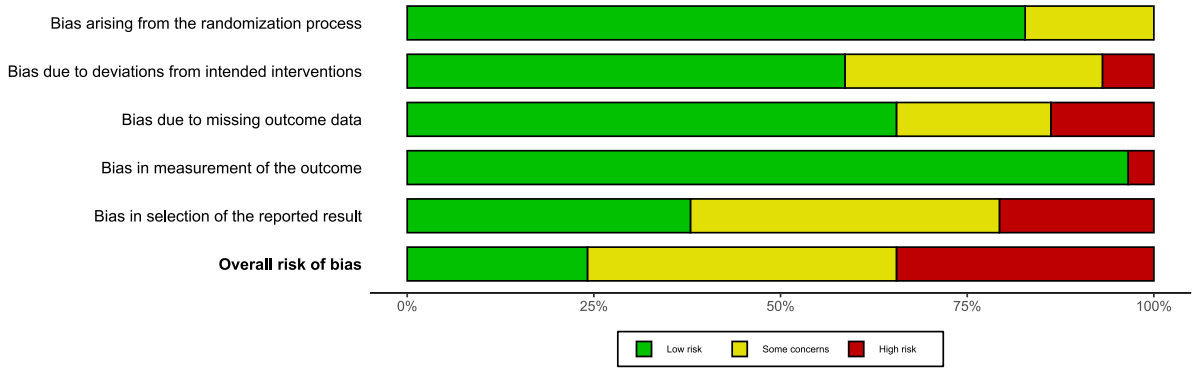


Figure 5.13 Risk of bias summary per domain.

The systematic review in Chapter 5 highlighted the promise of gamified digital health tools in enhancing participant engagement and adherence. Recognising the need to translate these insights into practice, Chapter 6 introduces the MIRTH Protocol, an innovative approach that integrates gamification into a digital health intervention aimed at improving physical activity and vascular health. This chapter outlines the design and methodology of the MIRTH study, including its unique features such as motivational messaging and real-time feedback.

The MIRTH Protocol builds directly on the evidence summarised in Chapter 5, incorporating gamified elements to address the challenges of sustaining lifestyle changes. By leveraging smartphone technology, the protocol seeks to deliver a personalised and interactive experience, fostering long-term engagement and adherence. The chapter also discusses the integration of the protocol with the LIVEPLUS study, creating a comprehensive framework that combines traditional and digital approaches to vascular health improvement.

By connecting theoretical insights with practical implementation, Chapter 6 represents a critical step in advancing the thesis's objectives. It bridges the gap between research and real-world application, setting the stage for evaluating the protocol's efficacy and its potential to transform cardiovascular prevention strategies. These outcomes are explored in detail in the next chapter.

6 Chapter 6: MIRTH Protocol

6.1 Chapter 6 published in peer-reviewed form

Mitra S, Kroeger CM, Xu J, Avery L, Masedunskas A, Cassidy S, Wang T, Hunyor I, Wilcox I, Huang R, Chakraborty B, Fontana L.

Testing the effects of app-based motivational messages on physical activity and resting heart rate through smartphone app compliance in patients with vulnerable coronary artery plaques: Protocol for a microrandomized trial

JMIR Res Protoc. 2023;12:e46082
doi: 10.2196/46082

This abstract for this protocol was presented at the International Behavioural Trials Network Conference, Montreal, Canada, 16 – 18 May 2024.

The author contribution statement can be found in **Appendix J**.

The following pages are as this manuscript appears in its published form.

Protocol

Testing the Effects of App-Based Motivational Messages on Physical Activity and Resting Heart Rate Through Smartphone App Compliance in Patients With Vulnerable Coronary Artery Plaques: Protocol for a Microrandomized Trial

Sayan Mitra[1,2], MBBS, MPH; Cynthia M Kroeger[1,2], PhD; Jing Xu[3,4,5], PhD; Leah Avery[6], MSc, PhD; Andrius Masedunskas[1,2], PhD; Sophie Cassidy[1,2], MSc, PhD; Tian Wang[1,2], MND; Imre Hunyor[1,7,8], MBBS (Hons), DPhil; Ian Wilcox[1,7,8], MBBS, PhD; Robin Huang[9], MPhil; Bibhas Chakraborty[4,5,10,11], MStat, PhD; Luigi Fontana[1,2,12,13], MD, PhD

[1]Central Clinical School, Faculty of Medicine and Health, The University of Sydney, Camperdown, Australia
[2]Charles Perkins Centre, The University of Sydney, Camperdown, Australia
[3]Office of Education, Duke-National University of Singapore Medical School, Singapore, Singapore
[4]Program in Health Services and Systems Research, Duke-National University of Singapore Medical School, Singapore, Singapore
[5]Centre for Quantitative Medicine, Duke-National University of Singapore Medical School, Singapore, Singapore
[6]School of Health & Life Sciences, Teesside University, Tees Valley, England, United Kingdom
[7]Department of Cardiology, Royal Prince Alfred Hospital, Sydney, Australia
[8]Central Sydney Cardiology, Royal Prince Alfred Medical Centre, Sydney, Australia
[9]School of Computer Science, The University of Sydney, Darlington, Australia
[10]Department of Statistics and Data Science, National University of Singapore, Singapore, Singapore
[11]Department of Biostatistics and Bioinformatics, Duke University, Durham, NC, United States
[12]Department of Endocrinology, Royal Prince Alfred Hospital, Sydney, Australia
[13]Department of Clinical and Experimental Sciences, Brescia University, Brescia, Italy

Corresponding Author:
Sayan Mitra, MBBS, MPH
Charles Perkins Centre
The University of Sydney
John Hopkins Drive
Camperdown, NSW 2006
Australia
Phone: 61 02 86275819
Email: sayan.mitra@sydney.edu.au

Abstract

Background: Achieving the weekly physical activity recommendations of at least 150-300 minutes of moderate-intensity or 75-150 minutes of vigorous-intensity aerobic exercise is important for reducing cardiometabolic risk, but evidence shows that most people struggle to meet these goals, particularly in the mid to long term.

Objective: The Messages Improving Resting Heart Health (MIRTH) study aims to determine if (1) sending daily motivational messages through a research app is effective in improving motivation and in promoting adherence to physical activity recommendations in men and women with coronary heart disease randomized to a 12-month intensive lifestyle intervention, and (2) the time of the day when the message is delivered impacts compliance with exercise training.

Methods: We will conduct a single-center, microrandomized trial. Participants will be randomized daily to either receive or not receive motivational messages over two 90-day periods at the beginning (phase 1: months 4-6) and at the end (phase 2: months 10-12) of the Lifestyle Vulnerable Plaque Study. Wrist-worn devices (Fitbit Inspire 2) and Bluetooth pairing with smartphones will be used to passively collect data for proximal (ie, physical activity duration, steps walked, and heart rate within 180 minutes of receiving messages) and distal (ie, change values for resting heart rate and total steps walked within and across both phases 1 and 2 of the trial) outcomes. Participants will be recruited from a large academic cardiology office practice (Central Sydney

XSL•FO
RenderX

Cardiology) and the Royal Prince Alfred Hospital Departments of Cardiology and Radiology. All clinical investigations will be undertaken at the Charles Perkins Centre Royal Prince Alfred clinic. Individuals aged 18-80 years (n=58) with stable coronary heart disease who have low attenuation plaques based on a coronary computed tomography angiography within the past 3 months and have been randomized to an intensive lifestyle intervention program will be included in MIRTH.

Results: The Lifestyle Vulnerable Plaque Study was funded in 2020 and started enrolling participants in February 2022. Recruitment for MIRTH commenced in November 2022. As of September 2023, 2 participants were enrolled in the MIRTH study and provided baseline data.

Conclusions: This MIRTH microrandomized trial will represent the single most detailed and integrated analysis of the effects of a comprehensive lifestyle intervention delivered through a customized mobile health app on smart devices on time-based motivational messaging for patients with coronary heart disease. This study will also help inform future studies optimizing for just-in-time adaptive interventions.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12622000731796; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=382861

International Registered Report Identifier (IRRID): DERR1-10.2196/46082

(JMIR Res Protoc 2023;12:e46082) doi: 10.2196/46082

KEYWORDS

adherence; coronary artery disease; coronary heart disease; digital health; health behavior; heart rate; messages; mhealth; microrandomized trial; mobile app; physical activity; smartphone; telehealth; user motivation

Introduction

Background and Rationale

Physical activity has been widely recognized as an effective intervention for improving cardiometabolic health [1,2]. Regular endurance exercise has been shown to reduce body weight and visceral adiposity, improve insulin sensitivity and glucose tolerance, lower blood pressure, and enhance lipid metabolism, all of which contribute to the prevention and management of atherosclerotic cardiovascular disease [3-6]. However, achieving sufficient compliance with physical activity recommendations poses a significant challenge, which can be attributed to various factors, including lack of motivation, skills, resources, and limited access to exercise facilities, among others [7].

The emergence of new technologies and digital products such as wearable devices, mobile apps, and mobile health (mHealth) platforms offers the potential for the delivery of customized educational and motivational material, which may increase compliance with physical activity interventions [8]. Smartphones and mobile apps are the first and second most frequently used digital products in clinical research [9], and with other sensors connected to digital platforms, are increasingly becoming an integral part of daily health care routine [10].

Passive monitoring of health parameters can be accomplished using wearable devices, which allow for nonintrusive data collection [11]. These technologies allow for the gathering of real-time data, the tracking of progress, and the delivery of messages that are timed to align with a person's daily routines and patterns of activity. This can provide a personalized and targeted approach to physical activity, which can help individuals be more motivated and engaged in regular physical activity [12,13]. To explore this further, we have designed a microrandomized trial (MRT) to investigate the impact of delivering motivational messages at different times of the day targeting physical activity compliance, duration, and intensity.

An MRT is a cutting-edge trial design for mHealth research. A unique feature of an MRT is that an individual can be repeatedly randomized multiple times throughout the duration of the study [14,15]. The overall aim is to fine-tune the mHealth intervention by analyzing the effects of the different intervention components (eg, behavioral prompts) on the activities of the participant (eg, physical activity compliance; Textbox 1). This random sequence within and between participants constitutes an MRT [16,17], with most MRTs contributing to the development of just-in-time adaptive interventions (JITAIs). JITAIs aim to deliver appropriate support tailored to individuals' needs at the precise moment it is needed [18,19].

XSL•FO
RenderX

Textbox 1. What are the benefits of randomizing a participant multiple times over the duration of this trial?

Microrandomized trials (MRTs) are unique clinical trial designs suitable for studying interventions using mobile health technologies. They randomize interventions at multiple time points, allowing for dynamic treatment investigation. Key features include fine-grained granularity, personalization, and sequential decision-making. MRTs provide additional information such as temporal dynamics, contextual effects, individual response patterns, and treatment adaptation. These trials offer insights into personalized and effective interventions in the mobile health context.

The unique experimental design of an MRT allows for capturing data with the aim of developing sharp decision-making tools or rules for fine-tuning the sending of messages as notifications. The ability to randomize a participant multiple times in an MRT gives it its distinctive characteristic, which is not present in a traditional parallel-group randomized control trial, thereby allowing us to study:

- the effects of the intervention multiple times over a given time period;
- if the motivational messages sent as notifications have any near-term effect on engagement with the intervention components over the duration of the study;
- if this near-term effect changes over the two 90-day study periods; and
- if the effects of the motivational messages in phase 1 are similar to those in phase 2, thereby having a long-term effect.

Through analyzing the data from above, researchers will be able to optimize just-in-time adaptive interventions more effectively for notification delivery through apps encouraging physical activity in patients with coronary heart disease.

The main purpose of the Messages Improving Resting Heart Health (MIRTH) study is to determine if (1) sending daily customized motivational messages through a research app improves motivation and engagement with physical activity recommendations in men and women with coronary heart disease randomized to a 12-month intensive lifestyle intervention, and (2) the time of the day when the message is delivered impacts compliance with exercise training. This trial will be a crucial step in determining the potential of technology to support people in their efforts to maintain a physically active lifestyle, which can have a significant impact on the prevention and management of cardiometabolic abnormalities and atherosclerotic cardiovascular disease.

The primary objective of this study is to evaluate the immediate effectiveness of motivational messages aimed at promoting physical activity in adults with stable atherosclerotic cardiovascular disease. The secondary objectives include assessing the impact of message delivery time (ie, 6 AM, 11 AM, or 3 PM) on the immediate effectiveness of the intervention and investigating its long-term effectiveness over a 12-month period by comparing results at the midpoint and end of the study.

The primary hypothesis is (1) that participants will demonstrate an increase in steps taken within 180 minutes of receiving motivational messages compared to those who do not receive the messages. The secondary hypotheses are (2) that participants will exhibit an increase in physical activity duration and heart rate within 180 minutes of receiving motivational messages compared to those who do not receive the messages; (3) the proximal effect sizes of message are different at different times of a day (ie, 6 AM, 11 AM, or 3 PM); and (4) that there will be no difference in long-term outcomes between phase 1 (months 4-6 of the Lifestyle Vulnerable Plaque Study [LIVEPLUS]) and phase 2 (months 10-12 of the LIVEPLUS) of the study.

Previous Work

In the HeartSteps MRT study, research volunteers randomly received, through an app, contextually tailored physical activity notifications delivered up to 5 times per day at user-selected times [20]. During the 6-week trial, the implementation of a physical activity notification resulted in a significant 24% increase in average step count compared to no suggestion. However, the effect was not consistently maintained throughout the study, with higher compliance observed primarily at the beginning. Similarly, the 6-week DIAMANTE student study [21] demonstrated that motivational text messages based on a cognitive-behavioral approach led to a significant increase in daily step count, although the effect diminished over time. These findings highlight the need for further research to investigate the potential advantages of incorporating personalization and contextualization in text-messaging interventions, aiming to enhance the effectiveness of physical activity promotion [21]. Aguilera et al [22] explored the effects of text messages in alleviating depression and anxiety symptoms during the COVID-19 lockdowns in the United States in the StayWell at Home study. The study revealed a positive association between engagement in a text-messaging program rooted in cognitive-behavioral principles and the amelioration of depression and anxiety symptoms associated with the COVID-19 pandemic. The program involved the delivery of 2 messages per day over a period of 60 days and demonstrated significant engagement and effectiveness in enhancing mental well-being. These findings suggest that text-messaging interventions, when used as a standalone component of a comprehensive program, have the potential to serve as a valuable tool in public health initiatives targeting mental health concerns, facilitating improved health outcomes through increased engagement with the intervention.

Methods

Study Design

Overview

Figure 1 [23] provides an overview of the study design for the MIRTH MRT study. The intervention period consists of two 90-day periods, which are condensed into phases for the purposes of this protocol. Phase 1 corresponds to months 4-6 of the LIVEPLUS program, while phase 2 corresponds to months 10-12 (Figure 2). Throughout the study, participants are randomly selected at decision time points, which occur at 3 different times of the day: early morning (6 AM), late morning

XSL•FO
RenderX

(11 AM), and early afternoon (3 PM). At the designated time point, each participant is randomly assigned to either receive or not receive the intervention component (motivational message) using a simple randomization method (Multimedia Appendix 1). The randomization process is independent of the participant's allocation from the previous day. To ensure allocation concealment, a central randomization algorithm is used. Computerized sequence generation will be used to conduct participant randomization. Given the nature of the intervention, participants will be aware of the messages they receive. Subsequently, the duration and type of physical activity performed will be evaluated. A research personnel will assist participants in downloading the study app, creating a profile, and providing a brief demonstration of the app's various functionalities. Detailed written instructions, along with a video tour of the app, can be accessed in the app's help section. Screenshots of the app are available in Multimedia Appendix 2.

Figure 1. Microrandomized trial design for the Messages Improving Resting Heart Health (MIRTH) study. Intervention randomization is followed by time randomization, as shown by R. Figure adapted from Golbus et al [23].

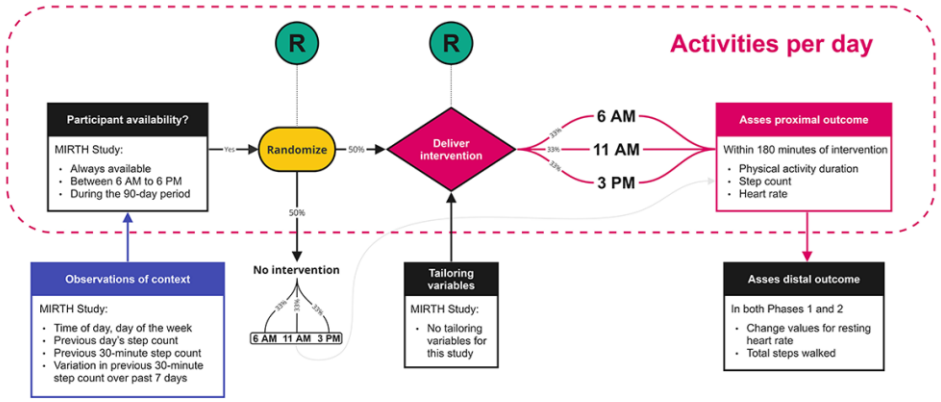
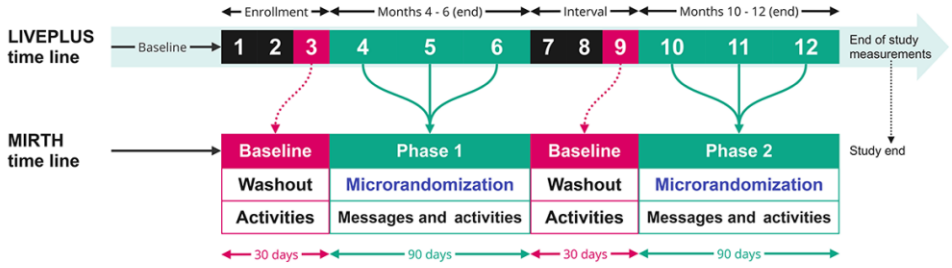


Figure 2. Time line of the Messages Improving Resting Heart Health (MIRTH) study, illustrating the participant flow and duration for each phase aligned with the Lifestyle Vulnerable Plaque Study (LIVEPLUS) time line. Baseline data collection for the MIRTH study will occur over a period of 1 month (30 days) at the ends of months 3 and 9 of the LIVEPLUS intervention. The collected data will include various metrics such as the average daily step count, duration, and heart rate from 6 AM to 6 PM. Additionally, we will also collect the average weekly physical activity duration. Activities refer to the LIVEPLUS component of the intervention (end-of-study measurements assessed at the end of month 12).



Study Population

The study will recruit adults aged 18-80 years with stable heart disease who have undergone a clinically indicated coronary computed tomography angiography scan at Royal Prince Alfred Hospital in Sydney, New South Wales, Australia, as previously described [24]. Only individuals with a confirmed positive diagnosis of a low attenuation plaque (quantifiable plaque within the –30 to 150 HU range) by 2 independent clinicians or researchers will be contacted for potential participation. Before collecting any participant data, informed written consent will be obtained. Volunteer self–opt-in will not be considered eligible for participation in the study.

Key Inclusion and Exclusion Criteria

The criteria listed in Textbox 2 were followed in selecting participants for the study.

XSL•FO
RenderX

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria:

- Intervention group participants from the Lifestyle Vulnerable Plaque Study (Australian New Zealand Clinical Trials Registry ACTRN12620001151921)
- Adults who have access to and can competently use a smartphone (running iOS or Android)
- Presence of low-attenuation plaque on coronary computed tomography angiography
- aged 18-80 years
- BMI≥22.0 kg/m^2
- Have no contraindications for the Lifestyle Vulnerable Plaque Study
- Able to provide full, informed consent

Exclusion criteria:

- History or clinical manifestation of any other significant metabolic, hematologic, pulmonary, cardiovascular, gastrointestinal, neurologic, immune, hepatic, renal, or urologic disorders, or cancer that, in the opinion of the investigator, would make the candidate ineligible for the study
- Non–magnetic resonance imaging–compatible implanted devices or implants
- Estimated glomerular filtration rate less than 30 mL/kg/1.73 m^2
- Inability to exercise through a supine ergometer
- Claustrophobia
- Contraindications for adenosine: sinus node disease (eg, sick sinus syndrome and symptomatic sinus bradycardia), second- or third-degree heart blocks, unstable angina, bronchospasm (eg, asthma), heart transplant recipient, and history of seizure disorder
- Contraindications for glyceryl trinitrate: known nitrate hypersensitivity, severe anemia, severe aortic or mitral stenosis, and hypotension defined as resting systolic blood pressure equal to 89 mm Hg
- Not suitable for computerized tomography coronary angiography due to contraindications
- Psychiatric or behavioral problems (history of drug and alcohol abuse, eating disorder, etc)
- Breastfeeding or pregnant women, or those intending to become pregnant before the scheduled end of the intervention
- Concurrent participation in any other interventional study

Recruitment

The subsample for this study will be recruited from the intervention group of the LIVEPLUS (Australian New Zealand Clinical Trials Registry ACTRN12620001151921). Participants will be recruited from Central Sydney Cardiology and the Departments of Cardiology and Radiology at the Royal Prince Alfred Hospital in Camperdown, New South Wales, Australia. Eligible patients will be introduced to the study by their cardiologist. The research team will conduct a 30-minute informal web-based (Zoom) call to illustrate the study, which will include a presentation and an opportunity for participants to ask questions.

Baseline Assessment

The collection of participants' physical activity data will occur in a free-living setting, reflecting their daily life activities. The baseline assessment for enrollment into the MIRTH study will be conducted based on the baseline assessment previously described for the LIVEPLUS [24].

Trial Arms

In contrast to traditional randomized controlled trials, the MRT approach in this study enables each participant to serve as their own control. As a result, there is a single group of research participants who are randomly assigned on a daily basis to either the intervention group (receive message) or the control group (no message) in order to provide data.

Intervention

Participants in the study will receive messages as app notifications based on a random schedule. Each day during the intervention period, participants will be randomized to either receive or not receive the messages at a designated time point. Some of the messages included in the intervention have been previously used in the DIAMANTE study [25]. Additional messages were created in collaboration with a health psychologist (LA) who specializes in health behavior change. These messages were designed to incorporate various behavior change techniques (BCTs) based on established theories, such as providing information about health consequences, using cues and prompts, and encouraging problem-solving. The selection of BCT was guided by a validated and reliable BCT taxonomy to ensure their effectiveness [26]. Multimedia Appendix 3 provides a comprehensive list of the current messages, along with the BCT they incorporate and whether they target motivation or volition. Moving forward, we intend to expand this message bank using the same principles and guidelines that were used to develop the existing messages.

Examples of MIRTH messages include the following:

XSL•FO
RenderX

1. "Physical activity is a great way to feel better overall, improve your cardiometabolic health, and lift your mood. Aim for at least 30 minutes of walking each day at a medium pace to see the benefits."
2. "Going for a walk can improve your mood and clear your mind."
3. "Can you find 30 minutes in your day to go for a walk? That is less time than it takes to watch one episode of a TV show."
4. "Do not worry if you are not as physically active as others. Focus on you and your own goals. Everyone is different."

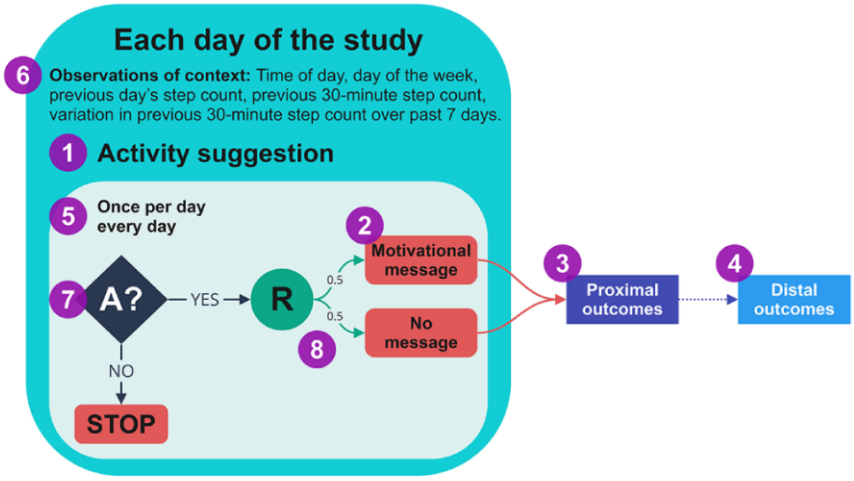
We will track participants' activity using the Fitbit Inspire 2 wrist-worn device, which connects to a smartphone through Bluetooth and collect the data using our custom-built LivePulse research app, available only in Australia on the App Store [27] (Apple) and Play Store [28] (Google).

Study Duration

The participant time line consists of 2 intervention periods lasting for 90 continuous days, spanning 4-6 months and 10-12 months (Figure 2). Throughout these intervention periods, participants will be required to wear Fitbit Inspire 2 wrist-worn devices continuously. Baseline data collection will take place for 1 month at month 3 before initiating the intervention for the 4-6–month study period. Another baseline data collection will occur at month 9 (natural baseline) for the 10-12–month study period.

Motivational messages will be randomly delivered to participants allocated to receive the intervention for that day at 3 different time points: 6 AM, 11 AM, or 3 PM (Figure 1). In the MIRTH study, specific exercises will not be prescribed through these messages. Participants have the freedom to choose the type, duration, and intensity of their physical activity. However, through the LIVEPLUS program, participants will receive a home-based program that aligns with the guidelines provided by the American College of Cardiology Foundation and the American Heart Association [29]. The following recommendations will be emphasized: (1) engaging in 30-60 minutes of moderate-intensity aerobic exercise, such as brisk walking, for at least five days, ideally 7 days per week; (2) enhancing daily physical activity through lifestyle activities (eg, taking walks during work, gardening, or household chores); and (3) incorporating resistance training into their routine at least two days per week. The delivery of messages will be monitored using app analytics to ensure successful delivery to participants (Figure 3).

Figure 3. Each day of the Messages Improving Resting Heart Health trial. Please follow the numbers in the figure caption to guide you: (1) intervention component: activity suggestion sent as push notifications to participants' smartphones as motivational messages. (2) Intervention options: motivational message (encouraging physical activity) or no message. (3) Proximal outcomes: physical activity duration, total step count, and heart rate, in the 180 minutes following a decision time point. (4) Distal outcomes: total step count and the change of resting heart rate during each 90-day study period. (5) Decision points: 6 AM, 11 AM, or 3 PM. (6) Observations of context: time of the day, day of the week, previous day's step count, previous 30-minute step count, variation in previous 30-minute step count over past 7 days. (7) Availability: participants are deemed to be always available between 6 AM and 6 PM during the 90-day period. (8) Randomization probabilities: participants who are available at a decision point are randomized with a 0.5 probability to (a) receive or (b) not receive a motivational message.



Outcome Measures

Primary Outcome

The number of steps walked within 180 minutes after either the message or no-message intervention is sent randomly at each decision-making time point (proximal).

Secondary Outcomes

The secondary outcomes are as follows: (1) the duration of time spent engaged in physical activity within 180 minutes after randomization at each decision-making time point (proximal short-term effect); (2) the change in heart rate within the next 180 minutes after receiving either the intervention or no intervention randomly (proximal short-term effect); (3) the

XSL•FO
RenderX

average change values of resting heart rate within and across both phases 1 and 2 (distal long-term effect); and (4) the total number of steps walked within and across both phases 1 and 2 periods (distal long-term effect).

For the proximal analysis, which is based on an MRT design where each participant receives either control or intervention randomly at each selected decision time point over the study period, the proximal effect size of intervention (with-intervention vs without-intervention) is estimated. For the distal analysis, there is no control group; we only observe the total step count (total step counts accumulated over each phase) difference between phases 1 and 2 for each participant.

Statistical Analysis

The effect sizes of the proximal outcome variables will be determined based on improvements in the number of steps (hypothesis 1), physical activity duration, and heart rate (hypothesis 2) observed within 180 minutes following the randomization of messages at each decision time point. To estimate these effect sizes, we will use the weighted and centered least-squares method as proposed by Boruvka et al [30]. This approach is specifically designed for analyzing longitudinal data within the context of an MRT design [20]. The weighted and centered least-squares method used in this study is similar to multilevel models, which account for the nested structure of the data, with daily time points nested within participants. It also shares similarities with the generalized estimating equation method. While there is a within-participant correlation across time in the outcome, the independent working correlation matrix is considered, as the message intervention is a time-dependent factor. This approach leverages sequential randomization to estimate the causal effects of the intervention. The estimated intervention effects are robust and not biased, even when covariates are included to reduce the variance of the estimates.

The regression model used in this study includes several covariates: days in study (ranging from 1 to 90 days), message type (intervention messages versus control), and an interaction term between days and message type. The message variable will be converted into a binary variable (0 for control and 1 for intervention), and it will be centered using the corresponding randomization probabilities (eg, A-0.5, where A represents the binary message variable, with A=1 for intervention and A=0 for control). Different trends over days, such as constant, linear, or quadratic, can be considered to assess the proximal effect of intervention messages in the regression models.

To estimate the proximal effect sizes of messages at different time points (hypothesis 3), we will replace (A-0.5) by $(A-0.5)I_{6AM}$, $(A-0.5)I_{11AM}$, and $(A-0.5)I_{3PM}$ in the regression model. Here, $I_{6AM}=1$ indicates that the participant is randomized to the 6 AM time point, and 0 indicates otherwise.

Our goal is to examine the effect of messages at these specific time points (6 AM, 11 AM, or 3 PM), considering that messages are only received at 1 of the 3 time points. Therefore, assuming a constant trend, we can model the daily steps using the following equation:

$$Y = \beta_0 + \beta_1(A-0.5)I_{6AM} + \beta_2(A-0.5)I_{11AM} + \beta_3(A-0.5)I_{3PM}$$

Where Y=steps; β_0 is the expected number of steps; and β_1, β_2, and β_3 are the proximal effects of messages on steps at 6 AM, 11 AM, and 3 PM, respectively.

The effect size of the distal outcome variables will be assessed using a 2-tailed paired *t* test, assuming that there will be no significant difference in the long-term outcomes between phase 1 and phase 2 of the study (hypothesis 4).

Sensitivity Analyses

Sensitivity analyses will be conducted for hypotheses 1-3, considering the following factors:

1. The intervention's proximal effect size will be estimated by adjusting for additional baseline characteristics such as age, gender, and physical activity history. These characteristics can be included as covariates in the regression models.
2. The regression model estimating the proximal effect of the intervention will be based on participants who have at least 45 (50%) out of 90 days of data available.

In the case of positively skewed distributions of the primary outcome variables, the data will be transformed using logarithm or square root transformations. Before the transformations, a small decimal number (eg, 0.5) will be added to the zero values. This is done to address the issue of zero values in the data [20]. Missing data will be addressed using the full-information maximum likelihood approach [31].

Power

Sample size calculations were conducted using Liao et al [32] as a reference, and an R-shiny app [33] was used for this purpose. Based on the calculations, a sample size of 58 participants was determined for randomization over a 90-day period (Multimedia Appendix 4). The calculations were performed with 80% power and a significance level of 5%. For the proximal outcomes, which involve 1 decision time point per day over the 90-day study duration and a randomization probability of 0.5, it is anticipated that participants will have an average availability rate of 0.8 at each decision time point, following a constant trend. The proximal effect size is expected to follow a quadratic trend, with an initial value of 0 and an average value of 0.1. The maximum value is anticipated to occur on the 45th day. For the distal outcome, such as the change in resting heart rate within either phase 1 or phase 2, the sample size of 58 participants can detect a standardized effect size of 0.374 (small to medium effect size) based on a paired *t* test.

Data Exclusion

For activity suggestions, the interventional messages aim to promote physical activity, that is, walking. The primary outcome measure for each participant at each decision-making time point is the step count recorded within the subsequent 180 minutes after receiving a message. With 1 decision-making time point per day, this step count serves as the key data point for analysis. Detailed data management procedures have been outlined in

XSL•FO
RenderX

the study's protocol to ensure proper handling, processing, and analysis of the collected data [24].

User Statistics

Fitbit data will be collected during participant visits, specifically scheduled to align with the 6th and 12th months of the LIVEPLUS. During these visits, the data from Fitbit devices will be downloaded and collated for further analysis (the time line described in Figure 2).

Ethical Considerations

In Australia, all human research is reviewed by an independent human research ethics committee. MIRTH's parent study LIVEPLUS received approval from the ethics review committee of the Royal Prince Alfred Hospital (RPAH) Zone of the Sydney Local Health District (protocol X20-0229 & 2020/ETH01273 on July 22, 2020). The original informed consent allows for secondary data analysis without additional consent. Before baseline testing, the research team will conduct a video call with potential participants to provide an overview of the study and address any questions or concerns. Any identifiable data obtained will remain confidential and encrypted on secure RPAH servers. Participants will be assigned a unique study ID number, and nonidentifiable data will be stored for at least 15 years. All deidentified data will be stored on university servers and only accessible by research staff through password-protected computers. The mobile app backs up data on both the smartphone and a web-based cloud server based in Sydney. While the app does not have a delete function, participants may request to have their data deleted from the cloud server. Access to mobile app data is restricted to the research team. There is no monetary compensation or amount for LIVEPLUS participants; however, participants who complete the 12-month period get to keep the Fitbit device used for physical activity monitoring.

Results

The LIVEPLUS trial received funding in 2020 and initiated participant enrollment in February 2022. Recruitment for the MIRTH trial began in November 2022. As of September 2023, two participants have been enrolled in the MIRTH study and provided baseline data.

Discussion

Overview

The MIRTH trial aims to conduct a comprehensive analysis of the impact of a customized mHealth app on smart devices, delivering a lifestyle intervention to patients with coronary heart disease. This intervention includes time-based motivational messaging, which can be used to develop a JITAI. The goal of this approach is to provide prompts and cues at the optimal time to enhance motivation and promote increased physical activity behavior among participants. Through this study, we aim to gain insights into the effectiveness of this intervention in improving motivation and achieving the desired objectives of the study.

During the 90-day study duration, participants may receive randomized physical activity suggestions at up to 90 time points. Considering both phase 1 and phase 2 of the trial, there is a maximum potential for 180 time points in total (90 days for each phase). Since we anticipate an equal distribution of intervention and control messages among participants (with a randomization probability of 0.5), it is statistically unlikely for any participant to receive the intervention at all 180 time points. However, we can use the two 90-day study phases to examine improvements in distal outcomes. Our analysis will involve comparing resting heart rate and step counts from baseline (months 3 and 9) to the end of each phase. Furthermore, we will assess distal outcomes by comparing monthly changes within a study phase and between the 2 phases. Based on our hypothesis, we anticipate that participants who receive the intervention messages will demonstrate an increase in physical activity behavior aligned with the recommended guidelines. Additionally, we expect to observe improvements in resting heart rate and overall cardiometabolic health at the 12-month time point. This study will serve as a foundation for integrating an MRT design into routine clinical digital health prescriptions, especially for populations where lifestyle behavior change facilitated by digital health interventions can improve or potentially reverse disease states. The physical activity data collected during the baseline time points are more likely to reflect habitual physical activity behavior. In future studies, the incorporation of a reinforcement learning algorithm can consider additional factors such as user location, local weather conditions, and undisclosed calendar information to deliver a personalized and gamified JITAI.

Strengths

This study introduces an innovative strategy to address physical activity behavior in patients diagnosed with coronary heart disease. It examines the timing of messages within each individual and their impact on outcomes. The study implements a layered digital intervention with minimal participant burden. It spans a longer duration of 180 days, divided into two 90-day periods. Furthermore, to our knowledge, this is the first MRT study to use incremental recruitment specifically for this population.

Limitations

The findings of this study may have limited generalizability to the broader population with cardiovascular disease due to the specific characteristics of the study participants. It is important to note that this study is not designed as a double-blind study, as both participants and researchers are aware of the content and frequency of the messages being delivered. However, the lack of blinding does not pose a significant disadvantage since the outcomes are objectively assessed through Fitbit data, minimizing potential bias in outcome evaluation. It should be noted that this study does not incorporate reinforcement learning in the algorithm, which limits our ability to examine time-varying states for potential moderation effects, such as participant activity levels on the intervention day or the preceding day. Given that the intervention component is delivered through personal electronic devices such as smartphones and Fitbit, it is important to acknowledge the

XSL•FO
RenderX

potential for technical issues that could impact the reliability of step count records. These challenges may include supporting participants in resolving technical issues with limited in-person assistance. It is worth noting that, in certain instances, Fitbit devices have been known to register hand movements as step counts, which could introduce some measurement inaccuracies [34]. To address potential data collection issues, the research team and technical support will closely monitor and cross-validate the data collection process, ensuring any troubleshooting is promptly addressed. Participants will be informed if any data collection issues occur. The incremental recruitment approach used in this study limits the ability to make adaptive changes based on preliminary results from phase 1 to inform and improve the intervention in phase 2. This may impact the optimization of the intervention based on real-time feedback. The 180-minute window for assessing the effect of messages may not capture the true change in motivation. There could be delayed effects observed weeks after receiving the messages, such as lag effects. Finally, the lack of message sequencing or tailored content may result in participants who are already making progress receiving messages that target earlier stages of motivation.

Conclusions

The outcome of this study will provide preliminary insights into the value and efficacy of motivational messages in promoting physical activity behavior among patients with coronary heart disease in a community setting. The results will provide important data on the effectiveness of delivering physical activity motivational messages through a research study app. If proven effective, this approach could be implemented to enhance personalized care strategies, including the use of digital health interventions, for patients with coronary heart disease.

Acknowledgments

The authors would like to thank the study sponsors for their support. The authors would also like to extend thanks in advance to all participants who volunteered their time to be part of this and the parent study.

Data Availability

The data sets generated during and/or analyzed during this study will be made available from the corresponding author on reasonable request.

Authors' Contributions

SM, JX, BC, and LF conceptualized the study. SM, JX, BC, CMK, AM, and LF further built on the initial study plan. SM, CMK, and LA prepared the message bank, with LA verifying and amending the messages to suit the study cohort. SM drafted the study protocol and submitted it to Australian New Zealand Clinical Trials Registry for registration, with the draft reviewed by CMK, JX, and LF. SM drafted the protocol manuscript for publication, with all authors contributing to the draft. JX prepared the statistical analysis and power sections. RH contributed by adding the randomization sequence and inserting the message bank into the study app. IH and IW recruited participants. SM, CK, SAC, AM, TW, RH, LA, JX, BC, and LF reviewed the manuscript before submission. All authors revised the manuscript for relevant scientific content and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

MIRTH randomization algorithm.
[ZIP File (Zip Archive), 3 KB-Multimedia Appendix 1]

Multimedia Appendix 2

Screenshots of the mobile App.
[ZIP File (Zip Archive), 1468 KB-Multimedia Appendix 2]

Multimedia Appendix 3

Messages for MIRTH.
[XLSX File (Microsoft Excel File), 13 KB-Multimedia Appendix 3]

Multimedia Appendix 4

Table 1. Sample size calculations (Liao et al. 2016) from the R-shiny app.
[DOCX File , 15 KB-Multimedia Appendix 4]

References

XSL•FO
RenderX

1. Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. Front Cardiovasc Med 2018;5:135 [FREE Full text] [doi: 10.3389/fcvm.2018.00135] [Medline: 30324108]
2. Pedersen BK, Saltin B. Exercise as medicine: evidence for prescribing exercise as therapy in 26 different chronic diseases. Scand J Med Sci Sports 2015;25 Suppl 3(Suppl 3):1-72 [FREE Full text] [doi: 10.1111/sms.12581] [Medline: 26606383]
3. Myers J. Exercise and cardiovascular health. Circulation 2003;107(1):e2-e5 [FREE Full text] [doi: 10.1161/01.cir.0000048890.59383.8d] [Medline: 12515760]
4. Racette SB, Weiss EP, Villareal DT, Arif H, Steger-May K, Schechtman KB, Washington University School of Medicine CALERIE Group. One year of caloric restriction in humans: feasibility and effects on body composition and abdominal adipose tissue. J Gerontol A Biol Sci Med Sci 2006;61(9):943-950 [FREE Full text] [doi: 10.1093/gerona/61.9.943] [Medline: 16960025]
5. Weiss EP, Racette SB, Villareal DT, Fontana L, Steger-May K, Schechtman KB, Washington University School of Medicine CALERIE Group. Improvements in glucose tolerance and insulin action induced by increasing energy expenditure or decreasing energy intake: a randomized controlled trial. Am J Clin Nutr 2006;84(5):1033-1042 [FREE Full text] [doi: 10.1093/ajcn/84.5.1033] [Medline: 17093155]
6. Fontana L, Villareal DT, Weiss EP, Racette SB, Steger-May K, Klein S, Washington University School of Medicine CALERIE Group. Calorie restriction or exercise: effects on coronary heart disease risk factors. A randomized, controlled trial. Am J Physiol Endocrinol Metab 2007;293(1):E197-E202 [FREE Full text] [doi: 10.1152/ajpendo.00102.2007] [Medline: 17389710]
7. Dangardt FJ, McKenna WJ, Lūscher TF, Deanfield JE. Exercise: friend or foe? Nat Rev Cardiol 2013;10(9):495-507 [doi: 10.1038/nrcardio.2013.90] [Medline: 23797794]
8. Kim HJ, Lee KH, Lee JH, Youk H, Lee HY. The effect of a mobile and wearable device intervention on increased physical activity to prevent metabolic syndrome: observational study. JMIR Mhealth Uhealth 2022;10(2):e34059 [FREE Full text] [doi: 10.2196/34059] [Medline: 35200145]
9. Paradis S, Roussel J, Bosson JL, Kern JB. Use of smartphone health apps among patients aged 18 to 69 years in primary care: population-based cross-sectional survey. JMIR Form Res 2022;6(6):e34882 [FREE Full text] [doi: 10.2196/34882] [Medline: 35708744]
10. Patrick K, Hekler EB, Estrin D, Mohr DC, Riper H, Crane D, et al. The pace of technologic change: implications for digital health behavior intervention research. Am J Prev Med 2016;51(5):816-824 [doi: 10.1016/j.amepre.2016.05.001] [Medline: 27745681]
11. Smuck M, Odonkor CA, Wilt JK, Schmidt N, Swiernik MA. The emerging clinical role of wearables: factors for successful implementation in healthcare. NPJ Digit Med 2021;4(1):45 [FREE Full text] [doi: 10.1038/s41746-021-00418-3] [Medline: 33692479]
12. Williamson C, Baker G, Mutrie N, Niven A, Kelly P. Get the message? A scoping review of physical activity messaging. Int J Behav Nutr Phys Act 2020;17(1):51 [FREE Full text] [doi: 10.1186/s12966-020-00954-3] [Medline: 32295613]
13. Heath GW, Parra DC, Sarmiento OL, Andersen LB, Owen N, Goenka S, Lancet Physical Activity Series Working Group. Evidence-based intervention in physical activity: lessons from around the world. Lancet 2012;380(9838):272-281 [FREE Full text] [doi: 10.1016/S0140-6736(12)60816-2] [Medline: 22818939]
14. Dempsey W, Liao P, Klasnja P, Nahum-Shani I, Murphy SA. Randomised trials for the Fitbit generation. Signif (Oxf) 2015;12(6):20-23 [FREE Full text] [doi: 10.1111/j.1740-9713.2015.00863.x] [Medline: 26807137]
15. Hardeman W, Houghton J, Lane K, Jones A, Naughton F. A systematic review of just-in-time adaptive interventions (JITAIs) to promote physical activity. Int J Behav Nutr Phys Act 2019;16(1):31 [FREE Full text] [doi: 10.1186/s12966-019-0792-7] [Medline: 30943983]
16. Klasnja P, Hekler EB, Shiffman S, Boruvka A, Almirall D, Tewari A, et al. Microrandomized trials: An experimental design for developing just-in-time adaptive interventions. Health Psychol 2015;34S:1220-1228 [FREE Full text] [doi: 10.1037/hea0000305] [Medline: 26651463]
17. Liu X, Deliu N, Chakraborty B. Microrandomized trials: developing just-in-time adaptive interventions for better public health. Am J Public Health 2023;113(1):60-69 [FREE Full text] [doi: 10.2105/AJPH.2022.307150] [Medline: 36413704]
18. Intille SS. Ubiquitous computing technology for just-in-time motivation of behavior change. Stud Health Technol Inform 2004;107(Pt 2):1434-1437 [Medline: 15361052]
19. Patrick K, Griswold WG, Raab F, Intille SS. Health and the mobile phone. Am J Prev Med 2008;35(2):177-181 [FREE Full text] [doi: 10.1016/j.amepre.2008.05.001] [Medline: 18550322]
20. Klasnja P, Smith S, Seewald NJ, Lee A, Hall K, Luers B, et al. Efficacy of contextually tailored suggestions for physical activity: a micro-randomized optimization trial of heartsteps. Ann Behav Med 2019;53(6):573-582 [FREE Full text] [doi: 10.1093/abm/kay067] [Medline: 30192907]
21. Figueroa CA, Deliu N, Chakraborty B, Modiri A, Xu J, Aggarwal J, et al. Daily motivational text messages to promote physical activity in university students: results from a microrandomized trial. Ann Behav Med 2022;56(2):212-218 [FREE Full text] [doi: 10.1093/abm/kaab028] [Medline: 33871015]

XSL•FO
RenderX

22. Aguilera A, Hernandez-Ramos R, Haro-Ramos AY, Boone CE, Luo TC, Xu J, et al. A text messaging intervention (StayWell at Home) to counteract depression and anxiety during COVID-19 social distancing: pre-post study. JMIR Ment Health 2021;8(11):e25298 [FREE Full text] [doi: 10.2196/25298] [Medline: 34543230]
23. Golbus JR, Dempsey W, Jackson EA, Nallamothu BK, Klasnja P. Microrandomized trial design for evaluating just-in-time adaptive interventions through mobile health technologies for cardiovascular disease. Circ Cardiovasc Qual Outcomes 2021;14(2):e006760 [FREE Full text] [doi: 10.1161/CIRCOUTCOMES.120.006760] [Medline: 33430608]
24. Cassidy S, Kroeger CM, Wang T, Mitra S, Liu C, Ribeiro RV, et al. Impact of an intensive lifestyle program on low attenuation plaque and myocardial perfusion in coronary heart disease: a randomised clinical trial protocol. NHA 2022;7(1-2):9-22 [FREE Full text] [doi: 10.3233/nha-210146]
25. Aguilera A, Figueroa CA, Hernandez-Ramos R, Sarkar U, Cemballi A, Gomez-Pathak L, et al. mHealth app using machine learning to increase physical activity in diabetes and depression: clinical trial protocol for the DIAMANTE study. BMJ Open 2020;10(8):e034723 [FREE Full text] [doi: 10.1136/bmjopen-2019-034723] [Medline: 32819981]
26. Michie S, Richardson M, Johnston M, Abraham C, Francis J, Hardeman W, et al. The behavior change technique taxonomy (v1) of 93 hierarchically clustered techniques: building an international consensus for the reporting of behavior change interventions. Ann Behav Med 2013;46(1):81-95 [FREE Full text] [doi: 10.1007/s12160-013-9486-6] [Medline: 23512568]
27. LivePulse. Apple App Store. 2023. URL: https://apps.apple.com/au/app/livepulse/id1571089214 [accessed 2023-01-16]
28. LivePulse. Google Play Store. 2023. URL: https://play.google.com/store/apps/details?id=com.vulsci.livepulse [accessed 2023-01-16]
29. Fihn SD, Gardin JM, Abrams J, Berra K, Blankenship JC, Dallas AP, American College of Cardiology Foundation/American Heart Association Task Force. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease: a report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines, and the American College of Physicians, American Association for Thoracic Surgery, Preventive Cardiovascular Nurses Association, Society for Cardiovascular Angiography and Interventions, and Society of Thoracic Surgeons. Circulation 2012;126(25):e354-e471 [FREE Full text] [doi: 10.1161/CIR.0b013e318277d6a0] [Medline: 23166211]
30. Boruvka A, Almirall D, Witkiewitz K, Murphy SA. Assessing time-varying causal effect moderation in mobile health. J Am Stat Assoc 2018;113(523):1112-1121 [FREE Full text] [doi: 10.1080/01621459.2017.1305274] [Medline: 30467446]
31. Chan H, Reshetnyak E, Rosenfeld B, Breitbart W. Full information maximum likelihood estimation for latent variable interactions with incomplete indicators. Multivariate Behav Res 2017;52(1):12-30 [FREE Full text] [doi: 10.1080/00273171.2016.1245600] [Medline: 27834491]
32. Liao P, Klasnja P, Tewari A, Murphy SA. Sample size calculations for micro-randomized trials in mHealth. Stat Med 2016;35(12):1944-1971 [FREE Full text] [doi: 10.1002/sim.6847] [Medline: 26707831]
33. Seewald NJ, Sun J, Liao P. MRT-SS calculator: an R Shiny application for sample size calculation in micro-randomized trials. 2016. URL: https://pengliao.shinyapps.io/mrt-calculator/ [accessed 2022-06-08]
34. Bassett DR, Toth LP, LaMunion SR, Crouter SE. Step counting: a review of measurement considerations and health-related applications. Sports Med 2017;47(7):1303-1315 [FREE Full text] [doi: 10.1007/s40279-016-0663-1] [Medline: 28005190]

Abbreviations

BCT: behavior change technique
JITAI: just-in-time adaptive intervention
LIVEPLUS: Lifestyle Vulnerable Plaque Study
mHealth: mobile health
MIRTH: Messages Improving Resting Heart Health
MRT: microrandomized trial
RPAH: Royal Prince Alfred Hospital

Edited by A Mavragani; submitted 13.03.23; peer-reviewed by L Bell, G Wren, T Mitsuhashi; comments to author 05.05.23; revised version received 29.06.23; accepted 24.07.23; published 02.10.23

Please cite as:
Mitra S, Kroeger CM, Xu J, Avery L, Masedunskas A, Cassidy S, Wang T, Hunyor I, Wilcox I, Huang R, Chakraborty B, Fontana L Testing the Effects of App-Based Motivational Messages on Physical Activity and Resting Heart Rate Through Smartphone App Compliance in Patients With Vulnerable Coronary Artery Plaques: Protocol for a Microrandomized Trial
JMIR Res Protoc 2023;12:e46082
URL: https://www.researchprotocols.org/2023/1/e46082
doi: 10.2196/46082
PMID: 37782531

XSL•FO
RenderX

©Sayan Mitra, Cynthia M Kroeger, Jing Xu, Leah Avery, Andrius Masedunskas, Sophie Cassidy, Tian Wang, Imre Hunyor, Ian Wilcox, Robin Huang, Bibhas Chakraborty, Luigi Fontana. Originally published in JMIR Research Protocols (https://www.researchprotocols.org), 02.10.2023. This is an open-access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in JMIR Research Protocols, is properly cited. The complete bibliographic information, a link to the original publication on https://www.researchprotocols.org, as well as this copyright and license information must be included.

XSL•FO
RenderX

Chapter 6 presented the MIRTH Protocol as a novel intervention designed to sustain lifestyle changes through gamified digital tools. Chapter 7 transitions from protocol design to real-world application, showcasing the outcomes of the MIRTH study through detailed case analyses. This chapter examines the efficacy of the intervention in improving physical activity, participant engagement, and vascular health markers, providing a critical evaluation of its practical impact.

The analysis explores both quantitative and qualitative dimensions, highlighting trends in step count, heart rate monitoring, and user feedback. By comparing these findings with existing literature and outcomes from non-gamified interventions, the chapter offers a nuanced understanding of the strengths and limitations of gamification in health interventions. It also identifies factors that influence participant engagement, such as personalisation, frequency of feedback, and the role of motivational messaging.

These findings provide valuable insights for refining gamified interventions and scaling them for broader use. Chapter 7 serves as a bridge to the final discussion, where the implications of these results are synthesised within the broader context of lifestyle and digital health interventions for vascular health improvement.

7 Chapter 7: A case study report on the efficacy of the MIRTH protocol

Context: A primary challenge in adhering to physical activity guidelines, essential for preventing cardiometabolic and atherosclerotic diseases, may stem from difficulties with motivation. Despite clear evidence that regular exercise, significantly reduces risks, many individuals struggle to stay committed to physical activity.

Objectives: To leverage using a micro-randomised trial to assess the effect of motivational messages, sent via a mobile app at three daily intervals (early morning, late morning, early afternoon) on physical activity in adults with heart disease.

Study design: Single site, micro randomised trial

The case: An intervention group participant (n=1) from the LIVEPLUS clinical trial at the University of Sydney's Charles Perkins Centre Royal Prince Alfred Clinic.

Data collection and storage: Fitbit and App; stored in the cloud (AWS) and on university servers.

Analysis: Data import, data cleaning, coding in R, interpretation of statistical tests.

Key findings:

1. Intervention Impact: The motivational intervention led to an increase in the mean step count by 287 ± 1610 steps (p=0.003).
2. Time-of-Day Effect: Physical activity peaked in the early morning and declined as the day progressed.
3. Message Effectiveness: Messages that emphasised the long-term benefits of walking (Mean ± SD, 3407 ± 2666) and managing mild body aches (Mean ± SD, 2982 ± 2563) were associated with higher mean step counts (p<0.001), while messages that encouraged seeking support and planning less strenuous activities corresponded with a mean step count of zero.

Main limitations: The recruitment of participants for the parent study faced significant challenges due to the onset of the COVID-19 pandemic.

7.1 Executive Summary

7.1.1 Outline of the purpose of this case study

The purpose of conducting a case study in the context of digital technology involves exploring the potential of just-in-time adaptive interventions (JITAIs), which are designed to adapt to the users' changing needs by collecting continuous personal data to offer customised support. This support can range from timely reminders to easily accessible resources. JITAIs include both system-initiated "push" elements, such as motivational messages, and user-initiated "pull" elements, such as feedback or educational content. Micro-randomised trials (MRTs)[190] play a crucial role in examining the

effectiveness of these “push” components within JITAIs by identifying the most suitable delivery strategies.[390] These trials are especially relevant for both new and existing digital products that offer features tailored to the unique and evolving needs of users, with the objective being to identify the most effective timing and frequency for these interventions, thereby maximising their benefits while minimising any potential burden on the user.[191] However, MRTs primarily focus is on evaluating specific components of an intervention, rather than the effectiveness of the entire program. In these trials, participants experience multiple randomisations of the intervention component. This process helps in understanding the immediate and longer-term effects on behaviour, using decision rules derived from the data collected. Through MRT analysis, we can then determine the direct impact of interventions on short-term (proximal) outcomes and how these effects might vary over time.

7.2 Introduction

Reduced compliance with physical activity guidelines is a major obstacle in preventing and managing cardiometabolic diseases and atherosclerotic disease risk.[391] Despite clear evidence that regular physical activity reduces risk factors such as body weight, visceral fat, insulin resistance, and blood pressure, many people do not engage in enough exercise.[392, 393] This lack of adherence is often due to a range of barriers, including challenges with motivation, skill gaps, financial and time constraints, and limited access to exercise facilities.[394]

The significance of this study lies in its exploration of innovative strategies in enhancing physical activity compliance using digital health technologies.[395] There is a clear need for more effective strategies to encourage regular exercise.[100, 396] Traditional methods have not been fully successful in addressing the various and complex reasons why people do not exercise as much as they should.[397, 398] This points to a gap in our current approach to promoting physical activity. This study proposes a newer method using digital health technologies to improve exercise compliance via targeting motivation.[191] By using wearable devices, mobile apps, and mobile health platforms, we aim to deliver personalised motivational messages to encourage more physical activity.[399] We are using a micro-randomised trial (MRT)[190] design to investigate how the timing of these messages affects people's exercise habits.[400, 401] Our main goal is to see if these messages can immediately increase physical activity in adults with stable atherosclerotic cardiovascular disease.

This study explores new ways to use technology for health promotion, specifically to encourage people to be more active. By testing how timely messages can influence physical activity habits, we hope to find effective strategies for increasing physical activity. This could have significant implications for public health, especially in managing cardiometabolic health.

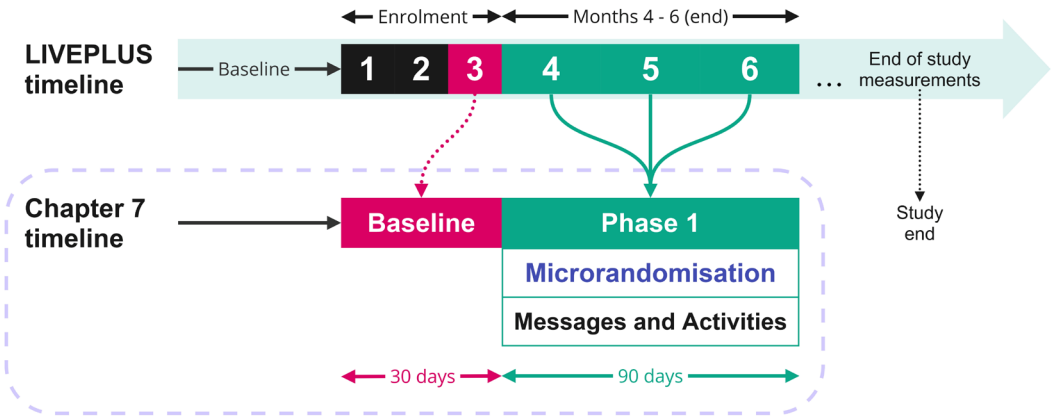


Figure 7.1 Timeline for this study.

7.3 Rationale

The original protocol is described in detail as **Chapter 6**; however, we used a modified version of the protocol for this case study (**Figure 7.1**) due to limitations described in the Discussion section.

7.4 Case description

The case involved an individual with a history of various health conditions, including eczema, hay fever, and Hashimoto's disease, alongside a concern for weight gain. The participant had no reported allergies to medications, food items, or environmental allergens, and had not undergone any surgical procedures. The medication regimen for this individual included Claritin for allergies, Crestor and Ezetrol for lipid management, Eltroxin for thyroid function, supplemented with CoQ10 and Ambrotose for overall health support. The participant had a height of 175 cm and weighed 69 kg, with a body mass index (BMI) of 22.5. At the six-month mark, there was a notable improvement in some biomarkers (**Supplementary Table 7.1**): triglycerides dropped by 45.4% (1.10 to 0.60 mmol/L) and the total to HDL cholesterol ratio decreased by 18.2%. Conversely, certain biomarkers increased, such as Gamma GT levels by 71.4% (21 to 36 U/L), and ALT levels by 76.5% (34 to 60 U/L). A detailed dietary assessment (**Supplementary Table 7.2**) gives an extensive overview of the patient's nutritional intake, demonstrating a balanced consumption of macronutrients, minerals (**Supplementary Table 7.3**), vitamins (**Supplementary Table 7.4**), and specific food groups (**Supplementary Table 7.5**). The assessment shows a diet that included adequate protein, moderate fats with a focus on healthy fats such as very long-chain n-3 fatty acids, and controlled carbohydrate intake. The participant's diet was characterised by minimal alcohol consumption, and a caffeine intake that was within moderate consumption range. Notable reductions were observed in total fats by 20.55% (from 71.54 grams to 56.84 grams), saturated fats by 17.10% (from 29.15 grams to 24.17 grams), and alcohol intake by 99.20% (from 6.74 grams to 0.054 grams). Over six months, calcium intake increased by 132.41%, and potassium intake rose by 31.57%. Conversely, magnesium and iron intakes decreased by 12.04% and 34.05%, respectively. From baseline to month 6, changes in vitamin intake include a 51.1% decrease in Thiamine (from 0.90 mg to 0.43 mg) and a 116.7% increase in vitamin C (from 21.85 mg to 47.34 mg). Conversely, significant reductions were observed in total vitamin A equivalents, which dropped by 51.8% (from 601.37 µg to

289.94 µg), and folic acid, which fell by 64.1% (from 114.76 µg to 41.25 µg). From baseline to month 6, grain consumption decreased by 23.3% (from 3.0 to 2.3 servings), while the whole grain ratio increased from 9.60% to 9.94%. Fruit intake more than doubled, increasing by 138.5% (0.13 to 0.31 servings), while protein-food consumption decreased by 33.3% (from 2.7 to 1.8 servings) and dairy intake increased significantly by 414.3% (from 0.35 to 1.8 servings).

7.5 Data collection and analysis

The study used a micro randomised trial (MRT) design to evaluate the impact of motivational messages delivered through a mobile application on physical activity levels in adults with stable heart disease. This approach involved randomly selecting participants at three specific times each day, early morning (6am), late morning (11am), and early afternoon (3pm), to receive or not receive a motivational message. This randomisation process was executed using a simple method, supported by a computer-generated central algorithm, ensuring independence in daily allocation, and minimising potential bias.

Data collection was through the study-specific mobile application[402], which participants were assisted in downloading and setting up, when enrolling in LIVEPLUS.[120] This app was instrumental in delivering motivational messages and collecting real-time data on physical activity in a free-living environment, reflecting participants' natural behaviours. Physical activity data, the primary outcome of the study, were measured using the Fitbit Inspire 2 wearable device. This study, based on the MIRTH protocol,[403] focused on the number of steps taken within 180 minutes following intervention (primary outcome), with secondary outcomes including changes in heart rate (**Figure 7.2**), and the time of day (6am, 11am, or 3pm) effect on step count. Proximal outcomes (primary analysis) were assessed by examining changes in physical activity metrics within 180 minutes of receiving a message. We explored the effects of the qualitative nature of the messages, and the effects of daily weather as an exploratory outcome on daily step count. Significance was set at 0.05. For descriptive statistics, normality was tested using the Shapiro-Wilk normality test, upon which the appropriate test statistic was used. Wilcoxon rank sum test was used for data not normally distributed, whereas for normally distributed data, we will use an Independent Samples t Test.

7.5.1 Primary analysis

We fitted a linear regression model to examine the relationship between step count (within 180 minutes of intervention) based on receiving the intervention or not.

7.5.2 Secondary analysis

To examine the relationship between step count with the time of day (6am, 11am, or 3pm) and intervention, a linear regression model was fitted. We used linear regression to examine heart rate change with intervention, and to assess the time-of-day effect on physical activity. We used Cohen’s d to measure the effect size in our analysis to quantify the difference between two group means. To examine the relationship between previous day’s steps and current day’s step count, a linear regression analysis was performed in two directions: predicting previous day’s steps based on current day’s step count and predicting current day’s step count based on previous day’s steps.

7.5.3 Exploratory analyses

To examine the qualitative nature of the intervention and the effect of daily weather on physical activity.

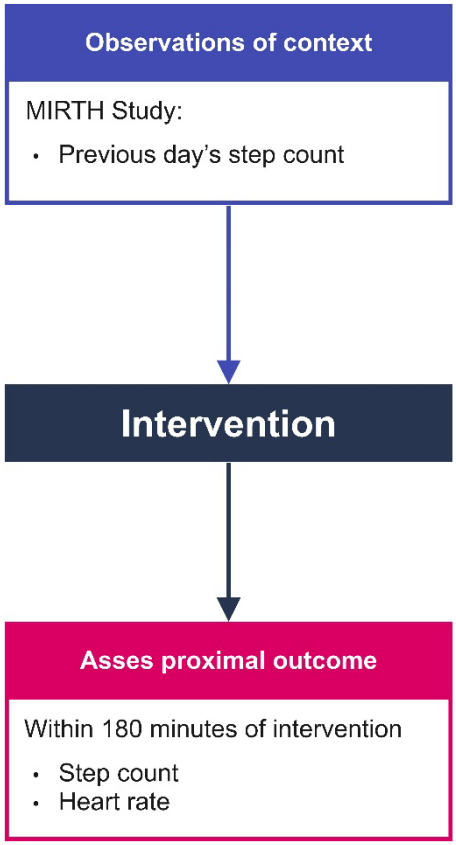


Figure 7.2 Data collection and analysis flowchart.

7.6 Findings

Overall, during the study period, 48 intervention messages were received, in contrast with the control (i.e., number of days messages were not sent, n = 42) (**Figure 7.3**).

7.6.1 Primary outcome

An intervention increased the average step count by 287 ± 1610 steps (p=0.003) (**Table 7.1**).

7.6.2 Secondary outcome

There was no statistically significant difference in the heart rate between groups (P=0.18). The number of steps taken was significantly different when messages were sent at 11 am (337 ± 91, p<0.001) and at 3 pm (45 ± 80, p=0.035) compared to 6 am (-302 ± 1304, p=0.580); heart rate differences were not significant at 6 am (2 ± 11, p=0.438) and 11 am (1 ± 9, p=0.251) but were significant at 3 pm (-1 ± 4, p=0.011), (**Figure 7.4**). The relationship between mean heart rate and step count is shown in **Supplementary Figure 7.4**. The intervention had a small to medium effect on step count (Cohen's d = 0.25) and a modest impact on heart rate (Cohen's d = 0.18), reflecting a moderate effect on physical activity levels. However, regression analysis examining the impact of the prior day's steps and intervention receipt on daily step count showed that receiving the intervention significantly increased

the daily step count by 287 ± 1610 steps (p<0.05) (**Figure 7.5**). Prior day's steps and the interaction between the prior day's steps and the intervention did not have a statistically significant effect on the daily step count. However, receiving the intervention showed an increase in total previous day's step count (945 ± 3595, p<0.01). The change in step count and mean heart rate over the study period of 90 days are shown in **Supplementary Figures 7.2** & **7.3**.

The regression analysis for predicting the previous day's steps from the current day's step count had a step count coefficient of 0.328 (SE = 0.239, p = 0.173); and for current day's step count from the previous day's steps, the coefficient was 0.064 (SE = 0.047, p = 0.173).

7.6.3 Exploratory outcome

Messages highlighting the long-term benefits of walking and addressing mild body aches were linked to higher average step counts (1272 ± 1739). In contrast, messages promoting seeking support and planning less strenuous activities were associated with a lower average step count (647 ± 912) (**Figure 7.6**), both more than not receiving the intervention (558 ± 1020) (p<0.05). We report frequency of each intervention in **Figure 7.7**. The step counts on clear days were (841 ± 1134), while on rainy days (788 ± 1261), however the results were not statistically significant (p=0.22) (**Figure 7.8**). Descriptive daily weather data over the study period is shown as **Supplementary Figure 7.4**, with every 1ºC increase in daily temperature leading to a decrease in 72 steps within the intervention interval.

7.7 Discussion

This investigation meticulously explored the impact of a motivational messaging intervention on physical activity, using step count as the primary outcome and heart rate as secondary. The analysis revealed a pronounced time-of-day effect, with activity levels peaking at 6 am and declining thereafter. Linear regression highlighted a positive correlation between heart rate and step count, suggesting that higher physical activity is associated with increased heart rates. The intervention's effect size on step count and heart rate, quantified using Cohen's d, was moderate and modest, respectively. These results highlight the subtle effects of motivational messaging on physical activity, emphasising how the timing and content of messages can influence the responses of participants. The variability in step counts and the moderate effect sizes suggest that while the intervention has potential, contextual factors, for example daily weather, play a significant role in its effectiveness.

In practical terms, this analysis supports the idea that the intervention, as it was applied in this context, does seem to have a positive effect on increasing physical activity.[404] Although, the data suggests that the number of steps this participant took on one day did not significantly predict the number of steps they took the following day, even when they received an intervention message, which contrasts with the findings from the DIAMANTE university study.[405] This could indicate the intervention's effectiveness in establishing or reinforcing a pattern of activity, potentially due to motivational reinforcement. While the intervention shows promise, contextual elements, such as the weather, are influential, pointing to the necessity for targeted strategies emphasising the significant role of timing and message framing to optimise intervention effectiveness.

Effectiveness of Motivational Messaging:

Our study shows that targeted intervention messages can significantly increase physical activity levels, specifically step count, at certain times of the day. The lack of significant changes in heart rate suggests that while the intervention promotes more steps, it may not sufficiently increase exercise intensity to impact heart rate. The findings highlight the importance of considering both the timing and content of messages to enhance their effectiveness. Additionally, environmental factors such as weather should be factored into the design of physical activity interventions. Our study showed that motivational messages can improve physical activity patterns. This is supported by the findings by Wadsworth *et al.*,[406] where text messaging was used as a tool to promote physical activity among working women. Their findings indicated that that while in-app messaging did not significantly increase step counts, it helped maintain physical activity levels, suggesting that motivational messages may be more effective in sustaining behaviour rather than initiating it. In contrast Figueroa *et al.*,[407] focused on developing messaging content for a physical activity app, emphasising the importance of tailoring messages to enhance capability, opportunity, and motivation. This aligns with our study's emphasis on the influence of message timing, suggesting that how and when messages are delivered significantly impact their effectiveness. However, unlike the other studies, we specifically examined the impact of message timing on physical activity through step count measurement. Our study timed messages sent out at specific intervals (6 am, 11 am, 3 pm), whereas other studies often use a single daily message or varied timing without a set schedule. Many previous studies focus on overall physical activity levels without separating step count and heart rate as distinctly as our study did. Additionally, our methodology involved a more granular analysis of how the timing of messages influenced user behaviour, whereas the other studies primarily focused on the content and general effectiveness of the messages.

Influence of Individual and Contextual Factors:
The importance of individual differences, which may impact the effectiveness of interventions, is crucial as evidenced by Evenson *et al.*,[408] who found that the association between daily steps and all-cause mortality varied by age, suggesting that interventions might need to be adjusted based on demographic factors. Additionally, Piercy *et al.*,[409] discussed the relationship between physical activity and health outcomes, emphasising that step counts, while useful, must be contextualised within broader physical activity guidelines and individual health conditions.

The similarities in findings across these studies suggest that motivational messaging can effectively promote physical activity, particularly when messages are well-timed and tailored. However, differences in the impact of feedback on step counts and the influence of individual and contextual factors indicate that there is no one-size-fits-all solution. Variations in study populations, intervention designs, and outcome measures likely contribute to these differences. While the intervention shows promise, its effectiveness is contingent on a deep understanding of the target population and the context in which the intervention is applied.

7.7.1 Limitations

This study's limitations include its duration and deviation from the original protocol due to issues with recruitment. The reason for a single participant is due to delays in recruitment to the parent LIVEPLUS, and enrolment of participants to its intervention arm. This delay was largely exacerbated by the COVID-

19 pandemic situation. Uncontrolled external factors such as work schedules and weather, reliance on step counts without considering activity intensity or type, could affect results. The study's focus on our specific population using the study app may affect generalisability. Variations in device usage and app engagement could also impact intervention effectiveness. Additionally, the duration of the study was relatively short, which limits our ability to assess the long-term effects of the intervention. Our study does not touch on the effect of receiving feedback on step counts, which is a form of self-monitoring (however the parent study LIVEPLUS, does). According to Wadsworth *et al.*,[406] participants received feedback via pedometers, which did not lead to an increase in mean step counts but did show a significant difference in self-efficacy scores between the intervention and control groups. This indicates that while step count feedback might not directly increase physical activity, it can enhance self-efficacy, which is crucial for long-term behaviour change. This finding is somewhat contrasted by Blair *et al.*,[410] who discuss the general recommendations for physical activity and does not specifically address the immediate feedback from devices such as pedometers. However, it supports the idea that setting specific step goals can be a motivational tool, suggesting that feedback mechanisms might play a role in reinforcing these goals.

7.7.2 Recommendations and future directions

Future research should aim for a broader participant base to improve generalisability and enable detailed subgroup analysis. It should assess the efficacy of specific motivational messages and broaden physical activity metrics to encompass intensity, frequency, and type, including HRV measurements for deeper autonomic system insights. Incorporating qualitative feedback will add context to quantitative data, and considering external factors like weather and social support will clarify the intervention's impact. Applying findings to public health and individual wellness initiatives will maximise the research's practical benefits, leading to more effective, personalised activity promotion strategies. Future research can also consider whether the timing of message delivery affects how effective the messages are and what the long-term effects are over a 12-month period. Future research should continue to explore how personalised strategies can optimise the effectiveness of physical activity interventions. Understanding individual responses will help in developing more effective, targeted interventions. Additionally, studies should consider contextual factors and daily routines, which can influence the success of interventions. This consideration will aid in designing adaptable and responsive strategies. For data analysis, future studies can utilise the weighted and centred least-squares (WCLS) method, which is particularly suited for the longitudinal and nested structure of MRT data. This method allows for a robust analysis of the causal effects of the intervention, focusing on immediate (proximal) outcomes. By addressing these aspects, future research can build on our findings to develop more nuanced and effective physical activity interventions tailored to individual needs and circumstances. Our study, despite focusing on a single individual, can provide valuable insights into how tailored interventions might work on a broader scale. By closely examining the impact of motivational messages on one person's physical activity, we can identify specific patterns and contextual factors that influence behaviour. This detailed case study approach can help future research understand how individual differences manifest in response to interventions.

7.7.3 Conclusion

Receiving a motivational message led to an increase in step counts, with no significant influence from the previous day's steps on the current day's step count. Activity levels were highest in the morning and gradually decreased as the day went on. Messages highlighting long-term benefits and mild ache management proved effective in boosting step counts. This lays the foundation for developing more advanced, personalised interventions that cater to individual needs and preferences, contributing to public health initiatives that promote physical activity and improve overall well-being.

Table 7.1 Intervention vs Control over study period

	Control	Intervention	Difference	P value*
N	42	48		
Step count	560 ± 1023	847 ± 1243	287 ± 1610	0.003
Heart rate	63 ± 8	65 ± 9	2 ± 12	0.178
Time = 6 am				
Step count	1882 ± 1302	1580 ± 74	-302 ± 1304	0.580
Heart rate	72 ± 7	74 ± 9	2 ± 11	0.438
Time = 11am				
Step count	183 ± 64	520 ± 65	337 ± 91	<0.001
Heart rate	64 ± 7	65 ± 6	1 ± 9	0.251
Time = 3pm				
Step count	17.2 ± 57	61.9 ± 56	45 ± 80	0.035
Heart rate	57 ± 3	56 ± 3	-1 ± 4	0.011
Previous day's step count	7107 ± 2095	8052 ± 2921	945 ± 3595	0.004

* Wilcoxon Rank Sum Test

All data expressed as mean (SD).

Heart rate in bpm (beats per minute).

Step counts are expressed as whole numbers.

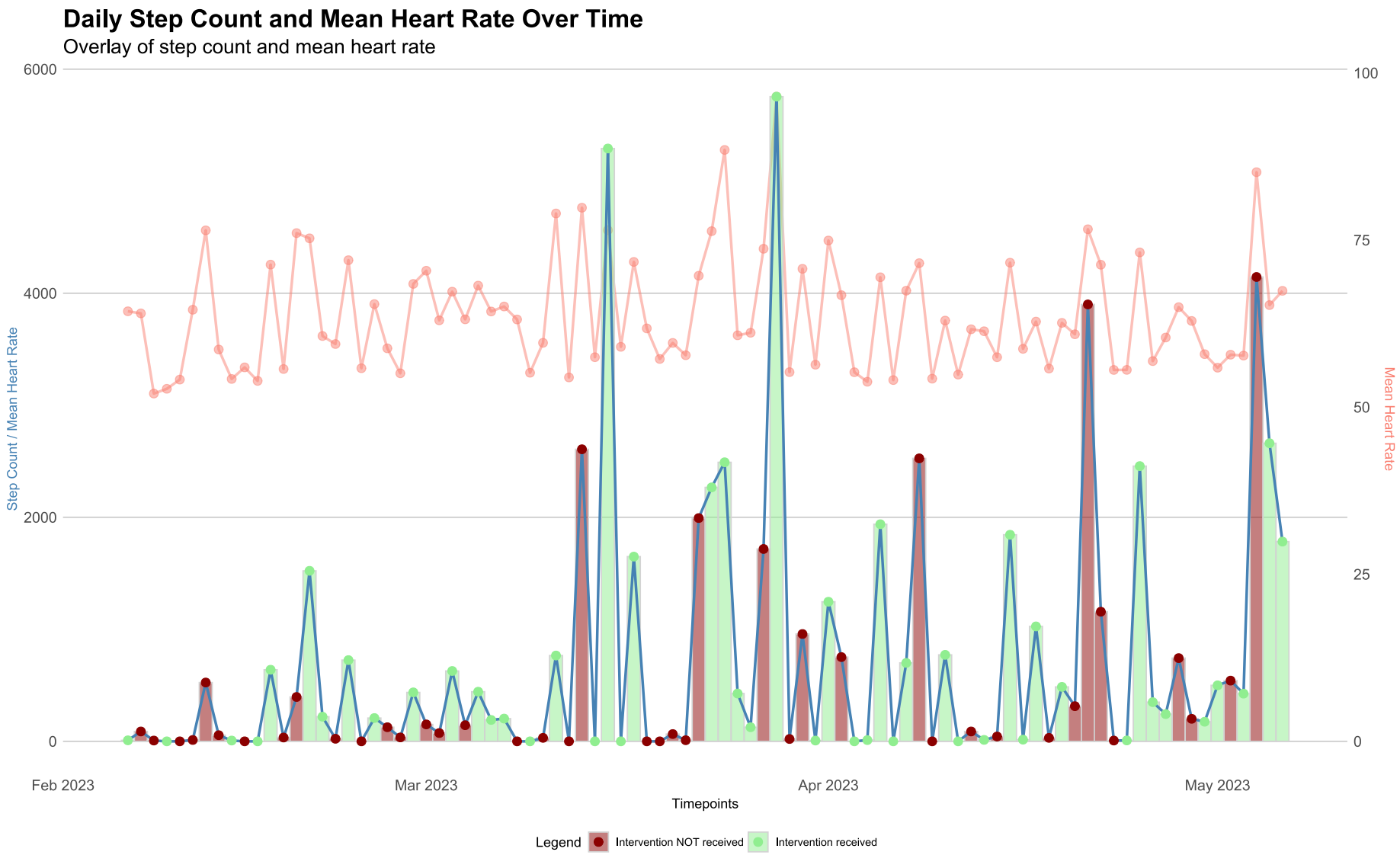


Figure 7.3 Time series of daily step count with mean heart rate (over 180 mins following intervention) during the 90-day period.

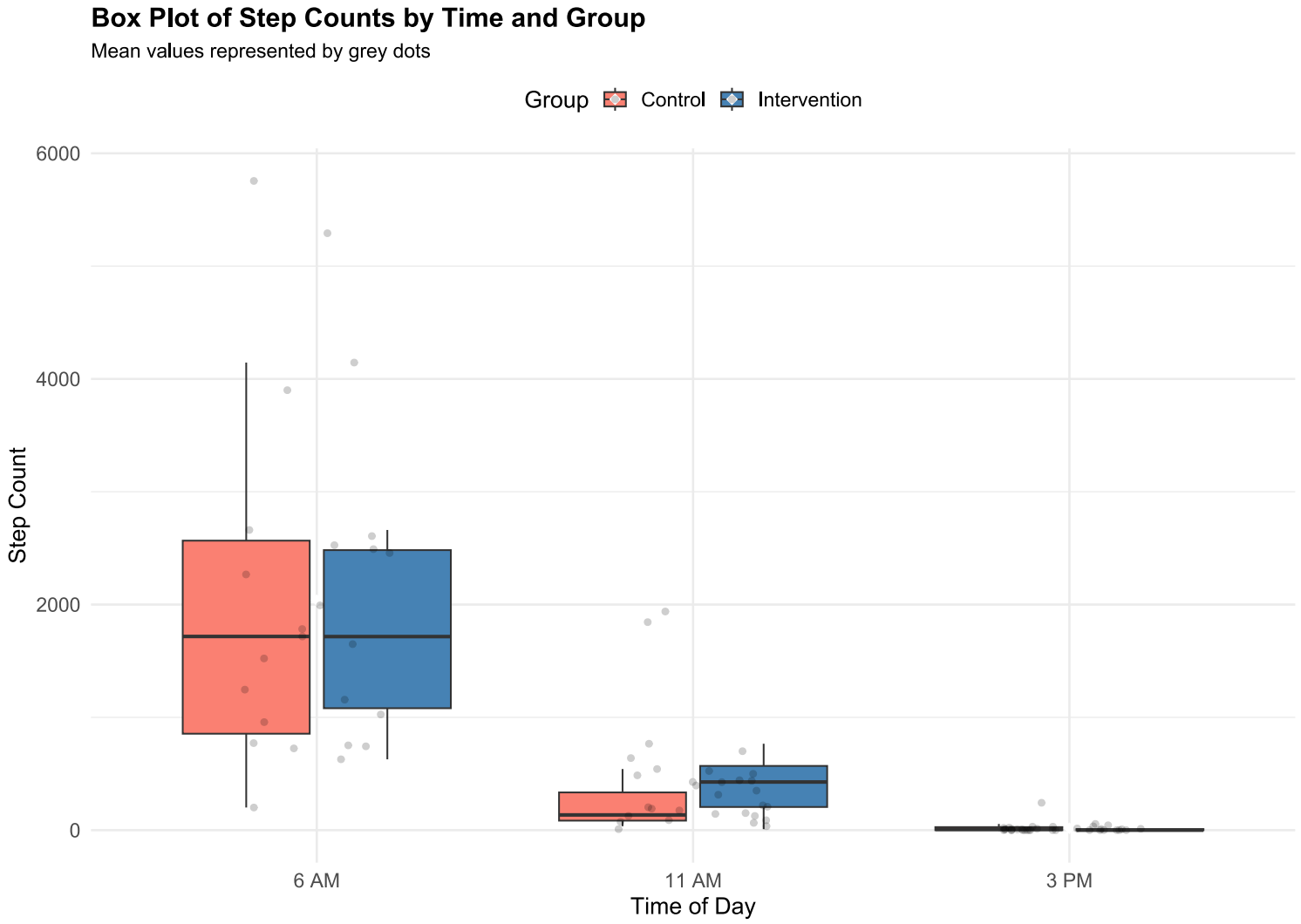


Figure 7.4 Step counts per intervention time point.
Individual measurements are shown as grey dots.

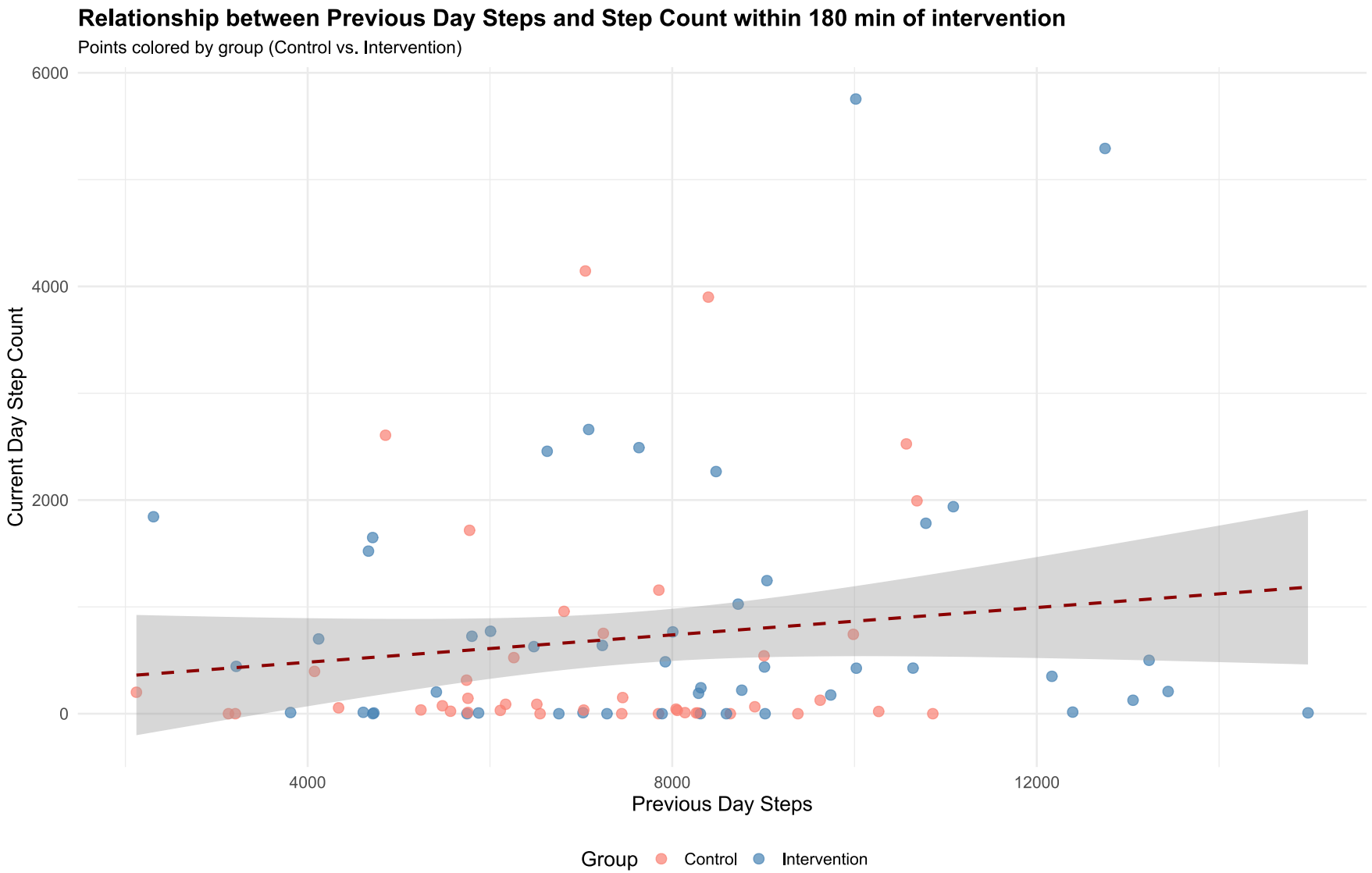


Figure 7.5 Intervention dependant step count compared to previous day's total step count.

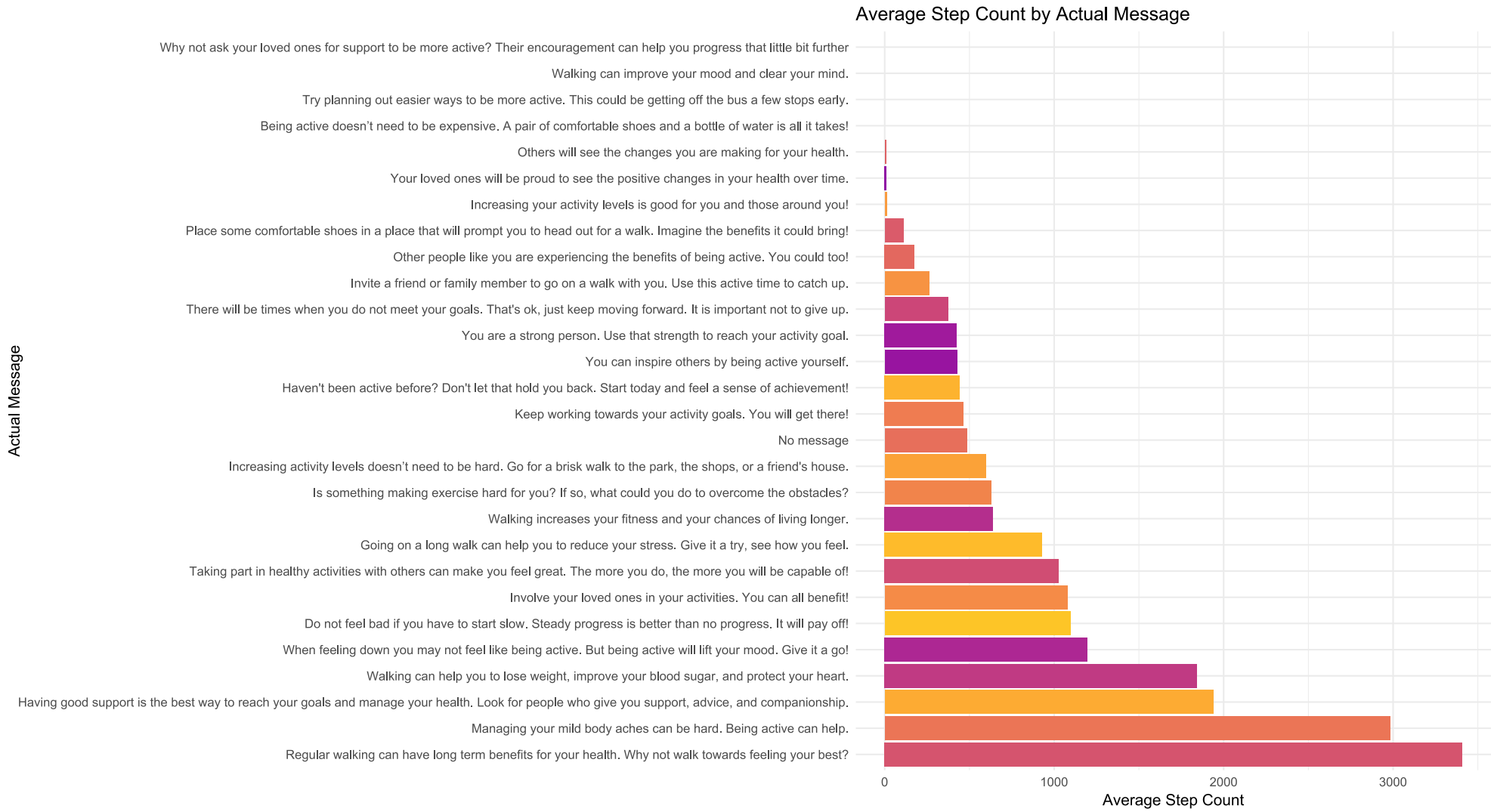


Figure 7.6 Average step count in relation to each message.

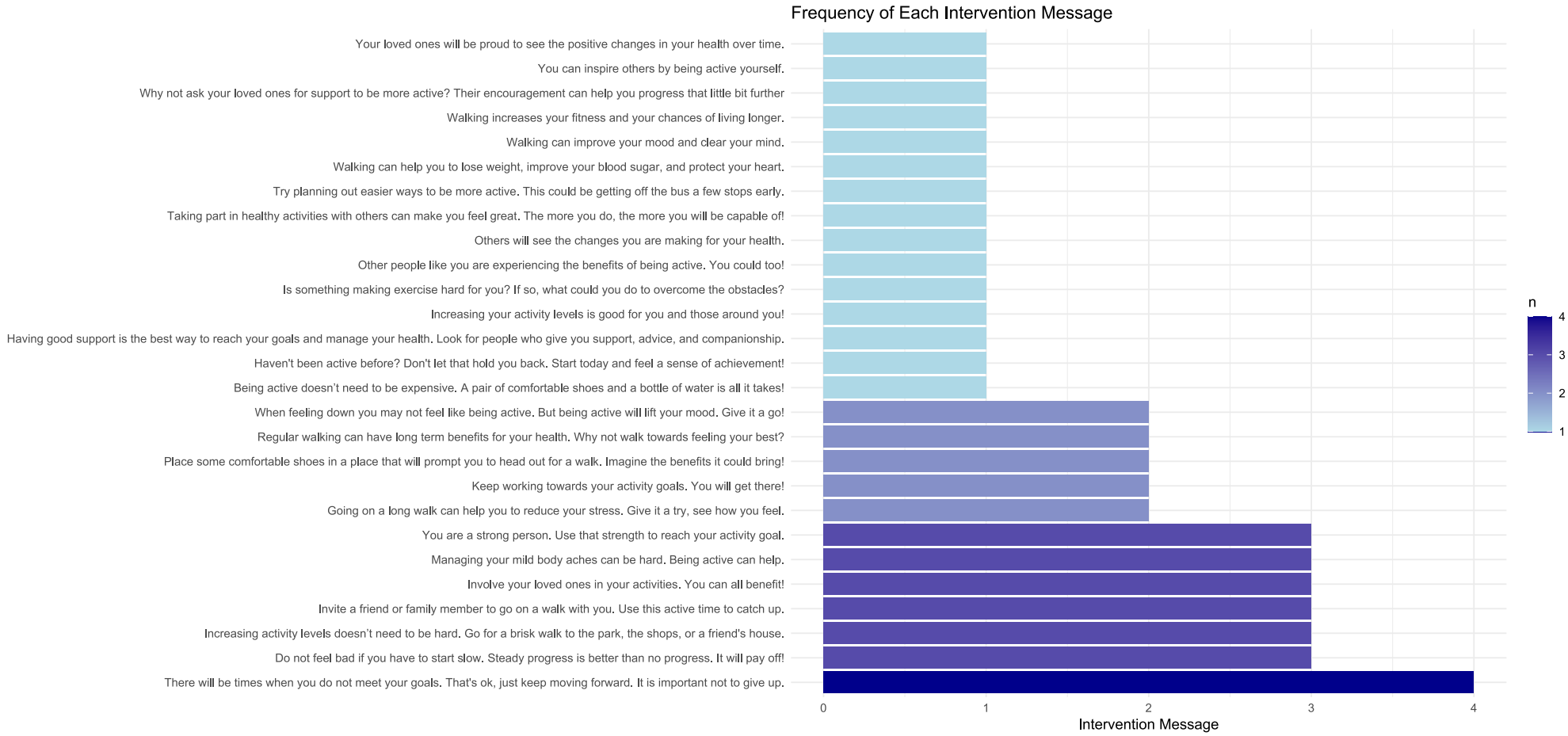


Figure 7.7 Frequency of intervention.

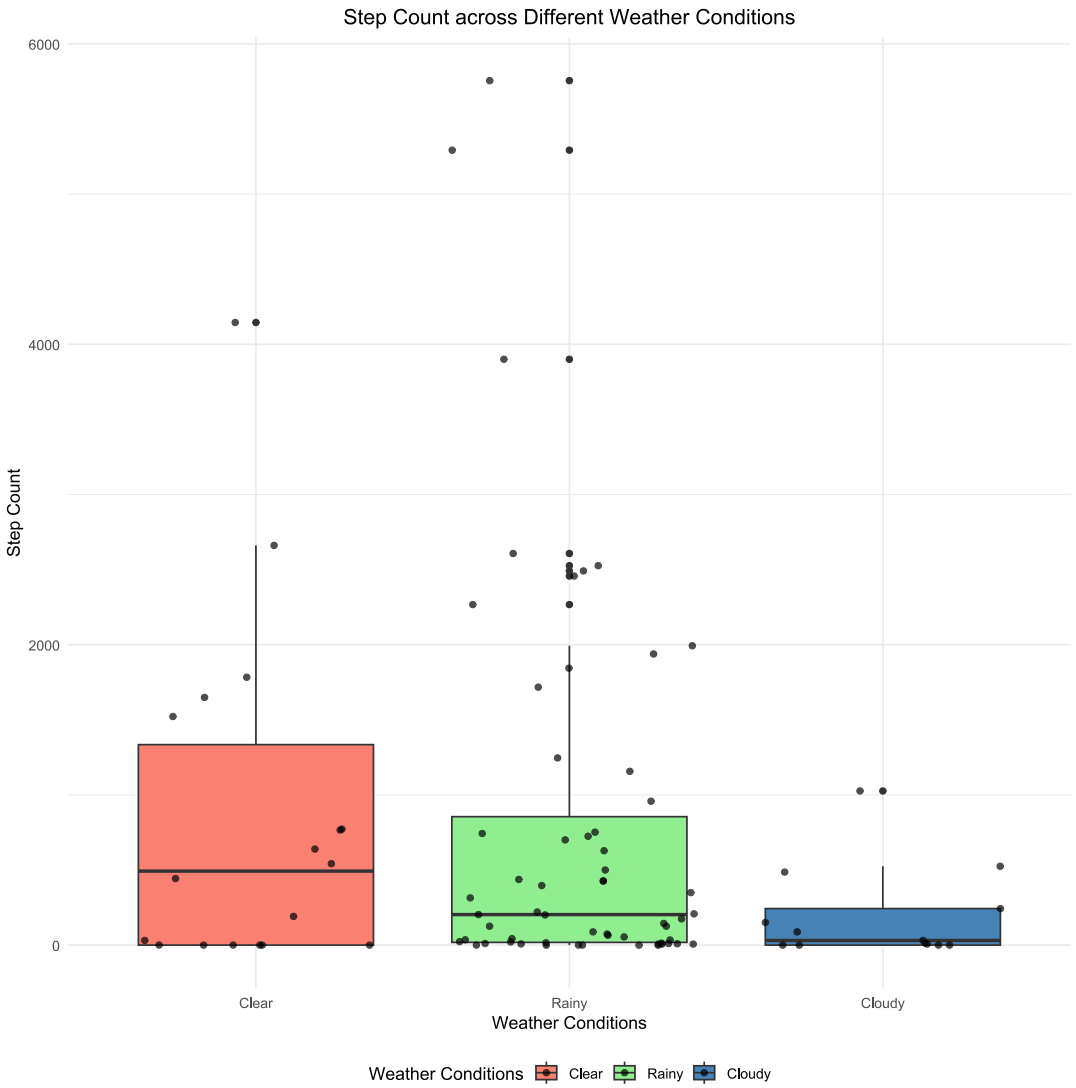


Figure 7.8 Step count across daily weather conditions.

The case study outcomes in Chapter 7 highlighted the potential of gamified digital health interventions while also revealing areas for improvement and further research. Chapter 8 synthesises these findings with insights from the preceding chapters, providing a comprehensive discussion of their implications for public health, clinical practice, and future research. This chapter reflects on the contributions of the thesis to the field of vascular health, emphasising the integration of lifestyle and digital interventions as a promising approach to combating cardiovascular diseases.

Chapter 8 critically evaluates the strengths and limitations of the research, considering methodological challenges, participant variability, and the scalability of interventions. It also explores the broader implications of the findings, such as their relevance to policy development, healthcare delivery, and the design of future studies. By connecting the diverse strands of research, the chapter offers a cohesive narrative that underscores the thesis's significance.

Finally, the chapter outlines recommendations for future work, focusing on enhancing intervention design, leveraging technological advancements, and addressing barriers to implementation. Chapter 8 concludes by reaffirming the thesis's central argument: that an integrated approach combining lifestyle modifications and digital health innovations is essential for addressing the growing burden of cardiovascular diseases.

8 Chapter 8: Discussion

The concluding chapter of this thesis provides an in-depth discussion of the principal findings, as illustrated in **Figure 8.1**. Additionally, it highlights potential avenues for future research that would expand and enhance the body of work presented in this thesis.

An improved understanding of vascular ageing and digital health intervention strategies

Prevalence of vascular ageing	**DHI RCT on vascular function**	**Digital health apps on cardiovascular risk**	**Results from a targeted DHI**
Key result 1 Higher carotid intima-media thickness (CIMT) was significantly associated with an increased incidence of coronary heart disease (CHD) and myocardial infarction (MI).	**Key result 1** Significant weight loss was observed among those with access to the app, indicating the potential of digital health interventions in promoting weight loss and improving vascular function.	**Key result 1** Apps with gamification elements led to improvements in biomarkers such as HbA1c and body weight, although there were no significant changes in LDL cholesterol and systolic blood pressure (SBP).	**Key result 1** Motivational messages had a positive impact on physical activity, with mid-morning messages (around 11 am) being the most effective in increasing daily step counts.
Key result 2 The cumulative burden of cardiometabolic risk factors, quantified by the CRBI score, showed a strong correlation with increased CIMT.	**Key result 2** While there were improvements in vascular function, cardiometabolic markers did not show significant changes in the short term, suggesting the need for longer-duration studies with more participants.	**Key result 2** User interest and engagement, driven by game elements targeting intrinsic motivation, were key factors in the success of gamified health interventions.	**Key result 2** Messages that emphasised long-term benefits and addressed mild body aches resulted in higher average step counts.
Key result 3 The CRBI score was a significant predictor of future cardiovascular events, highlighting the importance of comprehensive risk management in preventing cardiovascular diseases (CVDs).	**Key result 3** The digital platform to deliver this intense lifestyle intervention was effective in individuals with LAP.	**Key result 3** Gamification enhanced the overall functionality scores of the apps, making them effective tools for managing cardiometabolic health.	**Key result 3** Regardless of the message target, the intervention led to more steps compared to the control group, demonstrating the effectiveness of targeted, timely health interventions in promoting physical activity.

Figure 8.1 Summary of thesis outcomes.
CVD, cardiovascular disease; DHI, digital health intervention; RCT, randomised controlled trial.

8.1 Summary of key findings

By analysing data from the large prospective UKBB study (**Chapter 2**) with over 29,000 participants, all free of cardiovascular diseases at baseline, with ultrasound measurements of CIMT, we found that higher CIMT is linked to an increased risk of incident CHD, myocardial infarction, and heart failure, but not stroke, dementia, peripheral vascular disease, or aortic aneurysm. The near-linear dose-response relationship for CHD and MI highlights CIMT's potential as a predictive marker for these conditions, especially when combined with the cumulative cardiometabolic risk index (CRBI) score. Notably, CRBI was a stronger predictor of increased CIMT and the risk of developing CHD and MI than individual risk factors alone. These findings underscore the importance of maintaining optimal cardiometabolic risk factor levels to reduce CIMT and subsequent cardiovascular risk.

Preliminary findings from the ongoing LIVEPLUS trial, as detailed in **Chapter 4**, indicate that an intensive lifestyle intervention, which includes a 5:2 pescovegetarian diet, regular exercise training, and a stress-reduction mindfulness component, may lead to significant weight loss at 6 months. Early data indicate that the digital intervention used in this trial effectively aided both participants and researchers in monitoring and promoting adherence to lifestyle changes, such as tracking compliance with weight loss and physical activity volume and intensity. These findings underscore the potential of digital health tools to enhance cardiovascular function. Although significant improvements in vascular function were observed, the cardiometabolic markers did not yet show significant changes, likely due to the small number of participants recruited so far and the short duration of the study. We are confident that as we increase the sample size by recruiting more participants and follow them through the 12-month intervention, we will be able to draw more definitive conclusions regarding the sustained impact of these interventions.

These preliminary findings on the effectiveness of digital health technology are bolstered by data already published. **Chapter 5**'s systematic review on gamification provided compelling evidence that health applications incorporating game elements led to significant improvements in key biomarkers, such as body weight and circulating HbA1c levels. However, the review found no significant changes in LDL-cholesterol and systolic blood pressure. The success of these gamified health interventions was primarily driven by increased user engagement and sustained interest, which were attributed to the intrinsic motivation fostered by game elements. This highlights the potential of gamification to significantly enhance the functionality and effectiveness of health apps in managing cardiometabolic health, offering a dynamic and engaging approach to health management.

The preliminary results of the micro-randomised trial presented in **Chapter 7** suggest the powerful impact of motivational messages on physical activity levels. These preliminary findings suggest that messages sent during mid-morning, specifically around 11 am, were most effective in increasing daily step counts. Moreover, messages that emphasised long-term health benefits and addressed common concerns such as mild body aches resulted in higher average step counts. This highlights the potential critical importance of message timing and content in motivating physical activity. Irrespective of the specific message target, the intervention consistently led to a significant increase in steps compared to

the control group. These preliminary findings underscore the effectiveness of targeted, timely health interventions in promoting increased physical activity levels and supporting healthier lifestyles.

Chapter 8 summarises the key findings, implications, and limitations of the studies discussed throughout this thesis, with a particular emphasis on leveraging digital health interventions for managing cardiometabolic diseases. The chapter concludes by recommending targeted strategies to enhance the effectiveness of these digital interventions, particularly through the customisation of exercise programs for adults experiencing obesity-related cardiometabolic issues.

8.1.1 Lifestyle

Lifestyle interventions are essential in the prevention and management of atherosclerotic CVDs. As illustrated in **Chapter 4**, intensive lifestyle changes facilitated through digital platforms was effective in managing cardiovascular health among LAP individuals, leading to significant weight loss. This weight reduction is crucial for mitigating CVD risk. Moreover, the improvement in vascular function observed in a short timeframe, despite not yet reflecting in cardiometabolic markers, indicates the potential long-term benefits of sustained lifestyle modifications. **Chapter 7**'s findings on motivational messages further underscore the efficacy of lifestyle interventions. Messages emphasising long-term benefits of walking and addressing concerns like mild body aches resulted in higher average step counts, demonstrating that targeted, timely health interventions can effectively promote healthier habits. These lifestyle changes, reinforced through digital platforms and motivational messaging, align with public health strategies aiming to reduce the incidence of major cardiovascular events through behaviour change. Additionally, **Chapter 2**'s analysis of the UK Biobank cohort showed that higher CIMT values were strongly associated with increased risk of CHD and myocardial infarction, emphasising the critical role of lifestyle management in mitigating these risks. The findings from **Chapter 2** on CIMT highlight the foundational role of vascular markers in predicting CVD risk. This builds on the causal inferences made possible through the controlled interventions discussed in **Chapter 4**, where lifestyle changes were systematically assessed for their impact on vascular function and cardiometabolic health.

8.1.2 Digital Health

Digital health solutions offer promising avenues for enhancing patient outcomes in cardiovascular risk management. **Chapter 4**'s findings on the effectiveness of intensive lifestyle interventions via digital platforms in LAP individuals illustrate the feasibility and success of these interventions in real-world settings. These platforms facilitated significant weight loss, a crucial factor in reducing CVD risk. Furthermore, **Chapter 5**'s systematic review on gamification reveals that incorporating game elements into health apps significantly improves biomarkers such as HbA1c and body weight. Gamification enhances user interest and engagement, critical for sustained app use. The success of these digital interventions underscores the importance of leveraging technology to deliver personalised and engaging health management strategies. **Chapter 7**'s exploration of motivational messages through mobile technology confirms that well-timed and targeted digital interventions may promote physical activity and healthier lifestyles. These preliminary data suggest that mid-morning messages were particularly effective, indicating the importance of optimal timing in public health initiatives to maximise engagement and behaviour change. Digital nudges, tailored to individual needs and sent at strategic

times, have shown to significantly increase daily activity levels, promoting a more active and healthier lifestyle. The results in **Chapter 5** emphasise the potential of gamification to enhance user engagement and adherence, as further explored in **Chapter 7** using the MIRTH protocol. These findings suggest that digital interventions could complement traditional strategies, addressing adherence challenges noted in **Chapters 3** and **4**.

8.1.3 Vascular Function

Vascular function is a critical indicator of cardiovascular health, with clinical tools such as CIMT providing valuable insights into the risk of CHD and MI. **Chapter 2** highlights the significant association between higher CIMT and increased incidence of CHD and MI, suggesting that CIMT serves as a predictive clinical tool for major cardiovascular events. This finding underscores the importance of comprehensive cardiometabolic risk management to prevent CVDs, reinforcing the need for early interventions in at-risk individuals. The UK Biobank study, involving 29,292 participants, revealed significant variances in CIMT across different demographic and lifestyle factors. For instance, each additional year of age was associated with a 6.05 μm increase in CIMT, while being male contributed to a 13.02 μm higher CIMT compared to females. The cumulative burden of cardiometabolic risk factors, quantified by the CRBI score, was strongly associated with higher CIMT, highlighting the multifaceted nature of vascular health. Furthermore, **Chapter 4's** findings on the improvement of vascular function through intensive lifestyle interventions support the potential benefits of sustained lifestyle changes. Despite a minor increase in CIMT suggesting dietary interventions alone may not suffice, the comprehensive analysis of lifestyle, demographic, and cardiometabolic factors in **Chapter 2** contributes to a deeper understanding of vascular aging processes. These findings collectively highlight the critical role of vascular function monitoring and comprehensive risk management in the early detection and prevention of cardiovascular diseases.

8.1 Broader implications for clinical care

The findings from this thesis show the significant clinical implications of monitoring CIMT as a predictive tool for major cardiovascular events. The association between higher CIMT and increased incidence of CHD and MI suggests that regular CIMT assessments can enable early identification and intervention for at-risk individuals. This aligns with the broader clinical practice of comprehensive risk management, highlighting the necessity of addressing multiple cardiometabolic risk factors simultaneously. For example, maintaining a healthy diet can improve LDL cholesterol, glucose and blood pressure levels, while regular exercise can enhance insulin sensitivity, which are crucial for cardiovascular health. The CRBI score's robust predictive power for future cardiovascular events emphasises the need for a multifaceted approach in clinical care, distinct from existing tools such as the ASCVD Risk Estimator,[411] which does not incorporate CIMT measurements. The current Australian guidelines also do not include CIMT,[412] yet this thesis suggest its potential value. The association between CIMT and modifiable lifestyle behaviours, as highlighted in **Chapter 2**, underscores the critical role of addressing behavioural risk factors early in clinical care to mitigate the progression of atherosclerosis. Furthermore, the LIVEPLUS Protocol demonstrated that a structured, intensive lifestyle program could be implemented

in real-world clinical settings, offering a scalable approach to improve vascular outcomes across diverse patient populations

Furthermore, the results of this thesis show the feasibility of using digital platforms for cardiovascular management in specific patient cohorts. The improvements in vascular function observed in **Chapter 2** suggest that digital health interventions could contribute towards reducing CVD risk and plaque burden, although further research with longer durations and larger sample size is required to confirm these findings. **Chapter 5** specifically examined whether gamification could enhance weight loss, finding that health apps incorporating game elements indeed may lead to improved biomarkers such as HbA1c and body weight. These findings indicate that gamification may effectively increase user engagement and motivation, crucial for sustained health behaviour changes. Apps utilising gamification thus hold significant promise for health and weight loss interventions, aligning with Australian government policies to empower individuals with health information and promote self-management.

Additionally, the research underscores the efficacy of targeted, timely health interventions in promoting healthier lifestyles. Motivational messages that address individual motivations and concerns, such as long-term benefits and mild body aches, have been shown to be particularly effective in increasing physical activity levels, as confirmed by **Chapter 5**'s findings on intrinsic motivation. This thesis contributes to the growing body of evidence suggesting that optimal timing, such as mid-morning messages, can enhance the efficacy of public health interventions. However, more extensive studies are needed to understand the mechanisms behind health messaging effectiveness across diverse demographics and to evaluate the long-term impacts on sustained behaviour change. These insights are crucial for developing more effective public health strategies and interventions that can adapt to the needs of varied populations, ultimately improving cardiovascular health outcomes on a broader scale.

8.2 Limitations

Despite the valuable insights provided by this thesis, several limitations must be acknowledged. First, the study design of the UKBB, which involves CIMT measurements and their correlation with cardiometabolic risk factors, limits our ability to establish causation. While strong associations were observed, causality cannot be definitively determined. The inherent limitations of observational studies, such as residual confounding and reverse causality, remain significant despite statistical adjustments. Factors such as unmeasured behavioural or genetic influences may bias the observed associations between lifestyle factors and cardiometabolic outcomes. CIMT, while a useful predictor of cardiovascular risk, may not fully capture the complexity of atherosclerotic disease progression, as it serves as a surrogate marker with varying predictive accuracy based on population and measurement techniques. To establish causal relationships between CIMT, CRBI scores, and cardiovascular events, Mendelian randomisation are required. Second, the UK Biobank study population may not be fully representative of the broader population. Its cohort, predominantly comprising healthier and more health-conscious individuals, introduces a potential selection bias that could limit the generalisability of the findings. Furthermore, the demographic homogeneity of this cohort, especially regarding ethnicity, may not reflect the diverse populations encountered in clinical practice. The overrepresentation of health-conscious individuals within the UK Biobank cohort introduces healthy volunteer bias, which

could skew findings and limit applicability to less health-engaged populations. The lack of inclusion of individuals from rural areas, socioeconomically disadvantaged groups, or varying healthcare access settings reduces the generalisability of the findings, particularly for underserved populations. **Chapters 2**, **3**, and **4** highlight critical limitations, including the observational nature of some data, the small sample size in intervention studies, and the relatively short duration of follow-up. These factors limit the ability to draw definitive conclusions, although observed trends provide valuable insights into potential mechanisms and effects.

The digital health interventions examined in **Chapter 4**, although promising, were tested over relatively short durations and involved a small sample size. As a result, the long-term sustainability and generalisability of these interventions remain uncertain, highlighting the need for further research with extended follow-up periods and more diverse populations. The relatively short duration of follow-up across several interventions, ranging from weeks to months, may not reflect the long-term sustainability or health outcomes of the strategies evaluated. For interventions such as gamification and motivational messaging, the absence of longitudinal data means that the persistence of observed behavioural changes remains uncertain. **Chapter 5**'s analysis of gamification in health apps also faces limitations due to the heterogeneity among the included studies, the variability in app designs, and the potential for publication bias. While the meta-analysis provided comprehensive insights, it revealed considerable variability in outcome measures, which could impact the reliability and applicability of the findings. The systematic reviews, particularly those assessing gamification, faced methodological limitations due to substantial heterogeneity in study designs, app functionalities, and evaluation criteria, which challenge the interpretation of summary results. Positive outcomes were observed; however, the short follow-up periods may not capture the long-term effects or sustainability of these benefits. Additionally, the effectiveness of digital health interventions and gamification strategies may not be uniform across all demographics. Factors such as age, digital literacy, and socioeconomic status could influence engagement and outcomes. The effectiveness of digital health interventions is contingent on user proficiency with technology, yet variability in digital literacy, especially among older adults or individuals from low socioeconomic backgrounds, could impact engagement and outcomes. To address these issues, further research is needed to explore how these variables affect the efficacy of digital health tools. Larger and longer-term randomised controlled trials are essential to confirm the effectiveness and durability of these interventions.

The motivational messaging intervention assessed in **Chapter 7** demonstrated positive effects on physical activity; however, the study did not explore the intensity or quality of the activity, which are important factors in cardiovascular health. The timing and content of messages showed efficacy, but the mechanisms underlying these effects, and their long-term sustainability were not fully elucidated. The study also faced limitations in sample size and demographic diversity, which may impact the generalisability of the findings to broader populations. The underlying mechanisms driving the observed effects of motivational messaging and gamification strategies remain poorly understood, necessitating further research to clarify psychological and behavioural pathways.

Another limitation is the reliance on self-reported data for certain lifestyle factors, such as physical activity and dietary habits. Self-reported data can be prone to inaccuracies and biases, potentially affecting the reliability of the findings. Outcome measures such as self-reported physical activity or dietary patterns are inherently prone to recall bias and social desirability bias, potentially overestimating adherence or underreporting undesirable behaviours. Objective measurements, such as wearable device data, were not consistently used across studies, limiting the accuracy of assessments and comparability of findings. This can lead to over- or underestimation of the true effects of the interventions. Objective measures, such as wearable fitness trackers and dietary logs, would provide more accurate assessments. Additionally, while the CRBI score proved to be a strong predictor of cardiovascular events, its applicability across different ethnicities and populations needs further validation, given that the study primarily included participants from the UK Biobank. Lastly, the current Australian guidelines for CVD management do not include CIMT as a standard assessment tool, limiting the immediate clinical application of the thesis findings within the existing healthcare framework. Integrating CIMT and digital health strategies into routine clinical practice would require significant changes in clinical guidelines, training, and resource allocation. The integration of CIMT assessments and digital health interventions into routine clinical practice faces significant logistical and economic barriers, including the need for practitioner training, resource allocation, and updates to clinical guidelines. Current healthcare policies may not fully support the adoption of advanced digital tools or the inclusion of surrogate markers such as CIMT, further complicating clinical translation.

While the research presented in this thesis advances our understanding of cardiovascular risk management, the limitations related to study design, population diversity, measurement techniques, and the need for longer-term and larger-scale studies must be considered when interpreting the findings and their broader implications for clinical practice. Addressing these limitations will be crucial in advancing our understanding of cardiometabolic diseases and refining digital health interventions to maximise their benefit for individuals with or at risk of such conditions.

8.3 Future directions

Building on the findings of this thesis, several future research directions are proposed to advance the understanding and management of atherosclerotic CVD and CHD. Firstly, there is a need for Mendelian randomisation studies and randomised clinical trials to establish causal relationships between CIMT, CRBI scores, and cardiovascular events. Such studies will offer critical insights into the progression of atherosclerosis and the long-term effects of various interventions on cardiovascular outcomes. Additionally, future research should strive to include participants from diverse ethnic backgrounds and socioeconomic statuses to ensure that findings are generalisable to the broader population. This approach will help in understanding how different demographic factors influence cardiovascular health and the effectiveness of interventions.

To validate the findings related to digital health interventions and gamification, future research should focus on longer-duration studies with larger sample sizes. Large-scale, randomised controlled trials are needed to assess the long-term impacts of digital health platforms and gamification strategies on cardiovascular health, determining the sustainability of observed benefits. Incorporating objective

measures, such as wearable fitness trackers, continuous glucose monitors, and detailed dietary logs, can improve the accuracy of data on physical activity, dietary habits, and other lifestyle factors, reducing reliance on self-reported data. Additionally, research should explore the integration of these digital tools into routine clinical practice to enhance patient outcomes. Future studies should also aim to optimise digital health interventions by personalising content and leveraging advanced technologies like artificial intelligence and machine learning to tailor interventions in real-time and support behaviour change more effectively.

Further research is needed to understand the mechanisms behind the effectiveness of motivational and health messaging strategies. Investigating how various demographic groups respond to different message contents, timings, and delivery methods will help maximise engagement and behaviour change across diverse populations. Additionally, studying the psychological and behavioural mechanisms driving these responses will aid in developing more targeted public health interventions. Research should also explore how factors like age, digital literacy, and socioeconomic status influence engagement with digital health tools and the effectiveness of these interventions.

Future research should focus on comparative effectiveness studies to evaluate CIMT against established risk assessment methods like the ASCVD risk calculator, determining its added value in routine cardiovascular risk evaluation. Additionally, it is crucial to develop and assess multi-faceted approaches to cardiometabolic health, exploring how lifestyle modifications, pharmacological treatments, and digital health tools can synergistically reduce cardiovascular risk and enhance health outcomes. Interdisciplinary research integrating cardiology, behavioural science, digital health, and public health will be essential for creating comprehensive strategies for CVD prevention and management. Collaborative efforts among researchers, healthcare providers, and policymakers are needed to translate findings into practical, widely implemented interventions that reduce cardiovascular disease burden. Finally, research should emphasise integrating these insights into clinical practice and public health policies. Scaling up evidence-based interventions at the policy level will be vital for improving population health and developing more effective, personalised, and sustainable strategies for cardiovascular disease prevention and management.

8.4 Final recommendations

Based on the findings of this thesis, we suggest integrating CIMT into routine clinical practice in high-risk individuals due to its strong predictive value for CHD and heart failure. Moreover, combining CIMT measurements with traditional risk assessment tools may enhance the identification of high-risk individuals and support early intervention. Comprehensive risk management should include lifestyle modifications, pharmacological treatments, and continuous monitoring of cardiometabolic indicators. The effectiveness of digital health interventions demonstrated in this thesis suggests they should be considered for lifestyle changes, weight management, and cardiovascular health. Health apps with gamification elements can improve user engagement and outcomes, and collaboration between developers and healthcare providers is essential for creating effective gamified tools. Effective health

messaging should be well-timed and content-specific to enhance public health initiatives. Targeted messages addressing individual motivations can promote healthier behaviours. Future research should include diverse populations to ensure recommendations are inclusive and applicable across different demographics. Long-term studies are needed to confirm the sustained benefits of short-term interventions. Public health campaigns should raise awareness about cardiovascular risk assessment and lifestyle modifications, empowering individuals to manage their health effectively. Implementing these recommendations will improve cardiovascular disease prevention and management, leading to better health outcomes and reduced cardiovascular events.

8.5 Conclusions

This thesis highlights CIMT's crucial role as a predictive tool for atherosclerotic cardiovascular diseases (CVDs), demonstrating its strong link to coronary heart disease (CHD) and myocardial infarction. It emphasises the need to incorporate CIMT into routine clinical practice, complemented by comprehensive risk management strategies for high-risk individuals that address the cumulative burden of cardiometabolic risk factors. The research also indicates that digital health platforms can be effective for weight loss and improving vascular function, though more long-term studies are required. Additionally, gamification in health apps significantly boosts user engagement and improves biomarkers such as HbA1c and body weight. Targeted motivational messages were shown to effectively encourage physical activity and healthier lifestyle choices. By addressing these limitations in future research, this body of work provides a framework for advancing both scientific understanding and practical implementation of lifestyle interventions in cardiometabolic health.

References

1. Katta N, Loethen T, Lavie CJ, Alpert MA. Obesity and coronary heart disease: Epidemiology, pathology, and coronary artery imaging. Current Problems in Cardiology. 2021;46(3):100655.
2. World Health Organization. Cardiovascular diseases. [Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds).
3. Tsao CW, Aday AW, Almarzooq ZI, Alonso A, Beaton AZ, Bittencourt MS, et al. Heart disease and stroke statistics—2022 update: A report from the American Heart Association. Circulation. 2022;145(8):e153-e639.
4. Wong ND. Epidemiological studies of CHD and the evolution of preventive cardiology. Nature Reviews Cardiology. 2014;11(5):276-89.
5. Lichtenstein AH, Appel LJ, Vadiveloo M, Hu FB, Kris-Etherton PM, Rebholz CM, et al. 2021 dietary guidance to improve cardiovascular health: A scientific statement from the American Heart Association. Circulation. 2021;144(23):e472-e87.
6. Shaya GE, Leucker TM, Jones SR, Martin SS, Toth PP. Coronary heart disease risk: Low-density lipoprotein and beyond. Trends in Cardiovascular Medicine. 2022;32(4):181-94.
7. Kopp W. How Western diet and lifestyle drive the pandemic of obesity and civilization diseases. Diabetes Metab Syndr Obes. 2019;12:2221-36.
8. Mason KE, Pearce N, Cummins S. Associations between fast food and physical activity environments and adiposity in mid-life: cross-sectional, observational evidence from UK Biobank. Lancet Public Health. 2018;3(1):e24-e33.
9. Powell-Wiley TM, Poirier P, Burke LE, Després J-P, Gordon-Larsen P, Lavie CJ, et al. Obesity and cardiovascular disease: A scientific statement from the American Heart Association. Circulation. 2021;143(21):e984-e1010.
10. Long MT, Fox CS. The Framingham Heart Study — 67 years of discovery in metabolic disease. Nature Reviews Endocrinology. 2016;12(3):177-83.
11. Wilson PWF. Established risk factors and coronary artery disease: The Framingham Study. American Journal of Hypertension. 1994;7(7_Pt_2):7S-12S.
12. Thiriet M. Cardiovascular disease: An introduction. In: Thiriet M, editor. Vasculopathies: Behavioral, Chemical, Environmental, and Genetic Factors. Cham: Springer International Publishing; 2018. p. 1-90.
13. Ross R. Atherosclerosis — An inflammatory disease. New England Journal of Medicine. 1999;340(2):115-26.
14. Lusis AJ. Atherosclerosis. Nature. 2000;407(6801):233-41.
15. Huang PL. A comprehensive definition for metabolic syndrome. Dis Model Mech. 2009;2(5-6):231-7.
16. National Health Survey: First results. Australian Bureau of Statistics. [Available from: https://www.abs.gov.au/statistics/health/health-conditions-and-risks/national-health-survey/2017-18.
17. Australian Bureau of Statistics. Heart, stroke and vascular disease (December 2018): ABS Website; [Available from: https://www.abs.gov.au/statistics/health/health-conditions-and-risks/heart-stroke-and-vascular-disease/latest-release.
18. Heart, stroke and vascular disease: Australian facts. Australian Institute of Health and Welfare. [updated 17 June 2024. Available from: https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/hsvd-facts/contents/disease-types.
19. Australian Institute of Health and Welfare. Heart, stroke and vascular disease: Australian facts (February 2023): Web report; [Available from: https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/hsvd-facts/contents/about.
20. Australian Institute of Health and Welfare. Burden of disease. 2019.
21. Australian Institute of Health and Welfare. Trends in cardiovascular deaths (September 2017): Web report; [Available from: https://www.aihw.gov.au/getmedia/2ba74f7f-d812-4539-a006-ca39b34d8120/aihw-21213.pdf.
22. Carmena R, Duriez P, Fruchart J-C. Atherogenic lipoprotein particles in atherosclerosis. Circulation. 2004;109(23_suppl_1):III-2-III-7.
23. Mahmood S. Pathophysiology of coronary artery disease. In: Movahed A, Gnanasegaran G, Buscombe J, Hall M, editors. Integrating Cardiology for Nuclear Medicine Physicians: A Guide to Nuclear Medicine Physicians. Berlin, Heidelberg: Springer Berlin Heidelberg; 2009. p. 23-30.
24. Libby P, Buring JE, Badimon L, Hansson GK, Deanfield J, Bittencourt MS, et al. Atherosclerosis. Nature Reviews Disease Primers. 2019;5(1):56.
25. Haase R, Schlattmann P, Gueret P, Andreini D, Pontone G, Alkadhi H, et al. Diagnosis of obstructive coronary artery disease using computed tomography angiography in patients with stable

chest pain depending on clinical probability and in clinically important subgroups: Meta-analysis of individual patient data. BMJ (Clinical research ed). 2019;365:l1945.
26. Cohn JN. Arterial stiffness, vascular disease, and risk of cardiovascular events. Circulation. 2006;113(5):601-3.
27. Jackson SP. Arterial thrombosis—insidious, unpredictable and deadly. Nature Medicine. 2011;17(11):1423-36.
28. Mitchell GF, Powell JT. Arteriosclerosis. Arteriosclerosis, Thrombosis, and Vascular Biology. 2020;40(5):1025-7.
29. Kong P, Cui Z-Y, Huang X-F, Zhang D-D, Guo R-J, Han M. Inflammation and atherosclerosis: signaling pathways and therapeutic intervention. Signal Transduction and Targeted Therapy. 2022;7(1):131.
30. Gupta RM, Hadaya J, Trehan A, Zekavat SM, Roselli C, Klarin D, et al. A genetic variant associated with five vascular diseases is a distal regulator of endothelin-1 gene expression. Cell. 2017;170(3):522-33.e15.
31. Libby P, Ridker PM, Maseri A. Inflammation and Atherosclerosis. Circulation. 2002;105(9):1135-43.
32. Döring Y, Soehnlein O, Weber C. Neutrophil extracellular traps in atherosclerosis and atherothrombosis. Circulation Research. 2017;120(4):736-43.
33. Libby P, Ridker Paul M, Hansson Göran K, Atherothrombosis. LTNo. Inflammation in atherosclerosis. Journal of the American College of Cardiology. 2009;54(23):2129-38.
34. Perera D, Berry C, Hoole SP, Sinha A, Rahman H, Morris PD, et al. Invasive coronary physiology in patients with angina and non-obstructive coronary artery disease: a consensus document from the coronary microvascular dysfunction workstream of the British Heart Foundation/National Institute for Health Research Partnership. Heart. 2023;109(2):88.
35. Shao C, Wang J, Tian J, Tang Y-d. Coronary artery disease: From mechanism to clinical practice. In: Wang M, editor. Coronary Artery Disease: Therapeutics and Drug Discovery. Singapore: Springer Singapore; 2020. p. 1-36.
36. Causes and risk factors. National Heart Lung and Blood Institute. [Available from: https://www.nhlbi.nih.gov/health/coronary-heart-disease/causes.
37. Myocardial ischemia. Mayo Clinic. [Available from: https://www.mayoclinic.org/diseases-conditions/myocardial-ischemia/symptoms-causes/syc-20375417.
38. Bischops AC, De Neve J-W, Awasthi A, Vollmer S, Bärnighausen T, Geldsetzer P. A cross-sectional study of cardiovascular disease risk clustering at different socio-geographic levels in India. Nature Communications. 2020;11(1):5891.
39. Tian F, Chen L, Qian Z, Xia H, Zhang Z, Zhang J, et al. Ranking age-specific modifiable risk factors for cardiovascular disease and mortality: evidence from a population-based longitudinal study. eClinicalMedicine. 2023;64.
40. van Oort S, Beulens JWJ, van Ballegooijen AJ, Grobbee DE, Larsson SC. Association of cardiovascular risk factors and lifestyle behaviors with hypertension. Hypertension. 2020;76(6):1971-9.
41. Mozaffarian D, Wilson PWF, Kannel WB. Beyond established and novel risk factors. Circulation. 2008;117(23):3031-8.
42. Singar S, Kadyan S, Patoine C, Park G, Arjmandi B, Nagpal R. The effects of almond consumption on cardiovascular health and gut microbiome: A comprehensive review. Nutrients [Internet]. 2024; 16(12).
43. North BJ, Sinclair DA. The intersection between aging and cardiovascular disease. Circulation Research. 2012;110(8):1097-108.
44. Daly CA, Clemens F, Sendon JLL, Tavazzi L, Boersma E, Danchin N, et al. The clinical characteristics and investigations planned in patients with stable angina presenting to cardiologists in Europe: from the Euro Heart Survey of Stable Angina. European Heart Journal. 2005;26(10):996-1010.
45. Meloni A, Cadeddu C, Cugusi L, Donataccio MP, Deidda M, Sciomer S, et al. Gender differences and cardiometabolic risk: The importance of the risk factors. Int J Mol Sci. 2023;24(2).
46. Yang HJ, Koh E, Kang Y. Susceptibility of women to cardiovascular disease and the prevention potential of mind-body intervention by changes in neural circuits and cardiovascular physiology. Biomolecules. 2021;11(5).
47. Boutari C, Rizos CV, Doumas M, Liamis G, Skoumas I, Rallidis L, et al. Prevalence of diabetes and its association with atherosclerotic cardiovascular disease risk in patients with familial hypercholesterolemia: An analysis from the Hellenic Familial Hypercholesterolemia Registry (HELLAS-FH). Pharmaceuticals (Basel). 2022;16(1).

48. Taylor CN, Wang D, Larson MG, Lau ES, Benjamin EJ, D'Agostino RB, et al. Family history of modifiable risk factors and association with future cardiovascular disease. Journal of the American Heart Association. 2023;12(6):e027881.
49. Chaturvedi N. Ethnic differences in cardiovascular disease. Heart. 2003;89(6):681-6.
50. Fuchs FD, Whelton PK. High blood pressure and cardiovascular disease. Hypertension. 2020;75(2):285-92.
51. Consortium TGCR. Global effect of modifiable risk factors on cardiovascular disease and mortality. New England Journal of Medicine. 2023;389(14):1273-85.
52. Cornier M-A, Dabelea D, Hernandez TL, Lindstrom RC, Steig AJ, Stob NR, et al. The Metabolic Syndrome. Endocrine Reviews. 2008;29(7):777-822.
53. Samson SL, Garber AJ. Metabolic syndrome. Endocrinology and Metabolism Clinics. 2014;43(1):1-23.
54. Cameron AJ, Magliano DJ, Zimmet PZ, Welborn T, Shaw JE. The metabolic syndrome in Australia: Prevalence using four definitions. Diabetes Research and Clinical Practice. 2007;77(3):471-8.
55. Australian diabetes obesity and lifestyle study (AusDiab). [Available from: https://www.baker.edu.au/-/media/documents/impact/ausdiab/reports/ausdiab-report-2012.pdf.
56. Overweight and obesity among Australian children and adolescents. Australian Institute of Health and Welfare. [Available from: https://www.aihw.gov.au/reports/overweight-obesity/overweight-obesity-australian-children-adolescents/summary.
57. Libby P. Inflammation during the life cycle of the atherosclerotic plaque. Cardiovascular Research. 2021;117(13):2525-36.
58. Libby P. Inflammatory mechanisms: the molecular basis of inflammation and disease. Nutrition Reviews. 2007;65(suppl_3):S140-S6.
59. Wang Y, Osborne MT, Tung B, Li M, Li Y. Imaging cardiovascular calcification. Journal of the American Heart Association. 2018;7(13):e008564.
60. Wexler L, Brundage B, Crouse J, Detrano R, Fuster V, Maddahi J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. Circulation. 1996;94(5):1175-92.
61. Libby P, Theroux P. Pathophysiology of coronary artery disease. Circulation. 2005;111(25):3481-8.
62. Onnis C, Virmani R, Kawai K, Nardi V, Lerman A, Cademartiri F, et al. Coronary artery calcification: Current concepts and clinical implications. Circulation. 2024;149(3):251-66.
63. Obaid DR, Calvert PA, Gopalan D, Parker RA, Hoole SP, West NEJ, et al. Atherosclerotic plaque composition and classification identified by coronary computed tomography. Circulation: Cardiovascular Imaging. 2013;6(5):655-64.
64. Williams MC, Kwiecinski J, Doris M, McElhinney P, D'Souza MS, Cadet S, et al. Low-attenuation noncalcified plaque on coronary computed tomography angiography predicts myocardial infarction. Circulation. 2020;141(18):1452-62.
65. Virmani R, Burke AP, Kolodgie FD, Farb A. Vulnerable plaque: the pathology of unstable coronary lesions. J Interv Cardiol. 2002;15(6):439-46.
66. Stark K, Massberg S. Interplay between inflammation and thrombosis in cardiovascular pathology. Nature Reviews Cardiology. 2021;18(9):666-82.
67. Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. Inflammatory responses and inflammation-associated diseases in organs. Oncotarget. 2018;9(6):7204-18.
68. Rajendran P, Rengarajan T, Thangavel J, Nishigaki Y, Sakthisekaran D, Sethi G, et al. The vascular endothelium and human diseases. Int J Biol Sci. 2013;9(10):1057-69.
69. Townsley MI. Structure and composition of pulmonary arteries, capillaries, and veins. Comprehensive Physiology. p. 675-709.
70. Sandoo A, van Zanten JJCSV, Metsios GS, Carroll D, Kitas GD. The endothelium and its role in regulating vascular tone. Open Cardiovasc Med J. 2010;4:302-12.
71. Versari D, Daghini E, Virdis A, Ghiadoni L, Taddei S. Endothelial dysfunction as a target for prevention of cardiovascular disease. Diabetes Care. 2009;32 Suppl 2(Suppl 2):S314-S21.
72. Barquera S, Pedroza-Tobías A, Medina C, Hernández-Barrera L, Bibbins-Domingo K, Lozano R, et al. Global overview of the epidemiology of atherosclerotic cardiovascular disease. Archives of Medical Research. 2015;46(5):328-38.
73. Schutte AE, Kruger R, Gafane-Matemane LF, Breet Y, Strauss-Kruger M, Cruickshank JK. Ethnicity and arterial stiffness. Arteriosclerosis, Thrombosis, and Vascular Biology. 2020;40(5):1044-54.

74. Boutouyrie P, Chowienczyk P, Humphrey JD, Mitchell GF. Arterial stiffness and cardiovascular risk in hypertension. Circulation Research. 2021;128(7):864-86.
75. Zhang Y, Lacolley P, Protogerou AD, Safar ME. Arterial stiffness in hypertension and function of large arteries. American Journal of Hypertension. 2020;33(4):291-6.
76. Zheng M, Zhang X, Chen S, Song Y, Zhao Q, Gao X, et al. Arterial stiffness preceding diabetes. Circulation Research. 2020;127(12):1491-8.
77. Tsai JP, Hsu BG. Arterial stiffness: A brief review. Tzu Chi Med J. 2021;33(2):115-21.
78. Agbaje AO. Arterial stiffness precedes hypertension and metabolic risks in youth: a review. Journal of Hypertension. 2022;40(10).
79. Ecobici M, Stoicescu C. Arterial stiffness and hypertension - which comes first? Maedica (Bucur). 2017;12(3):184-90.
80. Feola M. The influence of arterial stiffness in heart failure: a clinical review. J Geriatr Cardiol. 2021;18(2):135-40.
81. Quinn U, Tomlinson LA, Cockcroft JR. Arterial stiffness. JRSM Cardiovasc Dis. 2012;1(6).
82. Sacre JW, Jennings GLR, Kingwell BA. Exercise and dietary influences on arterial stiffness in cardiometabolic disease. Hypertension. 2014;63(5):888-93.
83. Sakuragi S, Abhayaratna WP. Arterial stiffness: Methods of measurement, physiologic determinants and prediction of cardiovascular outcomes. International Journal of Cardiology. 2010;138(2):112-8.
84. Stehouwer CDA, Henry RMA, Ferreira I. Arterial stiffness in diabetes and the metabolic syndrome: a pathway to cardiovascular disease. Diabetologia. 2008;51(4):527-39.
85. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arterioscler Thromb Vasc Biol. 2005;25(5):932-43.
86. Chiuve SE, McCullough ML, Sacks FM, Rimm EB. Healthy lifestyle factors in the primary prevention of coronary heart disease among men. Circulation. 2006;114(2):160-7.
87. Rippe JM. Lifestyle strategies for risk factor reduction, prevention, and treatment of cardiovascular disease. Am J Lifestyle Med. 2019;13(2):204-12.
88. Tian D, Meng J. Exercise for prevention and relief of cardiovascular disease: prognoses, mechanisms, and approaches. Oxid Med Cell Longev. 2019;2019:3756750.
89. Hu FB. Diet and lifestyle influences on risk of coronary heart disease. Current Atherosclerosis Reports. 2009;11(4):257-63.
90. Giugliano D, Ceriello A, Esposito K. The effects of diet on inflammation: emphasis on the metabolic syndrome. J Am Coll Cardiol. 2006;48(4):677-85.
91. Tsigalou C, Konstantinidis T, Paraschaki A, Stavropoulou E, Voidarou C, Bezirtzoglou E. Mediterranean diet as a tool to combat inflammation and chronic diseases. An overview. Biomedicines. 2020;8(7).
92. Verschuren WMM, Boer JMA, Temme EHM. Optimal diet for cardiovascular and planetary health. Heart. 2022;108(15):1234.
93. Rowland I, Gibson G, Heinken A, Scott K, Swann J, Thiele I, et al. Gut microbiota functions: metabolism of nutrients and other food components. Eur J Nutr. 2018;57(1):1-24.
94. Wu HJ, Wu E. The role of gut microbiota in immune homeostasis and autoimmunity. Gut Microbes. 2012;3(1):4-14.
95. Fernandes J, Arts J, Dimond E, Hirshberg S, Lofgren IE. Dietary factors are associated with coronary heart disease risk factors in college students. Nutrition Research. 2013;33(8):647-52.
96. Fung TT, Willett WC, Stampfer MJ, Manson JE, Hu FB. Dietary patterns and the risk of coronary heart disease in women. Archives of internal medicine. 2001;161(15):1857-62.
97. Martínez-González MA, Gea A, Ruiz-Canela M. The Mediterranean diet and cardiovascular health. Circulation Research. 2019;124(5):779-98.
98. Pant A, Gribbin S, McIntyre D, Trivedi R, Marschner S, Laranjo L, et al. Primary prevention of cardiovascular disease in women with a Mediterranean diet: systematic review and meta-analysis. Heart. 2023;109(16):1208.
99. Gardner CD, Vadiveloo MK, Petersen KS, Anderson CAM, Springfield S, Van Horn L, et al. Popular dietary patterns: alignment with American heart association 2021 dietary guidance: A scientific statement from the American Heart Association. Circulation. 2023;147(22):1715-30.
100. Rock CL, Thomson C, Gansler T, Gapstur SM, McCullough ML, Patel AV, et al. American Cancer Society guideline for diet and physical activity for cancer prevention. CA: A Cancer Journal for Clinicians. 2020;70(4):245-71.
101. Bhupathiraju SN, Tucker KL. Coronary heart disease prevention: nutrients, foods, and dietary patterns. Clin Chim Acta. 2011;412(17-18):1493-514.

102. Butler T, Kerley CP, Altieri N, Alvarez J, Green J, Hinchliffe J, et al. Optimum nutritional strategies for cardiovascular disease prevention and rehabilitation (BACPR). Heart. 2020;106(10):724.
103. O'Keefe James H, Torres-Acosta N, O'Keefe Evan L, Saeed Ibrahim M, Lavie Carl J, Smith Sarah E, et al. A pesco-Mediterranean piet with intermittent fasting. Journal of the American College of Cardiology. 2020;76(12):1484-93.
104. Varady KA, Cienfuegos S, Ezpeleta M, Gabel K. Cardiometabolic benefits of intermittent fasting. Annu Rev Nutr. 2021;41:333-61.
105. Singh RB, Dubnov G, Niaz MA, Ghosh S, Singh R, Rastogi SS, et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean Diet Heart Study): a randomised single-blind trial. Lancet. 2002;360(9344):1455-61.
106. Martínez-González M, Toledo E, Arós F, Fiol M, Corella D, Salas-Salvadó J, et al. Extravirgin olive oil consumption reduces risk of atrial fibrillation: the PREDIMED (Prevención con Dieta Mediterránea) trial. Circulation. 2014;130(1):18-26.
107. Jääskeläinen E, Juola P, Hirvonen N, McGrath JJ, Saha S, Isohanni M, et al. A systematic review and meta-analysis of recovery in schizophrenia. Schizophr Bull. 2013;39(6):1296-306.
108. Healy GN, Dunstan DW, Salmon J, Cerin E, Shaw JE, Zimmet PZ, et al. Breaks in sedentary time: beneficial associations with metabolic risk. Diabetes Care. 2008;31(4):661-6.
109. Mattson MP, Longo VD, Harvie M. Impact of intermittent fasting on health and disease processes. Ageing research reviews. 2017;39:46-58.
110. Harder-Lauridsen NM, Nielsen ST, Mann SP, Lyngbæk MP, Benatti FB, Langkilde AR, et al. The effect of alternate-day caloric restriction on the metabolic consequences of 8 days of bed rest in healthy lean men: a randomized trial. Journal of applied physiology (Bethesda, Md : 1985). 2017;122(2):230-41.
111. Mattson MP, Allison DB, Fontana L, Harvie M, Longo VD, Malaisse WJ, et al. Meal frequency and timing in health and disease. Proceedings of the National Academy of Sciences. 2014;111(47):16647-53.
112. Saito M, Okamatsu-Ogura Y. Thermogenic brown fat in humans: implications in energy homeostasis, obesity and metabolic disorders. World J Mens Health. 2023;41(3):489-507.
113. Mattson MP, Moehl K, Ghena N, Schmaedick M, Cheng A. Intermittent metabolic switching, neuroplasticity and brain health. Nature Reviews Neuroscience. 2018;19(2):81-94.
114. Longo Valter D, Mattson Mark P. Fasting: Molecular mechanisms and clinical applications. Cell metabolism. 2014;19(2):181-92.
115. Michalsen A, Schneider S, Rodenbeck A, Lüdtke R, Huether G, Dobos GJ. The short-term effects of fasting on the neuroendocrine system in patients with chronic pain syndromes. Nutritional Neuroscience. 2003;6(1):11-8.
116. Fontana L, Partridge L. Promoting health and longevity through diet: From model organisms to humans. Cell. 2015;161(1):106-18.
117. Clifton KK, Ma CX, Fontana L, Peterson LL. Intermittent fasting in the prevention and treatment of cancer. CA: A Cancer Journal for Clinicians. 2021;71(6):527-46.
118. Kang J, Shi X, Fu J, Li H, Ma E, Chen W. Effects of an intermittent fasting 5:2 plus program on body weight in chinese adults with overweight or obesity: A pilot study. Nutrients [Internet]. 2022; 14(22).
119. Valenzuela PL, Carrera-Bastos P, Gálvez BG, Ruiz-Hurtado G, Ordovas JM, Ruilope LM, et al. Lifestyle interventions for the prevention and treatment of hypertension. Nature reviews Cardiology. 2021;18(4):251-75.
120. Cassidy S, Kroeger CM, Wang T, Mitra S, Liu C, Ribeiro RV, et al. Impact of an intensive lifestyle program on low attenuation plaque and myocardial perfusion in coronary heart disease: A randomised clinical trial protocol. Nutrition and healthy aging. 2022;7:9-22.
121. Valeria Tosti RAB, Beatrice Bertozzi, Nicola Veronese, Francesco Spelta, Edda Cava, Mark P. Mattson, Laura Piccio, Dayna S Early, Richard D Head, Luigi Fontana. When a calorie is not a calorie: metabolic and molecular effects of intermittent fasting in humans; exploratory outcomes of a randomized clinical trial. Aging Biology. 2022;1(Manuscript in Press).
122. Hajar R. Risk factors for coronary artery disease: Historical perspectives. Heart Views. 2017;18(3):109-14.
123. Carnethon MR. Physical activity and cardiovascular disease: how much is enough? Am J Lifestyle Med. 2009;3(1 Suppl):44s-9s.
124. Chen H, Chen C, Spanos M, Li G, Lu R, Bei Y, et al. Exercise training maintains cardiovascular health: signaling pathways involved and potential therapeutics. Signal Transduction and Targeted Therapy. 2022;7(1):306.

125. Nystoriak MA, Bhatnagar A. Cardiovascular Effects and Benefits of Exercise. Front Cardiovasc Med. 2018;5:135.
126. Pinckard K, Baskin KK, Stanford KI. Effects of exercise to improve cardiovascular health. Front Cardiovasc Med. 2019;6:69.
127. Krzentowski G, Pirnay F, Luyckx AS, Pallikarakis N, Lacroix M, Mosora F, et al. Metabolic adaptations in post-exercise recovery. Clin Physiol. 1982;2(4):277-88.
128. Muscella A, Stefàno E, Marsigliante S. The effects of exercise training on lipid metabolism and coronary heart disease. American Journal of Physiology-Heart and Circulatory Physiology. 2020;319(1):H76-H88.
129. Pifferi F, Laurent B, Plourde M. Lipid transport and metabolism at the blood-brain interface: Implications in health and disease. Frontiers in Physiology. 2021;12.
130. Bird SR, Hawley JA. Update on the effects of physical activity on insulin sensitivity in humans. BMJ Open Sport Exerc Med. 2016;2(1):e000143.
131. Press V, Freestone I, George CF. Physical activity: the evidence of benefit in the prevention of coronary heart disease. QJM: An International Journal of Medicine. 2003;96(4):245-51.
132. Shaper AG, Pocock SJ, Walker M, Cohen NM, Wale CJ, Thomson AG. British Regional Heart Study: cardiovascular risk factors in middle-aged men in 24 towns. Br Med J (Clin Res Ed). 1981;283(6285):179-86.
133. Folsom AR, Kushi LH, Anderson KE, Mink PJ, Olson JE, Hong CP, et al. Associations of general and abdominal obesity with multiple health outcomes in older women: the Iowa Women's Health Study. Archives of internal medicine. 2000;160(14):2117-28.
134. Pavey TG, Peeters G, Bauman AE, Brown WJ. Does vigorous physical activity provide additional benefits beyond those of moderate? Medicine and science in sports and exercise. 2013;45(10):1948-55.
135. Leitzmann MF, Park Y, Blair A, Ballard-Barbash R, Mouw T, Hollenbeck AR, et al. Physical activity recommendations and decreased risk of mortality. Archives of internal medicine. 2007;167(22):2453-60.
136. Kodama S, Saito K, Tanaka S, Maki M, Yachi Y, Asumi M, et al. Cardiorespiratory fitness as a quantitative predictor of all-cause mortality and cardiovascular events in healthy men and women: A meta-analysis. Jama. 2009;301(19):2024-35.
137. Jin M-N, Seo J, Kim BG, Kim GS, Lee HY, Byun YS, et al. Association of physical activity with the risk of major adverse cardiac and cerebrovascular events and mortality in patients with concomitant atrial fibrillation and coronary artery disease. International Journal of Arrhythmia. 2022;23(1):31.
138. Lee IM, Rexrode KM, Cook NR, Manson JE, Buring JE. Physical activity and coronary heart disease in women is "no pain, no gain" passé? Jama. 2001;285(11):1447-54.
139. Schnohr P, O'Keefe JH, Holtermann A, Lavie CJ, Lange P, Jensen GB, et al. Various leisure-time physical activities associated with widely divergent life expectancies: The Copenhagen City Heart Study. Mayo Clin Proc. 2018;93(12):1775-85.
140. Schnohr P, Marott JL, Jensen JS, Jensen GB. Intensity versus duration of cycling, impact on all-cause and coronary heart disease mortality: the Copenhagen City Heart Study. Eur J Prev Cardiol. 2012;19(1):73-80.
141. Winzer EB, Woitek F, Linke A. Physical activity in the prevention and treatment of coronary artery disease. Journal of the American Heart Association. 2018;7(4):e007725.
142. Siegel RD, Germer CK, Olendzki A. Mindfulness: What is it? Where did it come from? In: Didonna F, editor. Clinical Handbook of Mindfulness. New York, NY: Springer New York; 2009. p. 17-35.
143. Loucks EB, Britton WB, Howe CJ, Eaton CB, Buka SL. Positive associations of dispositional mindfulness with cardiovascular health: The New England Family Study. Int J Behav Med. 2015;22(4):540-50.
144. Loucks EB, Schuman-Olivier Z, Britton WB, Fresco DM, Desbordes G, Brewer JA, et al. Mindfulness and cardiovascular disease risk: state of the evidence, plausible mechanisms, and theoretical framework. Curr Cardiol Rep. 2015;17(12):112.
145. Lahtinen O, Aaltonen J, Kaakinen J, Franklin L, Hyönä J. The effects of app-based mindfulness practice on the well-being of university students and staff. Current Psychology. 2023;42(6):4412-21.
146. Gavrilova L, Zawadzki MJ. Examining How Headspace Impacts Mindfulness Mechanisms Over an 8-Week App-Based Mindfulness Intervention. Mindfulness. 2023;14(9):2236-49.

147. Cloonan S, Fowers R, Huberty J, Stecher C. Meditation App Habits and Mental Health: A Longitudinal Study of Meditation App Users During the COVID-19 Pandemic. Mindfulness. 2023;14(9):2276-86.
148. Levine GN, Lange RA, Bairey-Merz CN, Davidson RJ, Jamerson K, Mehta PK, et al. Meditation and cardiovascular risk reduction: a scientific statement from the american heart association. J Am Heart Assoc. 2017;6(10).
149. Oyebode O, Fowles J, Steeves D, Orji R. Machine learning techniques in adaptive and personalized systems for health and wellness. International Journal of Human–Computer Interaction. 2023;39(9):1938-62.
150. Castro R, Ribeiro-Alves M, Oliveira C, Romero CP, Perazzo H, Simjanoski M, et al. What are we measuring when we evaluate digital interventions for improving lifestyle? A scoping meta-review. Frontiers in Public Health. 2022;9.
151. Chatterjee A, Prinz A, Gerdes M, Martinez S. Digital interventions on healthy lifestyle management: Systematic review. J Med Internet Res. 2021;23(11):e26931.
152. Tromp J, Jindal D, Redfern J, Bhatt AB, Séverin T, Banerjee A, et al. World Heart Federation Roadmap for Digital Health in Cardiology. Global Heart. 2022.
153. Khan N, Marvel FA, Wang J, Martin SS. Digital health technologies to promote lifestyle change and adherence. Current Treatment Options in Cardiovascular Medicine. 2017;19(8):60.
154. Moller AC, Merchant G, Conroy DE, West R, Hekler E, Kugler KC, et al. Applying and advancing behavior change theories and techniques in the context of a digital health revolution: proposals for more effectively realizing untapped potential. Journal of Behavioral Medicine. 2017;40(1):85-98.
155. Prochaska JO, Marcus BH. The transtheoretical model: Applications to exercise. Advances in exercise adherence. Champaign, IL, England: Human Kinetics Publishers; 1994. p. 161-80.
156. Bunton R, Baldwin S, Flynn D, Whitelaw S. The 'stages of change' model in health promotion: Science and Ideology. Critical Public Health. 2000;10(1):55-70.
157. Rosenstock IM. Health Belief Model. Encyclopedia of psychology, Vol 4. Washington, DC, US: American Psychological Association; 2000. p. 78-80.
158. Ryan RM, Deci EL, Vansteenkiste M, Soenens B. Building a science of motivated persons: Self-determination theory's empirical approach to human experience and the regulation of behavior. Motivation Science. 2021;7(2):97-110.
159. Schunk DH. Social cognitive theory. APA educational psychology handbook, Vol 1: Theories, constructs, and critical issues. APA handbooks in psychology®. Washington, DC, US: American Psychological Association; 2012. p. 101-23.
160. Weng C, Tran KNP, Yang C-C, Huang H-I, Chen H. Can an augmented reality-integrated gamification approach enhance vocational high school students' learning outcomes and motivation in an electronics course? Education and Information Technologies. 2024;29(4):4025-53.
161. Ajzen I. The theory of planned behavior. Organizational Behavior and Human Decision Processes. 1991;50(2):179-211.
162. Dahlgren G, Whitehead M. European strategies for tackling social inequities in health: Levelling up Part 2. WHO Regional office for Europe Copenhagen; 2006.
163. Cislaghi B, Heise L. Using social norms theory for health promotion in low-income countries. Health Promotion International. 2019;34(3):616-23.
164. Sailer M, Hense JU, Mayr SK, Mandl H. How gamification motivates: An experimental study of the effects of specific game design elements on psychological need satisfaction. Computers in Human Behavior. 2017;69:371-80.
165. Von Bargen T, Zientz C, Haux R. Gamification for mHealth - A Review of playful mobile healthcare. Stud Health Technol Inform. 2014;202:225-8.
166. Krath J, Schürmann L, von Korflesch HFO. Revealing the theoretical basis of gamification: A systematic review and analysis of theory in research on gamification, serious games and game-based learning. Computers in Human Behavior. 2021;125:106963.
167. Johnson D, Deterding S, Kuhn KA, Staneva A, Stoyanov S, Hides L. Gamification for health and wellbeing: A systematic review of the literature. Internet Interv. 2016;6:89-106.
168. Lewey J, Murphy S, Zhang D, Putt ME, Elovitz MA, Riis V, et al. Effectiveness of a Text-Based Gamification Intervention to Improve Physical Activity Among Postpartum Individuals With Hypertensive Disorders of Pregnancy: A Randomized Clinical Trial. JAMA Cardiology. 2022;7(6):591-9.
169. Oddsson S. Effects of a gamified mobile application to support a lifestyle-change program in adults: A controlled pilot. Diabetes. 2017;66(Supplement_1):A42.

170. Lin Y, Tudor-Sfetea C, Siddiqui S, Sherwani Y, Ahmed M, Eisingerich AB. Effective behavioral changes through a digital mhealth app: exploring the impact of hedonic well-being, psychological empowerment and inspiration. JMIR Mhealth Uhealth. 2018;6(6):e10024.
171. Wong SH, Tan ZYA, Cheng LJ, Lau ST. Wearable technology-delivered lifestyle intervention amongst adults with overweight and obese: A systematic review and meta-regression. International Journal of Nursing Studies. 2022;127:104163.
172. Aguilera A, Figueroa CA, Hernandez-Ramos R, Sarkar U, Cemballi A, Gomez-Pathak L, et al. mHealth app using machine learning to increase physical activity in diabetes and depression: clinical trial protocol for the DIAMANTE Study. BMJ Open. 2020;10(8):e034723.
173. Avila-Garcia P, Hernandez-Ramos R, Nouri SS, Cemballi A, Sarkar U, Lyles CR, et al. Engaging users in the design of an mHealth, text message-based intervention to increase physical activity at a safety-net health care system. JAMIA Open. 2019;2(4):489-97.
174. Yen H-Y. Smart wearable devices as a psychological intervention for healthy lifestyle and quality of life: a randomized controlled trial. Quality of Life Research. 2021;30(3):791-802.
175. Dugas M, Gao G, Agarwal R. Unpacking mHealth interventions: A systematic review of behavior change techniques used in randomized controlled trials assessing mHealth effectiveness. DIGITAL HEALTH. 2020;6:2055207620905411.
176. Direito A, Carraça E, Rawstorn J, Whittaker R, Maddison R. mhealth technologies to influence physical activity and sedentary behaviors: behavior change techniques, systematic review and meta-analysis of randomized controlled trials. Annals of Behavioral Medicine. 2016;51(2):226-39.
177. Stephenson A, McDonough SM, Murphy MH, Nugent CD, Mair JL. Using computer, mobile and wearable technology enhanced interventions to reduce sedentary behaviour: a systematic review and meta-analysis. International Journal of Behavioral Nutrition and Physical Activity. 2017;14(1):105.
178. Kim H-N, Seo K. Smartphone-based health program for improving physical activity and tackling obesity for young adults: A systematic review and meta-analysis. International journal of environmental research and public health. 2019;17(1):15.
179. Chikwetu L, Miao Y, Woldetensae MK, Bell D, Goldenholz DM, Dunn J. Does deidentification of data from wearable devices give us a false sense of security? A systematic review. The Lancet Digital Health. 2023;5(4):e239-e47.
180. Bassanelli S, Vasta N, Bucchiarone A, Marconi A. Gamification for behavior change: A scientometric review. Acta Psychologica. 2022;228:103657.
181. Johnson D, Deterding S, Kuhn K-A, Staneva A, Stoyanov S, Hides L. Gamification for health and wellbeing: A systematic review of the literature. Internet Interventions. 2016;6:89-106.
182. Cotton V, Patel MS. Gamification use and design in popular health and fitness mobile applications. Am J Health Promot. 2019;33(3):448-51.
183. Gonze BB, Padovani RDC, Simoes MDS, Lauria V, Proença NL, Sperandio EF, et al. Use of a smartphone app to increase physical activity levels in insufficiently active adults: Feasibility sequential multiple assignment randomized trial (SMART). JMIR Res Protoc. 2020;9(10):e14322.
184. Klonoff DC. Behavioral theory: The missing ingredient for digital health tools to change behavior and increase adherence. J Diabetes Sci Technol. 2019;13(2):276-81.
185. Orji R, Moffatt K. Persuasive technology for health and wellness: State-of-the-art and emerging trends. Health Informatics J. 2018;24(1):66-91.
186. Priesterroth L, Grammes J, Holtz K, Reinwarth A, Kubiak T. Gamification and behavior change techniques in diabetes self-management apps. J Diabetes Sci Technol. 2019;13(5):954-8.
187. Nurmi J, Knittle K, Ginchev T, Khattak F, Helf C, Zwickl P, et al. Engaging users in the behavior change process with digitalized motivational interviewing and gamification: development and feasibility testing of the precious app. JMIR Mhealth Uhealth. 2020;8(1):e12884.
188. Sardi L, Idri A, Fernández-Alemán JL. A systematic review of gamification in e-Health. Journal of Biomedical Informatics. 2017;71:31-48.
189. Nahum-Shani I, Smith SN, Spring BJ, Collins LM, Witkiewitz K, Tewari A, et al. Just-in-Time Adaptive Interventions (JITAIs) in mobile health: Key components and design principles for ongoing health behavior support. Ann Behav Med. 2018;52(6):446-62.
190. Klasnja P, Hekler EB, Shiffman S, Boruvka A, Almirall D, Tewari A, et al. Microrandomized trials: An experimental design for developing just-in-time adaptive interventions. Health Psychol. 2015;34s(0):1220-8.
191. Klasnja P, Smith S, Seewald NJ, Lee A, Hall K, Luers B, et al. Efficacy of contextually tailored suggestions for physical activity: A micro-randomized optimization trial of HeartSteps. Ann Behav Med. 2019;53(6):573-82.
192. Hekler EB, Klasnja P, Traver V, Hendriks M. Realizing effective behavioral management of health: the metamorphosis of behavioral science methods. IEEE Pulse. 2013;4(5):29-34.

193. Santo K, Redfern J. Digital health innovations to improve cardiovascular disease care. Current Atherosclerosis Reports. 2020;22(12):71.
194. Slikker W. Biomarkers and their impact on precision medicine. Experimental Biology and Medicine. 2017;243(3):211-2.
195. Chakrapani AT. Biomarkers in Emergency Medicine. In: David SS, editor. Clinical Pathways in Emergency Medicine: Volume I. New Delhi: Springer India; 2016. p. 405-15.
196. Singh V, Martinezclark P, Pascual M, Shaw ES, O'Neill WW. Cardiac biomarkers - the old and the new: a review. Coron Artery Dis. 2010;21(4):244-56.
197. de Miranda FS, Barauna VG, dos Santos L, Costa G, Vassallo PF, Campos LC. Properties and application of cell-free DNA as a clinical biomarker. Int J Mol Sci [Internet]. 2021; 22(17).
198. Moqri M, Herzog C, Poganik JR, Ying K, Justice JN, Belsky DW, et al. Validation of biomarkers of aging. Nature Medicine. 2024;30(2):360-72.
199. Vasudevan S, Saha A, Tarver ME, Patel B. Digital biomarkers: Convergence of digital health technologies and biomarkers. npj Digital Medicine. 2022;5(1):36.
200. Vasudevan S, Saha A, Tarver ME, Patel B. Digital biomarkers: Convergence of digital health technologies and biomarkers. NPJ Digit Med. 2022;5(1):36.
201. Arigo D, Jake-Schoffman DE, Wolin K, Beckjord E, Hekler EB, Pagoto SL. The history and future of digital health in the field of behavioral medicine. Journal of Behavioral Medicine. 2019;42(1):67-83.
202. Dang A, Arora D, Rane P. Role of digital therapeutics and the changing future of healthcare. J Family Med Prim Care. 2020;9(5):2207-13.
203. Lupton D. Digital health now and in the future: Findings from a participatory design stakeholder workshop. DIGITAL HEALTH. 2017;3:2055207617740018.
204. Höchsmann C, Infanger D, Klenk C, Königstein K, Walz SP, Schmidt-Trucksäss A. Effectiveness of a behavior change technique-based smartphone game to improve intrinsic motivation and physical activity adherence in patients with type 2 diabetes: Randomized controlled trial. JMIR Serious Games. 2019;7(1):e11444.
205. Gallagher R, Chow C, Parker H, Neubeck L, Celermajer D, Redfern J, et al. Design and rationale of the MyHeartMate study: a randomised controlled trial of a game-based app to promote behaviour change in patients with cardiovascular disease. BMJ Open. 2019;9(5):e024269.
206. Clusmann J, Kolbinger FR, Muti HS, Carrero ZI, Eckardt J-N, Laleh NG, et al. The future landscape of large language models in medicine. Communications Medicine. 2023;3(1):141.
207. Li Y, Zhang D, Thapa J, Li W, Chen Z, Mu L, et al. The impact of expanding telehealth-delivered dietary interventions on long-term cardiometabolic health. Population Health Management. 2021;25(3):317-22.
208. Redfern J, Coorey G, Mulley J, Scaria A, Neubeck L, Hafiz N, et al. A digital health intervention for cardiovascular disease management in primary care (CONNECT) randomized controlled trial. NPJ Digit Med. 2020;3:117.
209. Schoeppe S, Alley S, Van Lippevelde W, Bray NA, Williams SL, Duncan MJ, et al. Efficacy of interventions that use apps to improve diet, physical activity and sedentary behaviour: a systematic review. International Journal of Behavioral Nutrition and Physical Activity. 2016;13(1):127.
210. Martínez-Rodríguez A, Martínez-Olcina M, Mora J, Navarro P, Caturla N, Jones J. New app-based dietary and lifestyle intervention on weight loss and cardiovascular health. Sensors. 2022;22(3):768.
211. de Magalhães JP. Distinguishing between driver and passenger mechanisms of aging. Nature Genetics. 2024;56(2):204-11.
212. Global incidence, prevalence, years lived with disability (YLDs), disability-adjusted life-years (DALYs), and healthy life expectancy (HALE) for 371 diseases and injuries in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2133-61.
213. Dai H, Much AA, Maor E, Asher E, Younis A, Xu Y, et al. Global, regional, and national burden of ischaemic heart disease and its attributable risk factors, 1990-2017: results from the Global Burden of Disease Study 2017. Eur Heart J Qual Care Clin Outcomes. 2022;8(1):50-60.
214. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global Burden of Cardiovascular Diseases and Risk Factors, 1990-2019: Update From the GBD 2019 Study. J Am Coll Cardiol. 2020;76(25):2982-3021.
215. Berger JS, Jordan CO, Lloyd-Jones D, Blumenthal RS. Screening for cardiovascular risk in asymptomatic patients. J Am Coll Cardiol. 2010;55(12):1169-77.
216. Naqvi TZ, Lee M-S. Carotid intima-media thickness and plaque in cardiovascular risk assessment. JACC: Cardiovascular Imaging. 2014;7(10):1025-38.

217. Takase M, Nakaya N, Nakamura T, Kogure M, Hatanaka R, Nakaya K, et al. Carotid intima media thickness and risk factor for atherosclerosis: Tohoku Medical Megabank community-based cohort study. J Atheroscler Thromb. 2023;30(10):1471-82.
218. Rundek T, Blanton SH, Bartels S, Dong C, Raval A, Demmer RT, et al. Traditional risk factors are not major contributors to the variance in carotid intima-media thickness. Stroke. 2013;44(8):2101-8.
219. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PW, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113(6):791-8.
220. Liu B, Ni J, Shi M, Bai L, Zhan C, Lu H, et al. Carotid Intima-media Thickness and its Association with Conventional Risk Factors in Low-income Adults: A Population-based Cross-Sectional Study in China. Scientific Reports. 2017;7(1):41500.
221. Murie-Fernandez M, Irimia P, Toledo E, Martínez-Vila E, Buil-Cosiales P, Serrano-Martínez M, et al. Carotid intima-media thickness changes with Mediterranean diet: a randomized trial (PREDIMED-Navarra). Atherosclerosis. 2011;219(1):158-62.
222. Sudlow C, Gallacher J, Allen N, Beral V, Burton P, Danesh J, et al. UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age. PLoS medicine. 2015;12(3):e1001779.
223. Biobank U. UK Biobank Category 100052: Diet [Available from: https://biobank.ndph.ox.ac.uk/showcase/label.cgi?id=100052.
224. Diet, nutrition and the prevention of chronic diseases: report of a joint WHO/FAO expert consultation, Geneva, 28 January -- 1 February 2002. (WHO technical report series ; 916) [Available from: https://www.who.int/publications/i/item/924120916X.
225. Public Health England in association with the Welsh Government, Food Standards Scotland and the Food Standards Agency in Northern Ireland. The Eatwell Guide. [Available from: https://www.gov.uk/government/publications/the-eatwell-guide.
226. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Medicine and science in sports and exercise. 2003;35(8):1381-95.
227. Ferrara M, De Gennaro L. How much sleep do we need? Sleep Medicine Reviews. 2001;5(2):155-79.
228. Ohayon MM, Vecchierini M-F. Normative sleep data, cognitive function and daily living activities in older adults in the community. Sleep. 2005;28(8):981-9.
229. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2022. Diabetes care. 2022;45(Suppl 1):S83-s96.
230. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2019;73(24):3168-209.
231. Whelton PK, Carey RM, Mancia G, Kreutz R, Bundy JD, Williams B. Harmonization of the American College of Cardiology/American Heart Association and European Society of Cardiology/European Society of Hypertension Blood Pressure/Hypertension Guidelines: Comparisons, Reflections, and Recommendations. Circulation. 2022;146(11):868-77.
232. UK Biobank imaging modality: Carotid ultrasound 2015 [Available from: https://biobank.ndph.ox.ac.uk/showcase/ukb/docs/carult_explan_doc.pdf.
233. Coffey S, Lewandowski AJ, Garratt S, Meijer R, Lynum S, Bedi R, et al. Protocol and quality assurance for carotid imaging in 100,000 participants of UK Biobank: development and assessment. Eur J Prev Cardiol. 2017;24(17):1799-806.
234. Ling Y, Wan Y, Barinas-Mitchell E, Fujiyoshi A, Cui H, Maimaiti A, et al. Varying definitions of carotid intima-media thickness and future cardiovascular disease: a systematic review and meta-analysis. J Am Heart Assoc. 2023:e031217.
235. de Groot E, van Leuven SI, Duivenvoorden R, Meuwese MC, Akdim F, Bots ML, et al. Measurement of carotid intima–media thickness to assess progression and regression of atherosclerosis. Nature Clinical Practice Cardiovascular Medicine. 2008;5(5):280-8.
236. Bakoyannis G, Touloumi G. Practical methods for competing risks data: A review. Statistical Methods in Medical Research. 2011;21(3):257-72.
237. Desquilbet L, Mariotti F. Dose-response analyses using restricted cubic spline functions in public health research. Statistics in Medicine. 2010;29(9):1037-57.

238. Lloyd-Jones DM, Leip EP, Larson MG, D'Agostino RB, Beiser A, Wilson PWF, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. Circulation. 2006;113(6):791-8.
239. Kraus WE, Bhapkar M, Huffman KM, Pieper CF, Krupa Das S, Redman LM, et al. 2 years of calorie restriction and cardiometabolic risk (CALERIE): exploratory outcomes of a multicentre, phase 2, randomised controlled trial. The lancet Diabetes & endocrinology. 2019.
240. Fontana L, Villareal DT, Weiss EP, Racette SB, Steger-May K, Klein S, et al. Calorie restriction or exercise: effects on coronary heart disease risk factors. A randomized, controlled trial. American Journal of Physiology-Endocrinology and Metabolism. 2007;293(1):E197-E202.
241. Fontana L, Meyer TE, Klein S, Holloszy JO. Long-term calorie restriction is highly effective in reducing the risk for atherosclerosis in humans. Proceedings of the national Academy of Sciences. 2004;101(17):6659-63.
242. Chambless LE, Heiss G, Folsom AR, Rosamond W, Szklo M, Sharrett AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the Atherosclerosis Risk in Communities (ARIC) Study, 1987-1993. Am J Epidemiol. 1997;146(6):483-94.
243. Salonen JT, Salonen R. Ultrasonographically assessed carotid morphology and the risk of coronary heart disease. Arterioscler Thromb. 1991;11(5):1245-9.
244. Hollander M, Hak AE, Koudstaal PJ, Bots ML, Grobbee DE, Hofman A, et al. Comparison between measures of atherosclerosis and risk of stroke: the Rotterdam Study. Stroke. 2003;34(10):2367-72.
245. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK, Jr. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. Cardiovascular Health Study Collaborative Research Group. The New England journal of medicine. 1999;340(1):14-22.
246. Silvestrini M, Vernieri F, Pasqualetti P, Matteis M, Passarelli F, Troisi E, et al. Impaired cerebral vasoreactivity and risk of stroke in patients with asymptomatic carotid artery stenosis. Jama. 2000;283(16):2122-7.
247. Raitakari OT, Juonala M, Kähönen M, Taittonen L, Laitinen T, Mäki-Torkko N, et al. Cardiovascular risk factors in childhood and carotid artery intima-media thickness in adulthood -: The Cardiovascular Risk in Young Finns Study. Jama-Journal of the American Medical Association. 2003;290(17):2277-83.
248. De Bosscher R, Dausin C, Claus P, Bogaert J, Dymarkowski S, Goetschalckx K, et al. Lifelong endurance exercise and its relation with coronary atherosclerosis. European Heart Journal. 2023;44(26):2388-99.
249. Müller J, Dahm V, Lorenz ES, Pressler A, Haller B, Grabs V, et al. Changes of intima-media thickness in marathon runners: A mid-term follow-up. Eur J Prev Cardiol. 2017;24(12):1336-42.
250. Aengevaeren VL, Mosterd A, Braber TL, Prakken NHJ, Doevendans PA, Grobbee DE, et al. Relationship between lifelong exercise volume and coronary atherosclerosis in athletes. Circulation. 2017;136(2):138-48.
251. Rubies C, Batlle M, Sanz-de la Garza M, Dantas AP, Jorba I, Fernandez G, et al. Long-Term Strenuous Exercise Promotes Vascular Injury by Selectively Damaging the Tunica Media: Experimental Evidence. JACC Basic Transl Sci. 2022;7(7):681-93.
252. Donato AJ, Machin DR, Lesniewski LA. Mechanisms of dysfunction in the aging vasculature and role in age-related disease. Circ Res. 2018;123(7):825-48.
253. Cecelja M, Chowienczyk P. Role of arterial stiffness in cardiovascular disease. JRSM Cardiovasc Dis. 2012;1(4).
254. Kim JM, Kim SS, Kim IJ, Kim JH, Kim BH, Kim MK, et al. Arterial stiffness is an independent predictor for risk of mortality in patients with type 2 diabetes mellitus: the REBOUND study. Cardiovasc Diabetol. 2020;19(1):143.
255. Mensah George A, Fuster V, Murray Christopher JL, Roth Gregory A, Mensah George A, Abate Yohannes H, et al. Global burden of cardiovascular diseases and risks, 1990-2022. Journal of the American College of Cardiology. 2023;82(25):2350-473.
256. Gaudel P, Neupane S, Koivisto AM, Kaunonen M, Rantanen A. Effects of intervention on lifestyle changes among coronary artery disease patients: A 6-month follow-up study. Nurs Open. 2022;9(4):2024-36.
257. Qu B, Qu T. Causes of changes in carotid intima-media thickness: a literature review. Cardiovascular Ultrasound. 2015;13(1):46.
258. Golbus JR, Gupta K, Stevens R, Jeganathan VSE, Luff E, Shi J, et al. A randomized trial of a mobile health intervention to augment cardiac rehabilitation. npj Digital Medicine. 2023;6(1):173.

259. Ku JP, Sim I. Mobile Health: making the leap to research and clinics. npj Digital Medicine. 2021;4(1):83.
260. Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, et al. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 study. Journal of the American College of Cardiology. 2020;76(25):2982-3021.
261. Amini M, Zayeri F, Salehi M. Trend analysis of cardiovascular disease mortality, incidence, and mortality-to-incidence ratio: results from global burden of disease study 2017. BMC Public Health. 2021;21(1):401.
262. Celermajer DS, Sorensen KE, Gooch VM, Spiegelhalter DJ, Miller OI, Sullivan ID, et al. Non-invasive detection of endothelial dysfunction in children and adults at risk of atherosclerosis. The Lancet. 1992;340(8828):1111-5.
263. Polak JF, O'Leary DH. Carotid intima-media thickness as surrogate for and predictor of CVD. Glob Heart. 2016;11(3):295-312.e3.
264. Cohn JN, Finkelstein S, McVeigh G, Morgan D, LeMay L, Robinson J, et al. Noninvasive pulse wave analysis for the early detection of vascular disease. Hypertension. 1995;26(3):503-8.
265. Chen C-H, Nevo E, Fetics B, Pak PH, Yin FCP, Maughan WL, et al. Estimation of central aortic pressure waveform by mathematical transformation of radial tonometry pressure. Circulation. 1997;95(7):1827-36.
266. Weber T, Auer J, O'Rourke MF, Kvas E, Lassnig E, Berent R, et al. Arterial stiffness, wave reflections, and the risk of coronary artery disease. Circulation. 2004;109(2):184-9.
267. Chirinos JA. Textbook of Arterial Stiffness and Pulsatile Hemodynamics in Health and Disease: Elsevier Science; 2022.
268. Park JS, Shin JH, Park JB, Choi DJ, Youn HJ, Park CG, et al. Central hemodynamics and the discrepancy between central blood pressure and brachial blood pressure. Medicine (Baltimore). 2022;101(40):e30484.
269. Vaduganathan M, Mensah George A, Turco Justine V, Fuster V, Roth Gregory A. The Global Burden of Cardiovascular Diseases and Risk. Journal of the American College of Cardiology. 2022;80(25):2361-71.
270. Said MA, Eppinga RN, Lipsic E, Verweij N, van der Harst P. Relationship of arterial stiffness index and pulse pressure with cardiovascular disease and mortality. Journal of the American Heart Association.7(2):e007621.
271. Heiss C, Rodriguez-Mateos A, Bapir M, Skene SS, Sies H, Kelm M. Flow-mediated dilation reference values for evaluation of endothelial function and cardiovascular health. Cardiovascular Research. 2023;119(1):283-93.
272. Iana Samova. Intima-media thickness: Appropriate evaluation and proper measurement, described. E-Journal of the ESC Council for Cardiology Practice. 2015;13(1).
273. Díaz A, Galli C, Tringler M, Ramírez A, Cabrera Fischer EI. Reference values of pulse wave velocity in healthy people from an urban and rural argentinean population. Int J Hypertens. 2014;2014:653239.
274. Cassidy S, Kroeger CM, Wang T, Mitra S, Liu C, Ribeiro R, et al. Impact of an intensive lifestyle program on low attenuation plaque and myocardial perfusion in coronary heart disease: A randomised clinical trial protocol. Nutrition and healthy aging. 2022;Preprint:1-14.
275. Lichtenstein AH, Appel LJ, Vadiveloo M, Hu FB, Kris-Etherton PM, Rebholz CM, et al. 2021 dietary guidance to improve cardiovascular health: A scientific statement from the American Heart Association. Circulation. 2021;144(23):e472-e87.
276. Spertus JA, Eagle KA, Krumholz HM, Mitchell KR, Normand S-LT. American College of Cardiology and American Heart Association methodology for the selection and creation of performance measures for quantifying the quality of cardiovascular care. Circulation. 2005;111(13):1703-12.
277. EHN Physical Activity Expert Group [Available from: https://ehnheart.org/network/ehn-expert-groups/physical-activity/.
278. Levine GN, Lange RA, Bairey-Merz CN, Davidson RJ, Jamerson K, Mehta PK, et al. Meditation and cardiovascular risk reduction. Journal of the American Heart Association. 2017;6(10):e002218.
279. Upper Extremities. In: Demetriades D, Inaba K, Velmahos G, editors. Atlas of Surgical Techniques in Trauma. 2 ed. Cambridge: Cambridge University Press; 2020. p. 343-72.
280. Corretti MC, Anderson TJ, Benjamin EJ, Celermajer D, Charbonneau F, Creager MA, et al. Guidelines for the ultrasound assessment of endothelial-dependent flow-mediated vasodilation of the brachial artery: A report of the International Brachial Artery Reactivity Task Force. Journal of the American College of Cardiology. 2002;39(2):257-65.

281. Feairheller DL, Diaz KM, Kashem MA, Thakkar SR, Veerabhadrappa P, Sturgeon KM, et al. Effects of moderate aerobic exercise training on vascular health and blood pressure in African Americans. The Journal of Clinical Hypertension. 2014;16(7):504-10.
282. Libby P, Ridker PM, Hansson GK. Progress and challenges in translating the biology of atherosclerosis. Nature. 2011;473(7347):317-25.
283. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness. Circulation. 2007;115(4):459-67.
284. Touboul PJ, Hennerici MG, Meairs S, Adams H, Amarenco P, Bornstein N, et al. Mannheim carotid intima-media thickness and plaque consensus (2004-2006-2011). An update on behalf of the advisory board of the 3rd, 4th and 5th watching the risk symposia, at the 13th, 15th and 20th European Stroke Conferences, Mannheim, Germany, 2004, Brussels, Belgium, 2006, and Hamburg, Germany, 2011. Cerebrovasc Dis. 2012;34(4):290-6.
285. Roman MJ, Moeller E, Davis A, Paget SA, Crow MK, Lockshin MD, et al. Preclinical carotid atherosclerosis in patients with rheumatoid arthritis. Ann Intern Med. 2006;144(4):249-56.
286. Clinic C. Carotid intima-media thickness (CIMT) test [Available from: https://my.clevelandclinic.org/health/diagnostics/24944-carotid-intima-media-thickness-cimt-test.
287. Philips. EPIQ 7 2024 [Available from: https://www.philips.com.au/healthcare/product/HC795200R/epiq-7-ultrasound-system-for-radiology.
288. Atcor. SphygmoCor XCEL Pulse Wave Analysis (PWA) System 2024 [Available from: https://atcormedical.com/technology/sphygmocor-pulse-wave-analysis/.
289. O'Rourke MF, Pauca A, Jiang X-J. Pulse wave analysis. Br J Clin Pharmacol. 2001;51(6):507-22.
290. Butlin M, Qasem A. Large artery stiffness assessment using SphygmoCor technology. Pulse. 2016;4(4):180-92.
291. Millasseau SC, Stewart AD, Patel SJ, Redwood SR, Chowienczyk PJ. Evaluation of carotid-femoral pulse wave velocity. Hypertension. 2005;45(2):222-6.
292. Patvardhan E, Heffernan KS, Ruan J, Hession M, Warner P, Karas RH, et al. Augmentation index derived from peripheral arterial tonometry correlates with cardiovascular risk factors. Cardiol Res Pract. 2011;2011:253758.
293. Jeroncic A, Gunjaca G, Mrsic DB, Mudnic I, Brizic I, Polasek O, et al. Normative equations for central augmentation index: assessment of inter-population applicability and how it could be improved. Scientific Reports. 2016;6(1):27016.
294. Buckberg GD, Towers B, Paglia DE, Mulder DG, Maloney JV. Subendocardial ischemia after cardiopulmonary bypass. The Journal of Thoracic and Cardiovascular Surgery. 1972;64(5):669-84.
295. Tsiachris D, Tsioufis C, Syrseloudis D, Roussos D, Tatsis I, Dimitriadis K, et al. Subendocardial viability ratio as an index of impaired coronary flow reserve in hypertensives without significant coronary artery stenoses. Journal of Human Hypertension. 2012;26(1):64-70.
296. Hoffman JI, Buckberg GD. Pathophysiology of subendocardial ischaemia. British Medical Journal. 1975;1(5949):76.
297. Hoffman JIE, Buckberg GD. The myocardial oxygen supply:demand index revisited. Journal of the American Heart Association.3(1):e000285.
298. Henzel J, Kruk M, Kępka C, Makarewicz-Wujec M, Wardziak Ł, Trochimiuk P, et al. Diet and lifestyle intervention-induced pattern of weight loss related to reduction in low-attenuation coronary plaque burden. Diagnostics [Internet]. 2024; 14(6).
299. Elkoustaf RA, Aldaas OM, Batiste CD, Mercer A, Robinson M, Newton D, et al. Lifestyle interventions and carotid plaque burden: A comparative analysis of two lifestyle intervention programs in patients with coronary artery disease. Perm J. 2019;23.
300. Pierce GL, Beske SD, Lawson BR, Southall KL, Benay FJ, Donato AJ, et al. Weight loss alone improves conduit and resistance artery endothelial function in young and older overweight/obese adults. Hypertension. 2008;52(1):72-9.
301. Hajek P, Przulj D, Pesola F, McRobbie H, Peerbux S, Phillips-Waller A, et al. A randomised controlled trial of the 5:2 diet. PLOS ONE. 2021;16(11):e0258853.
302. Lowe DA, Wu N, Rohdin-Bibby L, Moore AH, Kelly N, Liu YE, et al. Effects of time-restricted eating on weight loss and other metabolic parameters in women and men with overweight and obesity: The TREAT randomized clinical trial. JAMA Internal Medicine. 2020;180(11):1491-9.
303. The Look ARG. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes mellitus: Four-year results of the look AHEAD trial. Archives of internal medicine. 2010;170(17):1566-75.
304. Maruthur NM, Wang N-Y, Appel LJ. Lifestyle interventions reduce coronary heart disease risk. Circulation. 2009;119(15):2026-31.

305. Alharbi M, Gallagher R, Kirkness A, Sibbritt D, Tofler G. Long-term outcomes from Healthy Eating and Exercise Lifestyle Program for overweight people with heart disease and diabetes. European Journal of Cardiovascular Nursing. 2014;15(1):91-9.
306. Vlachopoulos C, Alexopoulos N, Stefanadis C. Lifestyle modification and arterial stiffness and wave reflections: A more natural way to prolong arterial health. Artery Research. 2006;1:S15-S22.
307. Gokce N, Karki S, Dobyns A, Zizza E, Sroczynski E, Palmisano JN, et al. Association of bariatric surgery with vascular outcomes. JAMA Network Open. 2021;4(7):e2115267-e.
308. Varady KA, Bhutani S, Klempel MC, Phillips SA. Improvements in vascular health by a low-fat diet, but not a high-fat diet, are mediated by changes in adipocyte biology. Nutrition Journal. 2011;10(1):8.
309. Rychter AM, Naskręt D, Zawada A, Ratajczak AE, Dobrowolska A, Krela-Kaźmierczak I. What can we change in diet and behaviour in order to decrease carotid intima-media thickness in patients with obesity? Journal of Personalized Medicine [Internet]. 2021; 11(6).
310. Liu J, Sze NSK, Narushima M, O'Leary D. Weight change and risk of atherosclerosis measured by carotid intima-media thickness (CIMT) from a prospective cohort-analysis of the first-wave follow-up data of the Canadian longitudinal study on aging (CLSA). J Cardiovasc Dev Dis. 2023;10(10).
311. Oren A, Vos LE, Uiterwaal CSPM, Grobbee DE, Bots ML. Cardiovascular risk factors and increased carotid intima-media thickness in healthy young adults: The Atherosclerosis Risk in Young Adults (ARYA) study. Archives of internal medicine. 2003;163(15):1787-92.
312. Fahs CA, Smith DL, Horn GP, Agiovlasitis S, Rossow LM, Echols G, et al. Impact of excess body weight on arterial structure, function, and blood pressure in firefighters. Am J Cardiol. 2009;104(10):1441-5.
313. Karason K, Wikstrand J, Sjöström L, Wendelhag I. Weight loss and progression of early atherosclerosis in the carotid artery: a four-year controlled study of obese subjects. Int J Obes Relat Metab Disord. 1999;23(9):948-56.
314. Choo J, Lee J, Cho J-H, Burke LE, Sekikawa A, Jae SY. Effects of weight management by exercise modes on markers of subclinical atherosclerosis and cardiometabolic profile among women with abdominal obesity: a randomized controlled trial. BMC Cardiovascular Disorders. 2014;14(1):82.
315. Skilton MR, Yeo SQ, Ne JY, Celermajer DS, Caterson ID, Lee CM. Weight loss and carotid intima-media thickness-a meta-analysis. Obesity (Silver Spring). 2017;25(2):357-62.
316. Patel AR, Hui H, Kuvin JT, Pandian NG, Karas RH. Modestly overweight women have vascular endothelial dysfunction. Clin Cardiol. 2009;32(5):269-73.
317. Yang S, Zhou Z, Miao H, Zhang Y. Effect of weight loss on blood pressure changes in overweight patients: A systematic review and meta-analysis. J Clin Hypertens (Greenwich). 2023;25(5):404-15.
318. Harsha DW, Bray GA. Weight loss and blood pressure control (Pro). Hypertension. 2008;51(6):1420-5.
319. Bacon SL, Sherwood A, Hinderliter A, Blumenthal JA. Effects of exercise, diet and weight loss on high blood pressure. Sports Med. 2004;34(5):307-16.
320. Long G, Behnam S, Geoff DCB, Bruno RdC, Christine LH, Anton S, et al. Comparison of dietary macronutrient patterns of 14 popular named dietary programmes for weight and cardiovascular risk factor reduction in adults: systematic review and network meta-analysis of randomised trials. BMJ (Clinical research ed). 2020;369:m696.
321. Blacher J, Asmar R, Djane S, London GM, Safar ME. Aortic pulse wave velocity as a marker of cardiovascular risk in hypertensive patients. Hypertension. 1999;33(5):1111-7.
322. Petersen KS, Blanch N, Keogh JB, Clifton PM. Effect of weight loss on pulse wave velocity: systematic review and meta-analysis. Arterioscler Thromb Vasc Biol. 2015;35(1):243-52.
323. Syed-Abdul MM. Relationship between carotid-femoral pulse wave velocity and diet-induced weight loss. Obesities [Internet]. 2022; 2(2):[148-56 pp.].
324. Stanek A, Grygiel-Górniak B, Brożyna-Tkaczyk K, Myśliński W, Cholewka A, Zolghadri S. The influence of dietary interventions on arterial stiffness in overweight and obese subjects. Nutrients [Internet]. 2023; 15(6).
325. Hughes TM, Althouse AD, Niemczyk NA, Hawkins MS, Kuipers AL, Sutton-Tyrrell K. Effects of weight loss and insulin reduction on arterial stiffness in the SAVE trial. Cardiovascular Diabetology. 2012;11(1):114.
326. Petersen KS, Blanch N, Keogh JB, Clifton PM. Effect of Weight Loss on Pulse Wave Velocity. Arteriosclerosis, Thrombosis, and Vascular Biology. 2015;35(1):243-52.
327. Yang MH, Kang SY, Lee JA, Kim YS, Sung EJ, Lee KY, et al. The effect of lifestyle changes on blood pressure control among hypertensive patients. Korean J Fam Med. 2017;38(4):173-80.

328. Zieman SJ, Melenovsky V, Kass DA. Mechanisms, pathophysiology, and therapy of arterial stiffness. Arteriosclerosis, Thrombosis, and Vascular Biology. 2005;25(5):932-43.
329. Oh YS. Arterial stiffness and hypertension. Clinical Hypertension. 2018;24(1):17.
330. Safar ME, Asmar R, Benetos A, Blacher J, Boutouyrie P, Lacolley P, et al. Interaction between hypertension and arterial stiffness. Hypertension. 2018;72(4):796-805.
331. Henein MY, Vancheri S, Longo G, Vancheri F. The role of inflammation in cardiovascular disease. Int J Mol Sci. 2022;23(21).
332. Sorriento D, Iaccarino G. Inflammation and cardiovascular diseases: The most recent findings. Int J Mol Sci. 2019;20(16).
333. Vascular structure, vascular function and vascular aging in adults diagnosed with persistent covid (ICOPER): ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2023 [Available from: https://clinicaltrials.gov/study/NCT05819840.
334. Exercise and vascular function in postmenopausal females with hypertension: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2023 [Available from: https://clinicaltrials.gov/study/NCT05597033.
335. Role of adiposomes in endothelial dysfunction: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US); 2023 [Available from: https://clinicaltrials.gov/study/NCT05199454.
336. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, et al. 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019;140(11):e596-e646.
337. Labrique A, Agarwal S, Tamrat T, Mehl G. WHO digital health guidelines: a milestone for global health. npj Digital Medicine. 2020;3(1):120.
338. WHO Guidelines approved by the guidelines Review Committee. WHO guideline Recommendations on Digital Interventions for Health System Strengthening. Geneva: World Health Organization; 2019.
339. Whitelaw S, Pellegrini DM, Mamas MA, Cowie M, Van Spall HGC. Barriers and facilitators of the uptake of digital health technology in cardiovascular care: a systematic scoping review. European Heart Journal - Digital Health. 2021;2(1):62-74.
340. Schueller SM. Grand challenges in human factors and digital health. Frontiers in Digital Health. 2021;3.
341. Santo K, Singleton A, Rogers K, Thiagalingam A, Chalmers J, Chow CK, et al. Medication reminder applications to improve adherence in coronary heart disease: a randomised clinical trial. Heart. 2019;105(4):323-9.
342. Deterding S, Dixon D, Khaled R, Nacke L. From game design elements to gamefulness: defining "gamification". Proceedings of the 15th International Academic MindTrek Conference: Envisioning Future Media Environments; Tampere, Finland: Association for Computing Machinery; 2011. p. 9–15.
343. Cheng VWS, Davenport T, Johnson D, Vella K, Hickie IB. Gamification in apps and technologies for improving mental health and well-being: Systematic review. JMIR Ment Health. 2019;6(6):e13717.
344. Deterding S, Sicart M, Nacke L, O'Hara K, Dixon D. Gamification. using game-design elements in non-gaming contexts. CHI '11 Extended Abstracts on Human Factors in Computing Systems; Vancouver, BC, Canada: Association for Computing Machinery; 2011. p. 2425–8.
345. Santo K, Redfern J. Digital health innovations to improve cardiovascular disease care. Curr Atheroscler Rep. 2020;22(12):71.
346. Thomas Craig KJ, Fusco N, Lindsley K, Snowdon JL, Willis VC, Arriaga YE, et al. Rapid review: Identification of digital health interventions in atherosclerotic-related cardiovascular disease populations to address racial, ethnic, and socioeconomic health disparities. Cardiovascular Digital Health Journal. 2020;1(3):139-48.
347. Global strategy on digital health 2020-2025. Geneva: World Health Organization; 2021 [Available from: https://apps.who.int/iris/bitstream/handle/10665/344249/9789240020924-eng.pdf.
348. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. Bmj. 2021;372:n71.
349. Shea BJ, Reeves BC, Wells G, Thuku M, Hamel C, Moran J, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. Bmj. 2017;358:j4008.
350. Higgins JPT TJ, Chandler J, Cumpston M, Li T, Page MJ, Welch VA (editors),. Cochrane Handbook for Systematic Reviews of Interventions version 6.2 (updated February 2021): Cochrane; 2021. Available from: www.training.cochrane.org/handbook.

351. Stoyanov SR, Hides L, Kavanagh DJ, Zelenko O, Tjondronegoro D, Mani M. Mobile App Rating Scale: A new tool for assessing the quality of health mobile apps. JMIR mHealth uHealth. 2015;3(1):e27.
352. Magno S, Ceccarini G, Pelosini C, Jaccheri R, Vitti J, Fierabracci P, et al. LDL-cholesterol lowering effect of a new dietary supplement: an open label, controlled, randomized, cross-over clinical trial in patients with mild-to-moderate hypercholesterolemia. Lipids in Health and Disease. 2018;17(1):124.
353. American Diabetes A. Standards of Care in Diabetes—2023 Abridged for Primary Care Providers. Clinical Diabetes. 2022;41(1):4-31.
354. Lenters-Westra E, Schindhelm RK, Bilo HJ, Groenier KH, Slingerland RJ. Differences in interpretation of haemoglobin A1c values among diabetes care professionals. Neth J Med. 2014;72(9):462-6.
355. Leon C, Tessa P, Kate S. HbA1c: a review of non-glycaemic variables. Journal of Clinical Pathology. 2019;72(1):12.
356. Rahimi K, Bidel Z, Nazarzadeh M, Copland E, Canoy D, Ramakrishnan R, et al. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. The Lancet. 2021;397(10285):1625-36.
357. Zhou B, Perel P, Mensah GA, Ezzati M. Global epidemiology, health burden and effective interventions for elevated blood pressure and hypertension. Nature Reviews Cardiology. 2021;18(11):785-802.
358. Oh SW, Kim KK, Kim SS, Park SK, Park S. Effect of an integrative mobile health intervention in patients with hypertension and diabetes: crossover study. JMIR Mhealth Uhealth. 2022;10(1):e27192.
359. Alonso-Domínguez R, García-Ortiz L, Patino-Alonso MC, Sánchez-Aguadero N, Gómez-Marcos MA, Recio-Rodríguez JI. Effectiveness of a multifactorial intervention in increasing adherence to the mediterranean diet among patients with diabetes mellitus type 2: A controlled and randomized study (EMID Study). Nutrients [Internet]. 2019; 11(1). Available from: https://mdpi-res.com/d_attachment/nutrients/nutrients-11-00162/article_deploy/nutrients-11-00162.pdf?version=1547438981.
360. Broers ER, Widdershoven J, Denollet J, Lodder P, Kop WJ, Wetzels M, et al. Personalized eHealth program for life-style change: Results from the “Do Cardiac Health Advanced New Generated Ecosystem (Do CHANGE 2)” randomized controlled trial. Psychosomatic Medicine. 2020;82(4).
361. Echeazarra L, Pereira J, Saracho R. TensioBot: A chatbot assistant for self-managed in-house blood pressure checking. J Med Syst. 2021;45(4):54.
362. Gonzalez-Sanchez J, Recio-Rodriguez JI, Fernandez-delRio A, Sanchez-Perez A, Magdalena-Belio JF, Gomez-Marcos MA, et al. Using a smartphone app in changing cardiovascular risk factors: A randomized controlled trial (EVIDENT II study). Int J Med Inform. 2019;125:13-21.
363. Haufe S, Kerling A, Protte G, Bayerle P, Stenner HT, Rolff S, et al. Telemonitoring-supported exercise training, metabolic syndrome severity, and work ability in company employees: a randomised controlled trial. The Lancet Public Health. 2019;4(7):e343-e52.
364. Hilmarsdóttir E, Sigurðardóttir Á K, Arnardóttir RH. A digital lifestyle program in outpatient treatment of type 2 diabetes: A randomized controlled study. J Diabetes Sci Technol. 2021;15(5):1134-41.
365. Höchsmann C, Müller O, Ambühl M, Klenk C, Königstein K, Infanger D, et al. Novel smartphone game improves physical activity behavior in type 2 diabetes. Am J Prev Med. 2019;57(1):41-50.
366. Lunde P, Bye A, Bergland A, Grimsmo J, Jarstad E, Nilsson BB. Long-term follow-up with a smartphone application improves exercise capacity post cardiac rehabilitation: A randomized controlled trial. Eur J Prev Cardiol. 2020;27(16):1782-92.
367. Bennett GG, Steinberg D, Askew S, Levine E, Foley P, Batch BC, et al. Effectiveness of an app and provider counseling for obesity treatment in primary care. American Journal of Preventive Medicine. 2018;55(6):777-86.
368. Dorsch MP, Cornellier ML, Poggi AD, Bilgen F, Chen P, Wu C, et al. Effects of a novel contextual just-in-time mobile app intervention (LowSalt4Life) on sodium intake in adults with hypertension: Pilot randomized controlled trial. JMIR Mhealth Uhealth. 2020;8(8):e16696.
369. Ifejika NL, Bhadane M, Cai CC, Noser EA, Grotta JC, Savitz SI. Use of a smartphone-based mobile app for weight management in obese minority stroke survivors: pilot randomized controlled trial with open blinded end point. JMIR Mhealth Uhealth. 2020;8(4):e17816.

370. Manigault KR, McKinley D, Patel S, Truong C, Nguyen S, Akil A, et al. The impact of a pharmacist-designed mobile application on blood pressure control and medication adherence in patients with hypertension. JACCP: JOURNAL OF THE AMERICAN COLLEGE OF CLINICAL PHARMACY. 2020;3(7):1286-95.
371. Persell SD, Peprah YA, Lipiszko D, Lee JY, Li JJ, Ciolino JD, et al. Effect of home blood pressure monitoring via a smartphone hypertension coaching application or tracking application on adults with uncontrolled hypertension: A randomized clinical trial. JAMA Netw Open. 2020;3(3):e200255.
372. Vaz CL, Carnes N, Pousti B, Zhao H, Williams KJ. A randomized controlled trial of an innovative, user-friendly, interactive smartphone app-based lifestyle intervention for weight loss. Obes Sci Pract. 2021;7(5):555-68.
373. Zha P, Qureshi R, Porter S, Chao Y-Y, Pacquiao D, Chase S, et al. Utilizing a mobile health intervention to manage hypertension in an underserved community. Western Journal of Nursing Research. 2019;42(3):201-9.
374. Logan AG, Irvine MJ, McIsaac WJ, Tisler A, Rossos PG, Easty A, et al. Effect of home blood pressure telemonitoring with self-care support on uncontrolled systolic hypertension in diabetics. Hypertension. 2012;60(1):51-7.
375. Bozorgi A, Hosseini H, Eftekhar H, Majdzadeh R, Yoonessi A, Ramezankhani A, et al. The effect of the mobile “blood pressure management application” on hypertension self-management enhancement: a randomized controlled trial. Trials. 2021;22(1):413.
376. Gong K, Yan YL, Li Y, Du J, Wang J, Han Y, et al. Mobile health applications for the management of primary hypertension: A multicenter, randomized, controlled trial. Medicine (Baltimore). 2020;99(16):e19715.
377. Gunawardena KC, Jackson R, Robinett I, Dhaniska L, Jayamanne S, Kalpani S, et al. The influence of the smart glucose manager mobile application on diabetes management. J Diabetes Sci Technol. 2019;13(1):75-81.
378. Kario K, Nomura A, Kato A, Harada N, Tanigawa T, So R, et al. Digital therapeutics for essential hypertension using a smartphone application: A randomized, open-label, multicenter pilot study. J Clin Hypertens (Greenwich). 2021;23(5):923-34.
379. Tekkeşin A, Hayıroğlu M, Çinier G, Özdemir YS, İnan D, Yüksel G, et al. Lifestyle intervention using mobile technology and smart devices in patients with high cardiovascular risk: A pragmatic randomised clinical trial. Atherosclerosis. 2021;319:21-7.
380. Wong EML, Leung DYP, Tam HL, Wang Q, Yeung KW, Leung AYM. The effect of a lifestyle intervention program using a mobile application for adults with metabolic syndrome, versus the effect of a program using a booklet: A pilot randomized controlled trial. Clin Interv Aging. 2021;16:633-44.
381. Yun YH, Kang E, Cho YM, Park SM, Kim YJ, Lee HY, et al. Efficacy of an electronic health management program for patients with cardiovascular risk: Randomized controlled trial. J Med Internet Res. 2020;22(1):e15057.
382. Zhai Y, Yu W. A mobile app for diabetes management: Impact on self-efficacy among patients with type 2 diabetes at a community hospital. Med Sci Monit. 2020;26:e926719.
383. Duncan MJ, Fenton S, Brown WJ, Collins CE, Glozier N, Kolt GS, et al. Efficacy of a multi-component m-health weight-loss intervention in overweight and obese adults: A randomised controlled trial. International Journal of Environmental Research and Public Health [Internet]. 2020; 17(17). Available from: https://mdpi-res.com/d_attachment/ijerph/ijerph-17-06200/article_deploy/ijerph-17-06200.pdf?version=1598449426.
384. Li A, Del Olmo MG, Fong M, Sim K, Lymer SJ, Cunich M, et al. Effect of a smartphone application (Perx) on medication adherence and clinical outcomes: a 12-month randomised controlled trial. BMJ Open. 2021;11(8):e047041.
385. Yudi MB, Clark DJ, Tsang D, Jelinek M, Kalten K, Joshi SB, et al. SMARTphone-based, early cardiac REHABilitation in patients with acute coronary syndromes: a randomized controlled trial. Coron Artery Dis. 2021;32(5):432-40.
386. Patel MS, Small DS, Harrison JD, Fortunato MP, Oon AL, Rareshide CAL, et al. Effectiveness of behaviorally designed gamification interventions with social incentives for increasing physical activity among overweight and obese adults across the united states: the STEP UP randomized clinical trial. JAMA Internal Medicine. 2019;179(12):1624-32.
387. Mazeas A, Duclos M, Pereira B, Chalabaev A. Evaluating the effectiveness of gamification on physical activity: Systematic review and meta-analysis of randomized controlled trials. J Med Internet Res. 2022;24(1):e26779.

388. Su JJ, Yu DS. Effects of a nurse-led eHealth cardiac rehabilitation programme on health outcomes of patients with coronary heart disease: A randomised controlled trial. Int J Nurs Stud. 2021;122:104040.
389. Su JJ, Paguio J, Baratedi WM, Abu-Odah H, Batalik L. Experience of coronary heart disease patients with a nurse-led eHealth cardiac rehabilitation: Qualitative process evaluation of a randomized controlled trial. Heart Lung. 2023;57:214-21.
390. Liu X, Deliu N, Chakraborty B. Microrandomized trials: Developing just-in-time adaptive interventions for better public health. Am J Public Health. 2023;113(1):60-9.
391. Nystoriak MA, Bhatnagar A. Cardiovascular effects and benefits of exercise. Front Cardiovasc Med. 2018;5.
392. Fontana L, Villareal DT, Weiss EP, Racette SB, Steger-May K, Klein S, et al. Calorie restriction or exercise: effects on coronary heart disease risk factors. A randomized, controlled trial. American journal of physiology Endocrinology and metabolism. 2007;293(1):E197-E202.
393. Myers J. Exercise and cardiovascular health. Circulation. 2003;107(1):e2-e5.
394. Dangardt FJ, McKenna WJ, Lüscher TF, Deanfield JE. Exercise: friend or foe? Nature reviews Cardiology. 2013;10(9):495-507.
395. Kim HJ, Lee KH, Lee JH, Youk H, Lee HY. The effect of a mobile and wearable device intervention on increased physical activity to prevent metabolic syndrome: Observational study. JMIR Mhealth Uhealth. 2022;10(2):e34059.
396. Izquierdo M, Merchant RA, Morley JE, Anker SD, Aprahamian I, Arai H, et al. International Exercise Recommendations in Older Adults (ICFSR): Expert consensus guidelines. The journal of nutrition, health & aging. 2021;25(7):824-53.
397. Paradis S, Roussel J, Bosson JL, Kern JB. Use of smartphone health apps among patients aged 18 to 69 years in primary care: Population-based cross-sectional survey. JMIR Form Res. 2022;6(6):e34882.
398. Patrick K, Hekler EB, Estrin D, Mohr DC, Riper H, Crane D, et al. The pace of technologic change: Implications for digital health behavior intervention research. Am J Prev Med. 2016;51(5):816-24.
399. Smuck M, Odonkor CA, Wilt JK, Schmidt N, Swiernik MA. The emerging clinical role of wearables: factors for successful implementation in healthcare. NPJ Digit Med. 2021;4(1):45.
400. Heath GW, Parra DC, Sarmiento OL, Andersen LB, Owen N, Goenka S, et al. Evidence-based intervention in physical activity: lessons from around the world. The Lancet. 2012;380(9838):272-81.
401. Williamson C, Baker G, Mutrie N, Niven A, Kelly P. Get the message? A scoping review of physical activity messaging. Int J Behav Nutr Phys Act. 2020;17(1):51.
402. LivePulse [Mobile app]: Google Play Store; 2022 [cited 2022. Available from: https://play.google.com/store/apps/details?id=com.vulsen.livepulse.
403. Mitra S, Kroeger CM, Xu J, Avery L, Masedunskas A, Cassidy S, et al. Testing the effects of app-based motivational messages on physical activity and resting heart rate through smartphone app compliance in patients with vulnerable coronary artery plaques: protocol for a microrandomized trial. JMIR Res Protoc. 2023;12:e46082.
404. Hardan-Khalil K, Costa CB, Fisher DG. Daily motivational text messages impact on college students' nutritional awareness and physical activity levels. J Am Coll Health. 2022;70(8):2511-8.
405. Figueroa CA, Deliu N, Chakraborty B, Modiri A, Xu J, Aggarwal J, et al. Daily motivational text messages to promote physical activity in university students: Results from a microrandomized trial. Annals of Behavioral Medicine. 2022;56(2):212-8.
406. Gell NM, Wadsworth DD. The use of text messaging to promote physical activity in working women: A randomized controlled trial. J Phys Act Health. 2015;12(6):756-63.
407. Pathak LE, Aguilera A, Williams JJ, Lyles CR, Hernandez-Ramos R, Miramontes J, et al. Developing messaging content for a physical activity smartphone app tailored to low-income patients: User-centered design and crowdsourcing approach. JMIR Mhealth Uhealth. 2021;9(5):e21177.
408. Paluch AE, Bajpai S, Bassett DR, Carnethon MR, Ekelund U, Evenson KR, et al. Daily steps and all-cause mortality: a meta-analysis of 15 international cohorts. The Lancet Public Health. 2022;7(3):e219-e28.
409. Kraus WE, Janz KF, Powell KE, Campbell WW, Jakicic JM, Troiano RP, et al. Daily step counts for measuring physical activity exposure and its relation to health. Medicine and science in sports and exercise. 2019;51(6):1206-12.
410. Tudor-Locke C, Craig CL, Brown WJ, Clemes SA, De Cocker K, Giles-Corti B, et al. How many steps/day are enough? for adults. International Journal of Behavioral Nutrition and Physical Activity. 2011;8(1):79.

411. Project risk reduction by therapy. ASCVD Risk Estimator. [Available from: https://tools.acc.org/ascvd-risk-estimator-plus/#!/calculate/estimate/.
412. Australian CVD risk calculator. Australian cardiovascular disease risk calculator. [Available from: https://www.cvdcheck.org.au/calculator.
413. Newman J. Intima-media thickness (IMT). In: Gellman MD, editor. Encyclopedia of Behavioral Medicine. Cham: Springer International Publishing; 2020. p. 1243-.
414. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. New England Journal of Medicine. 1999;340(1):14-22.
415. Craig CL, Marshall AL, Sjöström M, Bauman AE, Booth ML, Ainsworth BE, et al. International physical activity questionnaire: 12-country reliability and validity. Medicine & Science in Sports & Exercise. 2003;35(8).
416. Ness-Abramof R, Apovian CM. Waist circumference measurement in clinical practice. Nutrition in Clinical Practice. 2008;23(4):397-404.
417. Hu G, Tuomilehto J, Silventoinen K, Sarti C, Männistö S, Jousilahti P. Body mass index, waist circumference, and waist-hip ratio on the risk of total and type-specific stroke. Archives of internal medicine. 2007;167(13):1420-7.
418. Ren C, Zhang J, Xu Y, Xu B, Sun W, Sun J, et al. Association between carotid intima-media thickness and index of central fat distribution in middle-aged and elderly Chinese. Cardiovascular Diabetology. 2014;13(1):139.
419. Sofianopoulou E, Kaptoge SK, Afzal S, Jiang T, Gill D, Gundersen TE, et al. Estimating dose-response relationships for vitamin D with coronary heart disease, stroke, and all-cause mortality: observational and Mendelian randomisation analyses. The Lancet Diabetes & Endocrinology. 2024;12(1):e2-e11.
420. UK Biobank. Algorithmically defined outcomes (ADOs). 2022 [Available from: https://biobank.ndph.ox.ac.uk/ukb/ukb/docs/alg_outcome_main.pdf.
421. Monica T, Gregory N, Janet T, Greg M, Francesca ND. Valvular disease burden in the modern era of percutaneous and surgical interventions: the UK Biobank. Open Heart. 2022;9(2):e002039.
422. Jia Y, Li Y, Yu J, Jiang W, Liu Y, Zeng R, et al. Association between metabolic dysfunction-associated fatty liver disease and abdominal aortic aneurysm. Nutrition, Metabolism and Cardiovascular Diseases. 2023.
423. Kogan EV, Sciria CT, Liu CF, Wong SC, Bergman G, Ip JE, et al. Early stroke and mortality after percutaneous left atrial appendage occlusion in patients with atrial fibrillation. Stroke. 2023;54(4):947-54.
424. Beydoun HA, Beydoun MA, Meirelles O, Erickson LD, Gamaldo AA, Weiss J, et al. Cardiovascular health, infection burden, and incident dementia in the UK Biobank. Alzheimer's & Dementia. 2023;19(10):4475-87.
425. Bots Michiel L, Evans Gregory W, Riley Ward A, Grobbee Diederick E. Carotid intima-media thickness measurements in intervention studies. Stroke. 2003;34(12):2985-94.
426. Weather Query Builder. Visual Crossing Corporation. [Available from: https://www.visualcrossing.com/weather/weather-data-services/Sydney,Australia/us/2023-02-06/2023-05-06#.

Appendices

Appendix A: Supplementary material for Chapter 2

Appendix B: Supplementary material for Chapter 4

Appendix C: Supplementary material for Chapter 5

Appendix D: Supplementary material for Chapter 6

Appendix E: Supplementary material for Chapter 7

Appendix F: PICF for LIVEPLUS

Appendix G: Clinical Trial Research Agreement

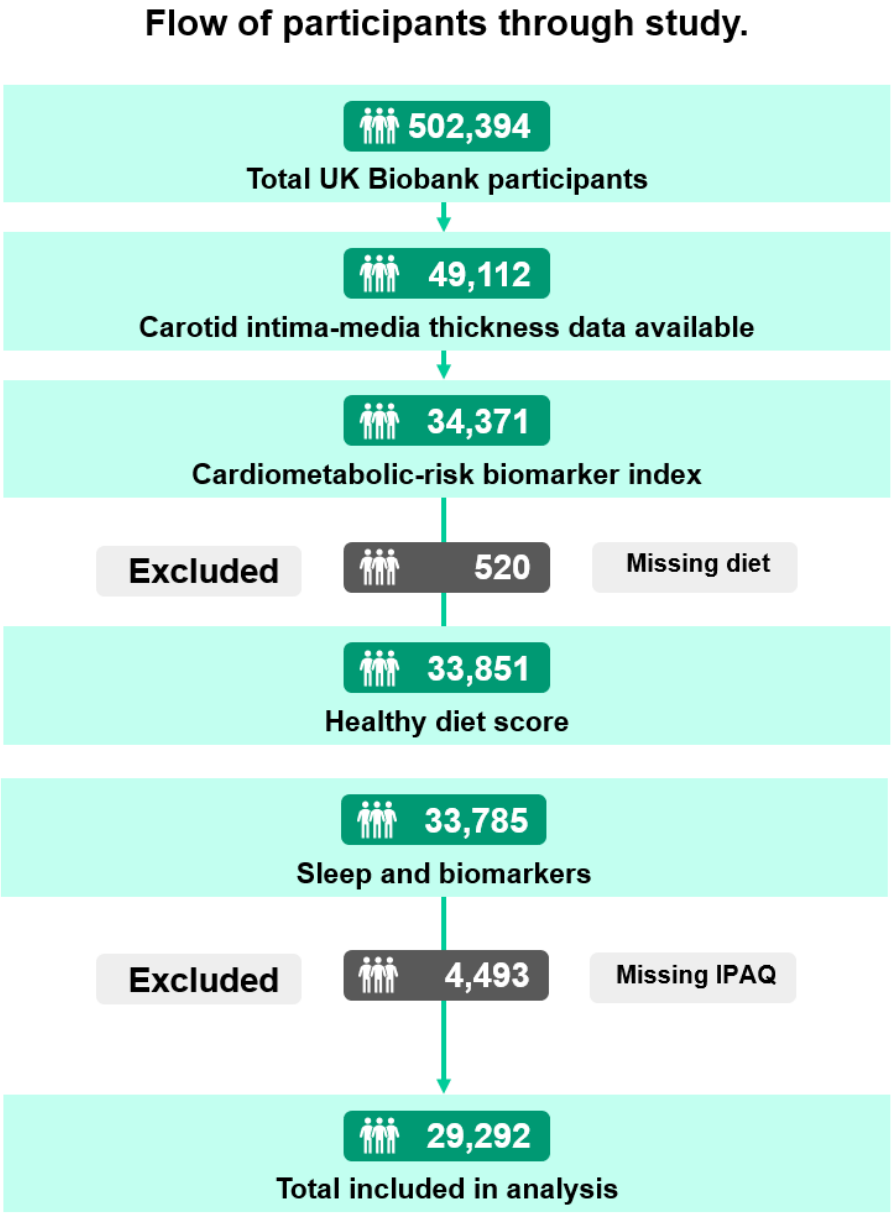
Appendix H: Author contribution statement Chapter 3

Appendix J: Author contribution statement Chapter 6

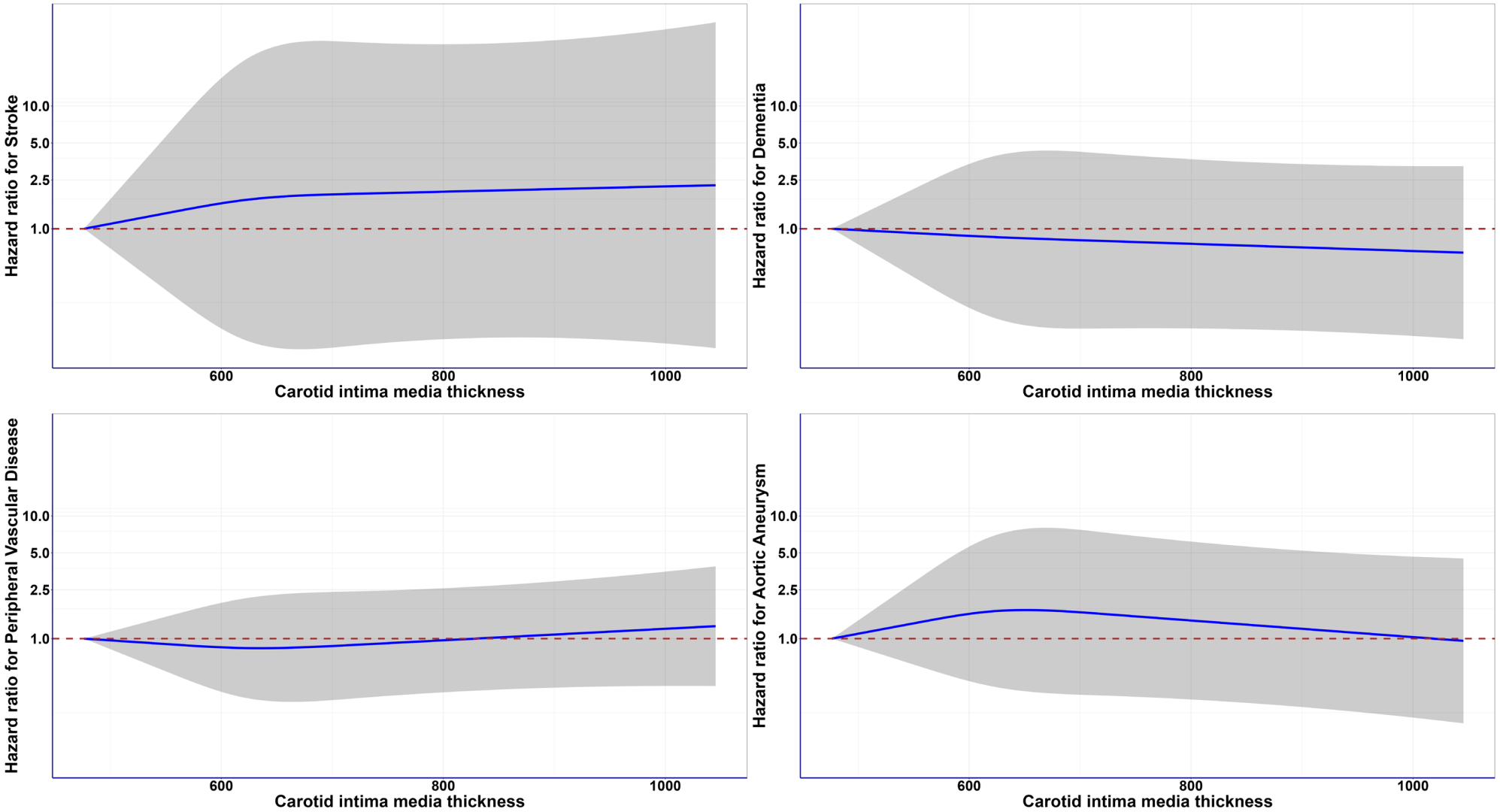
Appendix K: LIVEPLUS recruitment fliers

Appendix A
Supplementary material for Chapter 2

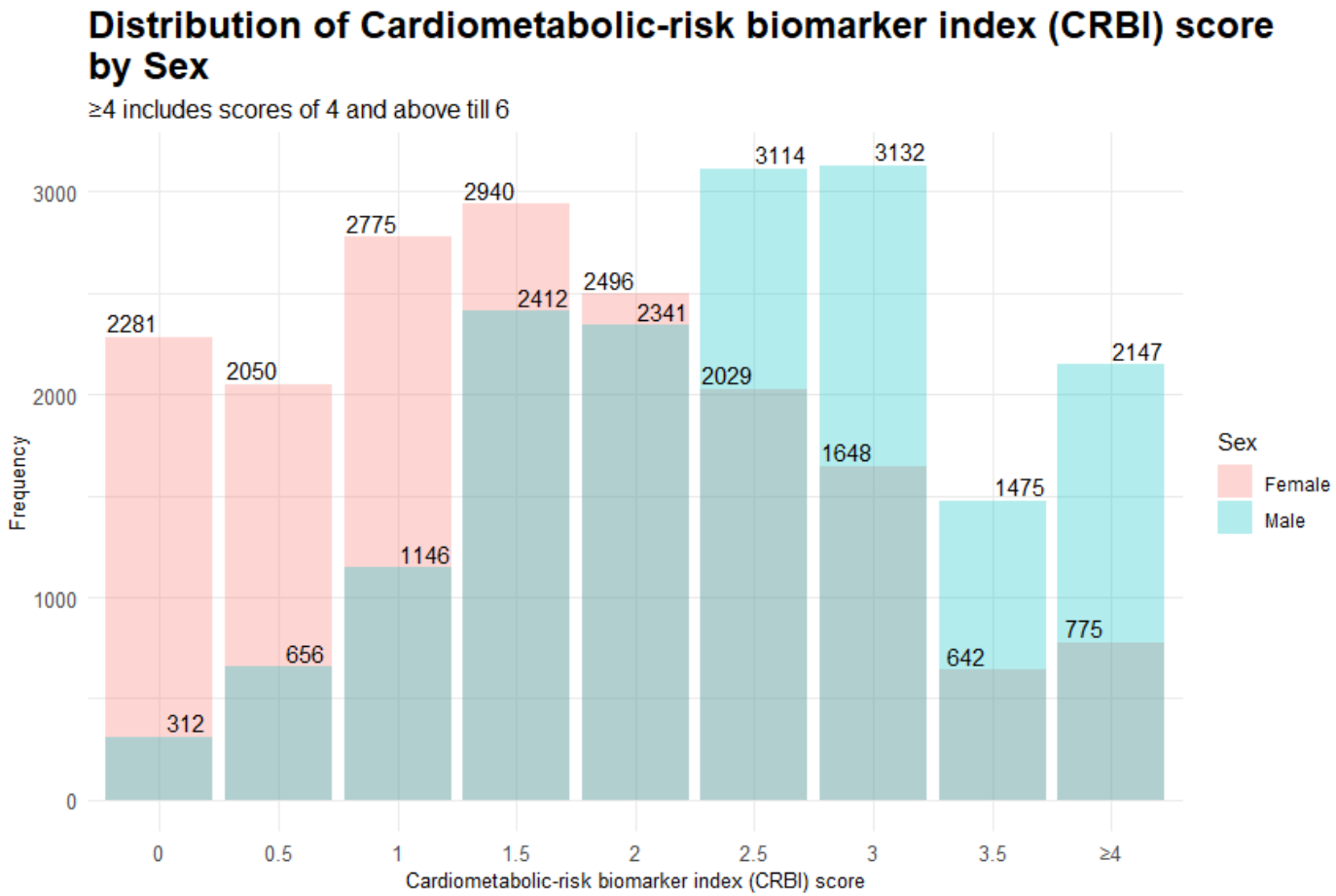
Supplementary Table of Contents for Chapter 2



Supplementary Figure 2.1. Flow diagram of participants in this study.

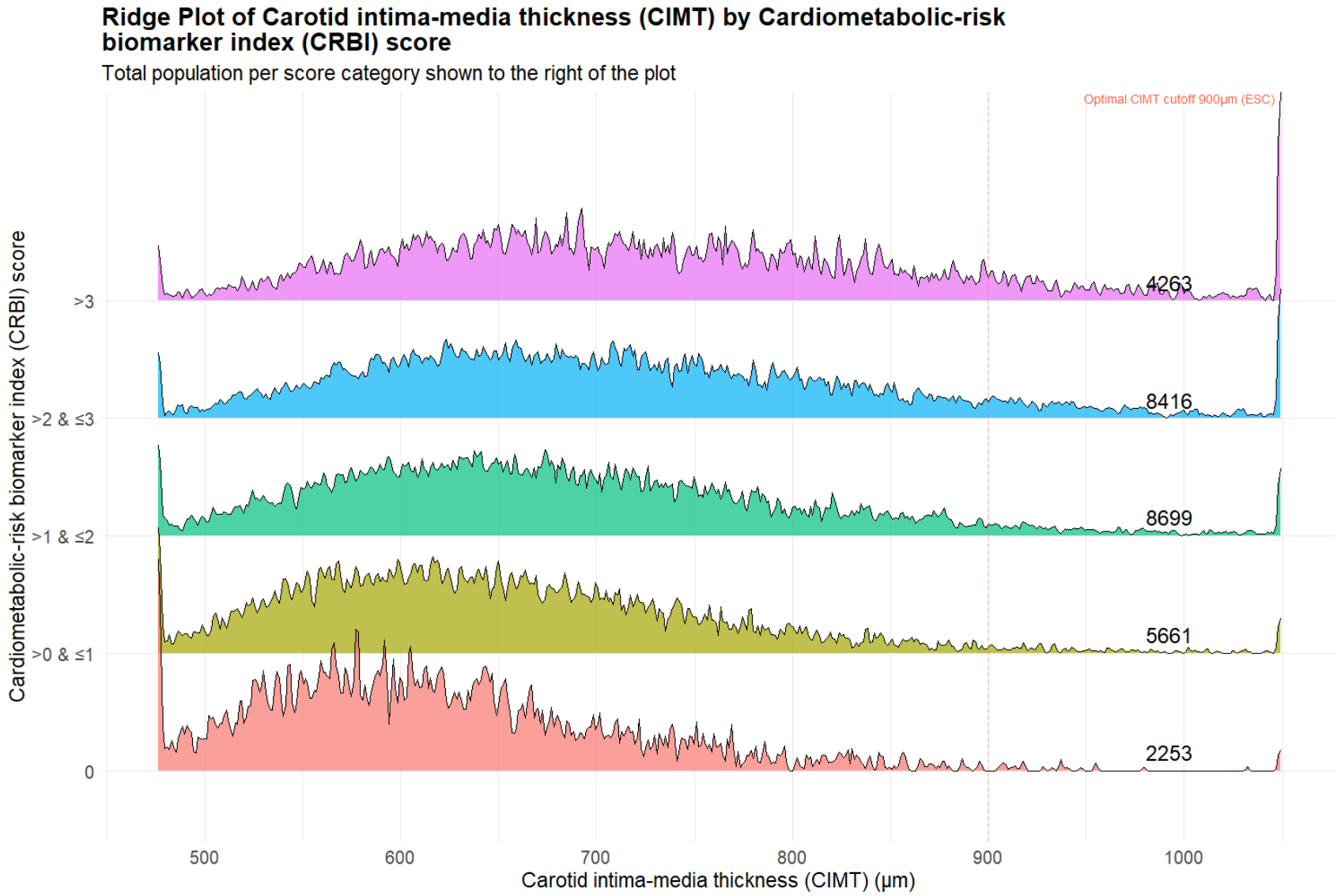


Supplementary Figure 2.2. Associations of CIMT and stroke (n=19), dementia (N=78), peripheral vascular disease (N=110), and aortic aneurysm (N=74) after adjusting for CRBI.

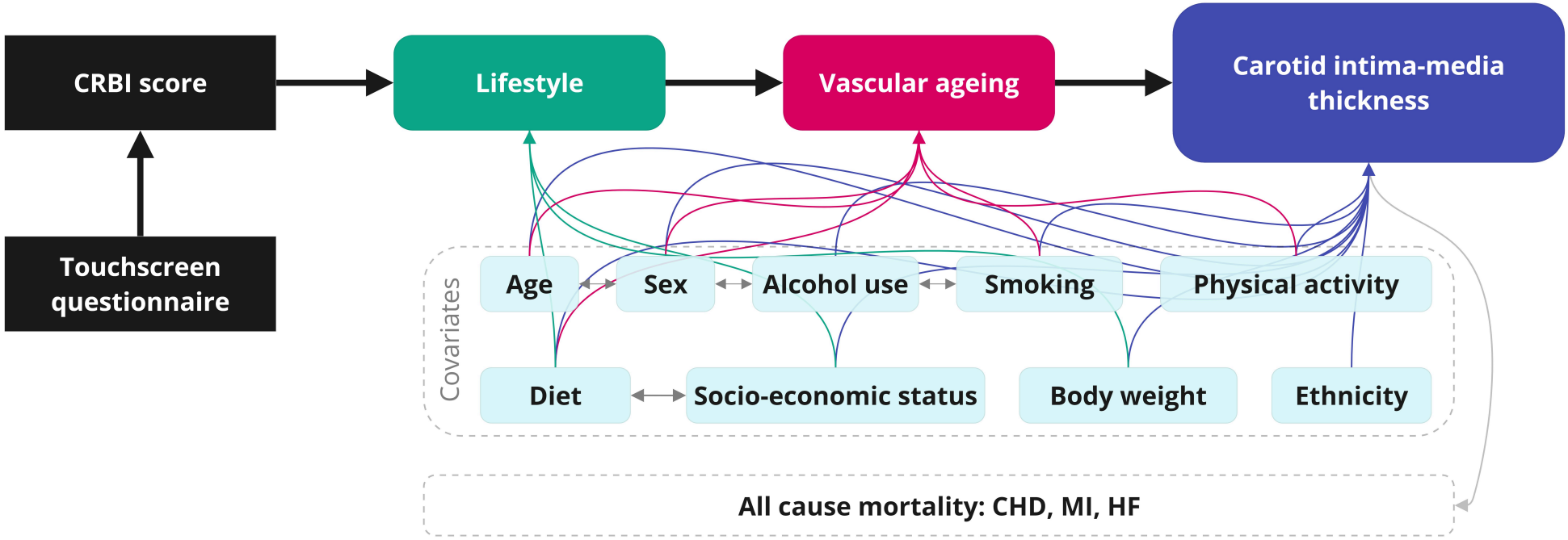


Supplementary Figure 2.3. Distribution of cardiometabolic-risk biomarker index score by sex.

CRBI scores of 0, >0 & ≤1, >1 & ≤2, >2 & ≤3, >3 correspond to optimal, low, moderate, high, and very high respectively.



Supplementary Figure 2.4. Carotid intima-media thickness values per CRBI score in our study population.



Supplementary Figure 2.5. Directed acyclic graph (DAG) demonstrating variables for the cardiometabolic-risk biomarker index (CRBI) from UK biobank biomarkers, and its association with vascular ageing via carotid intima-media thickness (CIMT).

In this Directed acyclic graph (DAG), the Cardiometabolic-risk biomarker index (CRBI) score is calculated based on the certain biomarker values from the UK Biobank. The CRBI score is used to measure health status, which is then associated with vascular ageing. Vascular ageing is assessed by carotid intima-media thickness (CIMT).

Other covariates such as age, sex, diet, socio-economic status, physical activity, smoking, alcohol use, and 'body weight' are also included in the DAG as additional nodes that may have direct or indirect effects on vascular ageing. Outcome and exposures are in different coloured bubbles.

CHD, coronary heart disease; MI, myocardial infarction; HF, heart failure

Supplementary Table 2.1. STROBE statement.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	Location in manuscript
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Section 2.1.2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Sections 2.1.2 & 2.1.3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Section 2.2
Objectives	3	State specific objectives, including any prespecified hypotheses	Section 2.2
Methods			
Study design	4	Present key elements of study design early in the paper	Section 2.3.1
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Section 2.3.1
Participants	6	*(a)* Give the eligibility criteria, and the sources and methods of selection of participants *(b)* For matched studies, give matching criteria and number of exposed and unexposed	Supplementary Figure 2.1
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Supplementary Table 2.2
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Supplementary Table 2.2
Bias	9	Describe any efforts to address potential sources of bias	NA
Study size	10	Explain how the study size was arrived at	Section 2.4.1

Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Section 2.3.6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Section 2.3.6
		(*b*) Describe any methods used to examine subgroups and interactions	NA
		(*c*) Explain how missing data were addressed	Section 2.3.4 (last three sentences)
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	NA
		(*e*) Describe any sensitivity analyses	NA
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—e.g. numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Section 2.4.1
		(b) Give reasons for non-participation at each stage	Supplementary Figure 2.1
		(c) Consider use of a flow diagram	Supplementary Figure 2.1
Descriptive data	14*	(a) Give characteristics of study participants (e.g. demographic, clinical, social) and information on exposures and potential confounders	Table 2.1
		(b) Indicate number of participants with missing data for each variable of interest	NA
Outcome data	15*	Report numbers of outcome events or summary measures	Section 2.4.2 to Section 2.4.5
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Table 2.1
		(*b*) Report category boundaries when continuous variables were categorized	Table 2.1
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period.	NA

Other analyses	17	Report other analyses done—e.g. analyses of subgroups and interactions, and sensitivity analyses	Table 2.2, Table 2.3, and Figure 2.3

Discussion

Key results	18	Summarise key results with reference to study objectives	Section 2.5
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Section 2.5
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Section 2.5
Generalisability	21	Discuss the generalisability (external validity) of the study results	Section 2.5
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	NA

*Give information separately for exposed and unexposed groups.
Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

Supplementary Table 2.2. Covariates, units, type, definitions, normal values, and UK Biobank field codes (if applicable).

Variable	Units	Type	Definition	Healthy levels	UK Biobank field code(s)
Age	years	Exposure	This is a derived variable based on date of birth and date of attending assessment centre and refers to the age of the participant on the day they attended an Assessment Centre, truncated to whole year part.	-	34
Sex	-	Exposure	Female/Male	-	31
Carotid intima media thickness (CIMT)	µm	Outcome	Ultrasound measurement of the two innermost layers of the arterial wall, where atherosclerotic damage begins before plaque occurrence.[413] It is a **marker of subclinical atherosclerosis**.[414] IMT values of more than 0.9 mm may be attributed to asymptomatic vascular damage; European Society of Cardiology (ESC).[272]	≤ 0.9mm (ESC)	22672, 22675, 22678, 22681, 22671, 22674, 22677, 22680, 22670, 22673, 22676, 22679
Sleep duration	hours	Exposure	About how many hours sleep do you get in every 24 hours (including naps)? If the time you spend sleeping varies a lot, give the average time for a 24-hour day in the last 4 weeks	NA	1160
Physical activity score	NA	Exposure	The physical activity score was calculated using participants' self-reported answers to questions from the International Physical Activity Questionnaire (IPAQ)[415].	NA	864, 874, 884, 894, 904, 914,
Waist circumference	cm	Exposure	Waist circumference refers to the measurement taken around the abdomen at the level of the natural waist, typically just above the hip bones. It is used as a simple anthropometric indicator to assess central obesity and the distribution of body fat. Waist circumference measurement provides valuable information about the amount of fat stored in the abdominal region, which is associated with an increased risk of various health conditions, including cardiovascular diseases, type 2 diabetes, and metabolic syndrome.[416]	94-102 cm for M 80-88 cm for F	48
Hip circumference	cm	Exposure	Hip circumference refers to the measurement taken around the widest part of the hips and buttocks. This anthropometric measurement is valuable for evaluating body composition and fat distribution. Hip circumference is often used in conjunction with waist circumference to calculate the waist-to-hip ratio, which provides insights into the distribution of body fat and its potential health implications.[417]	-	49
Waist-hip ratio (WHR)	-	Exposure	Different patterns of fat distribution, as indicated by variations in waist-to-hip ratio, can be associated with varying levels of health	*≤ 0.5[418]	48, 49

Variable	Units	Type	Definition	Healthy levels	UK Biobank field code(s)
			risks, particularly in relation to cardiovascular and metabolic health.[417]		
Alcohol intake frequency	Categorical (single)	Exposure	ACE touchscreen question “About how often do you drink alcohol?” “Daily or almost daily”, “Three or four times a week”, “Once or twice a week”, “Less often”, and “Never”	-	1558
Smoking status	Categorical	Exposure	“0=Never”, “1=Previous”, “2=Current”		20116
Use of cholesterol medication		Exposure			
Use of blood pressure medication		Exposure			
Use of diabetes medication		Exposure			
Diet	Various	Exposure	Fruits and vegetables (servings/day)		Various. See tables above
Vitamin intake	Y/N	Exposure	Essential nutrients vital for bodily functions		
Mineral intake	Y/N	Exposure	Inorganic substances required for a range of physiological processes		
Townsend	0-5	Exposure	Deprivation index measuring material deprivation in a population	-	189
BMI		Exposure	Weight / (height)^2	18.5 – 24.9	21001
Blood pressure	mmHg	Exposure	Force exerted by circulating blood on the walls of blood vessels	90/60 mmHg and 120/80 mmHg	4079, 4080
Sedentary time	hours	Exposure	Duration of inactivity or minimal physical movement: Calculated using time spent watching TV, using computer, and driving.		1070, 1080, 1090
Physical activity	Categorical		Any bodily movement produced by skeletal muscles requiring energy expenditure. Score of 2 means: high level of physical activity Score of 1 means: moderate level of physical activity Score of 0 means: low level of physical activity		See way above
Body weight	kg	Exposure	Total mass of a person, often used as an indicator of health		21002
WBC	x 10^9 cells/L	Exposure	White Blood Cells, a key component of the body's immune system	4 to 11 x 10^9 cells/L	30000
CRP	mg/L	Exposure	C-reactive Protein, a marker of inflammation in the body	<10 mg/L	30710
IGF-1	nmol/L	Exposure	Insulin-like Growth Factor 1, a hormone important for growth and development	1.3 – 195	30770
Cholesterol	mmol/L	Exposure	A waxy substance found in blood, essential for building cells but high levels can lead to health issues.	<5 mmol/L	30690
Triglycerides	mmol/L	Exposure	A type of fat found in the blood, used for energy or stored in the body.	<1.7 mmol/L	30870

Variable	Units	Type	Definition	Healthy levels	UK Biobank field code(s)
HDL	mmol/L	Exposure	High-Density Lipoprotein, often referred to as 'good' cholesterol, which helps remove other forms of cholesterol from the bloodstream	>1mmol/L for M, >1.2mmol/L for F	30760
HbA1c	mmol/mol	Exposure	Haemoglobin A1c, a measure of average blood glucose levels over the past 2 to 3 months	20-42 mmol/mol	30750
TC:HDL ratio	-	Exposure	The ratio of total cholesterol to high-density lipoprotein, used as an indicator of heart disease risk	Below 6	30690, 30760
Medication females			Medication females (cholesterol, blood pressure, diabetes, or take exogenous hormones)		6153
Medication males			Medication males (cholesterol, blood pressure or diabetes)		6177
LDL					30780

*For Men: A WHR of 0.9 or less is considered low risk, 0.9 to 0.99 is moderate risk, and 1.0 or higher is high risk.
For Women: A WHR of 0.8 or less is considered low risk, 0.81 to 0.84 is moderate risk, and 0.85 or higher is high risk.
A normal CIMT is generally less than 0.9 mm, 0.9 mm to 1.0 mm may indicate a moderate risk of cardiovascular disease, and greater than 1.0 mm is often considered a sign of increased risk.

Supplementary Table 2.3. Food groups (used for diet score creation).

Food groups	Consisting of	Unit/frequency of intake
Vegetable group	Cooked vegetables[†] + Salad/raw vegetables	heaped tablespoons/day (1 tablespoon = 14.175 grams)
Fruit group	Fresh fruit + Dried fruit	pieces/day
Unprocessed red meat group	Beef + lamb/mutton + pork intake	0 Never 1 Less than once a week 2 Once a week 3 2-4 times a week 4 5-6 times a week 5 Once or more daily
Fish group	Oily + non-oily intake scores	0 Never 1 Less than once a week 2 Once a week 3 2-4 times a week 4 5-6 times a week 5 Once or more daily
Processed meat group	ACE touchscreen question "How often do you eat processed meats (such as bacon, ham, sausages, meat pies, kebabs, burgers, chicken nuggets)?"	0 Never 1 Less than once a week 2 Once a week 3 2-4 times a week 4 5-6 times a week 5 Once or more daily

[†]Excluding potatoes

Supplementary Table 2.4. Diet score calculations based on food groups from FFQ.

Diet score calculations based on food groups as shown here:	
Fruits	≥ 3 servings/day (A standard serve is about 150g, 350kJ)
Vegetables	≥ 3 servings/day (A standard serve is about 75g, 100–350kJ)
Fish	≥ 2 servings/week, including once a week of oily fish (A standard serve is 500–600kJ, 100g cooked fish fillet, about 115g raw, or one small can of fish)
Processed meats	< 1 serving/week
Red meat (lamb/beef/pork)	< 2 servings/week (A standard serve is 500–600kJ, 65g cooked red meats such as beef, lamb/mutton, pork (about 90-100g raw)

In developing the food groups for diet score calculations, we used specific criteria based on the UK Biobank's Food Frequency Questionnaire (FFQ) reporting methodology. Each food group was meticulously defined to ensure comprehensive dietary assessment.
The diet score calculations were based on the following food groups:

- For fruits, the criteria stipulated a consumption of three or more servings per day, with a standard serving being approximately 150 grams, equivalent to 350 kilojoules. Similarly, the vegetable group required an intake of three or more servings per day, where each standard serving was about 75 grams, providing 100 to 350 kilojoules. The vegetable group consisted of both cooked vegetables and raw salad vegetables, measured in heaped tablespoons per day, with each tablespoon equating to approximately 14.175 grams.
- The fish group was categorised based on the consumption of two or more servings per week, including at least one serving of oily fish. A standard serving for fish was defined as 100 grams of cooked fish fillet, approximately 115 grams when raw, or one small can of fish, contributing 500 to 600 kilojoules. Intake frequencies for fish were scored from 0 (never) to 5 (once or more daily).
- Processed meat consumption was limited to less than one serving per week, with intake frequencies also scored from 0 (never) to 5 (once or more daily) based on the response to the ACE touchscreen question regarding the consumption of processed meats, such as bacon, ham, sausages, meat pies, kebabs, burgers, and chicken nuggets.
- For unprocessed red meat, including lamb, beef, and pork, the criteria stipulated a consumption of less than two servings per week. Each standard serving of red meat was set at 65 grams of cooked meat, roughly equivalent to 90 to 100 grams when raw, and provided 500 to 600 kilojoules. Intake frequencies for red meat were similarly scored from 0 (never) to 5 (once or more daily).

Therefore, the diet score ranged from 1 to 4, with an individual having a score of either 1, 2, 3, or 4, corresponding to poor, fair, healthy, or optimal, respectively.

Detailed explanation:

- Diet score 1 (**Poor**): This category indicates a diet that fails to meet any of the recommended criteria. It suggests low consumption of fruits and vegetables, inadequate fish intake, and high consumption of processed and red meats.
- Diet score 2 (**Fair**): This score reflects adherence to one of the dietary guidelines. For example, the individual might be consuming adequate amounts of fruits or vegetables, or their fish intake is sufficient, but other aspects of the diet are not aligned with the recommendations.
- Diet score 3 (**Healthy**): This score suggests adherence to two of the dietary guidelines. For instance, the individual might have a good intake of both fruits and vegetables but may not meet the criteria for fish, processed meats, or red meat consumption.

Diet score 4 (**Optimal**): This category indicates a well-balanced diet that adheres to most or all the guidelines. It suggests a diet rich in fruits and vegetables, adequate fish consumption, and limited intake of processed and red meats.

Supplementary Table 2.5. Diet groups based on dietary consumption.

Diet groups	Consisting of	Unit/frequency of intake
Vegan	Consumption of fruits, vegetables, grains and cereals, legumes and beans, nuts, and seeds **but not dairy products, eggs, fish, meat, poultry, and spreads**	Consumed/not consumed
Vegetarians	Consumption of dairy products and eggs but not fish, poultry, or red meat, i.e. lacto-ovo vegetarian);	Consumed/not consumed
Fish eaters	Consumption of dairy products, eggs, and fish but not poultry or red meat	Consumed/not consumed
White meat (Fish + poultry)	Consumption of dairy products, eggs, fish, and poultry **but not red meat**	Consumed/not consumed
Meat eaters	Consumption of dairy products, eggs, fish, poultry, and red meat	Consumed/not consumed

Supplementary Table 2.6. Cardiometabolic-risk biomarker index (CRBI).

Cardiometabolic biomarker index	Optimal (0)	Intermediate (1)	Poor (2)
HbA_{1c}	<5.7% AND not taking diabetes medication	5.7% to 6.4% OR <5.7% AND taking diabetes medication	≥6.5%
TC:HDLr	<3.5 AND not taking lipid lowering medication	3.5 to ≤5 OR <3.5 AND taking lipid lowering medication.	>5
Blood pressure	SBP <120 AND DBP <80 AND not taking BP-lowering medication	SBP 120-139 OR DBP 80-89 OR SBP < 120 AND DBP < 80 AND taking BP-lowering medication	SBP ≥140 OR DBP ≥ 90

Supplementary Table 2.7. Cardiometabolic-risk biomarker index (CRBI) score.

	Optimal	Intermediate	Poor
HbA1c	0	1	2
TC:HDLr	0	1	2
DBP	0	0.5	1
SBP	0	0.5	1

Supplementary Table 2.8. ICD-10 codes for outcomes and UK Biobank data fields.

			UK Biobank data fields for:	
		ICD-10 codes	**Date first reported**	**Source of report**
Cardiovascular diseases	**Coronary Heart Disease**	I25	131306	131307
	Myocardial Infarction*	I21, I22, I23	131298, 131300, 131302	131299, 131301, 131303
	Heart Failure	I50	131354	131355
	Aortic Aneurysm	I71	131382	131383
	Peripheral Vascular Disease	I73	131386	131387
	Stroke (Ischaemic)	I63	42008	42009
Dementia	**Alzheimer's disease**	G30	131036	131037
	Dementia (all cause)	A81.0, F00, F01, F02, F03, F05, G30, G31.0, G31.1, G31.8, and I67.3	42018	42019

*Non-fatal; Date first reported = Date for diagnosis; Source of report = Source of diagnosis
Coronary Heart Disease (Acute Coronary Syndrome - ACS): ICD-10 code: I25.1 (Chronic ischemic heart disease, which includes atherosclerotic cardiovascular disease, atherosclerotic heart disease, and coronary (artery) atherosclerosis).[419]
Myocardial Infarction (MI): I21, I22, I23: ICD-10 code: I21 (Acute myocardial infarction).[419, 420]
Heart Failure: ICD-10 code: (I50).[421]
Aortic Aneurysm: ICD-10 code: I71 (Aortic aneurysm and dissection)[422]
Peripheral Vascular Disease: ICD-10 code: I73.[423]
Stroke (Ischaemic): ICD-10 code: I63 (Cerebral infarction)[419, 420]
Dementia: ICD-10 code: F03 (Unspecified dementia) or more specific codes depending on type; F00 (Dementia in Alzheimer's disease), F01 (Vascular dementia), F02 (Dementia in other diseases classified elsewhere), F03 (Unspecified dementia), F05 (delirium superimposed on dementia) or G30 (Alzheimer's disease), G31 (Circumscribed brain atrophy), G31.1 (Senile degeneration of brain), I67.3 (Progressive vascular leukoencephalopathy).[420, 424]

Supplementary Table 2.9. Multicollinearity for linear regression between CMIT and all factors.

	GVIF	Df	GVIF^(1/(2*Df))
Age	1.153711	1	1.074109558
Sex	1.456256	1	1.206754414
Ethnicity	1.038024	1	1.018834603
C-reactive protein	1.036352	1	1.018013854
Townsend	1.044192	1	1.021857061
Sleep category	1.013347	2	1.003320078
IPAQ	1.030149	2	1.007453411
Diet score	1.047552	3	1.007772646
CRBI score	1.304812	1	1.142283815
Smoke score	1.070884	2	1.017268484
Alcohol intake	1.104901	4	1.012547579
Body weight	1.487498	1	1.219630372

Supplementary Table 2.10. Association of CRBI score and individual biomarkers with CIMT.

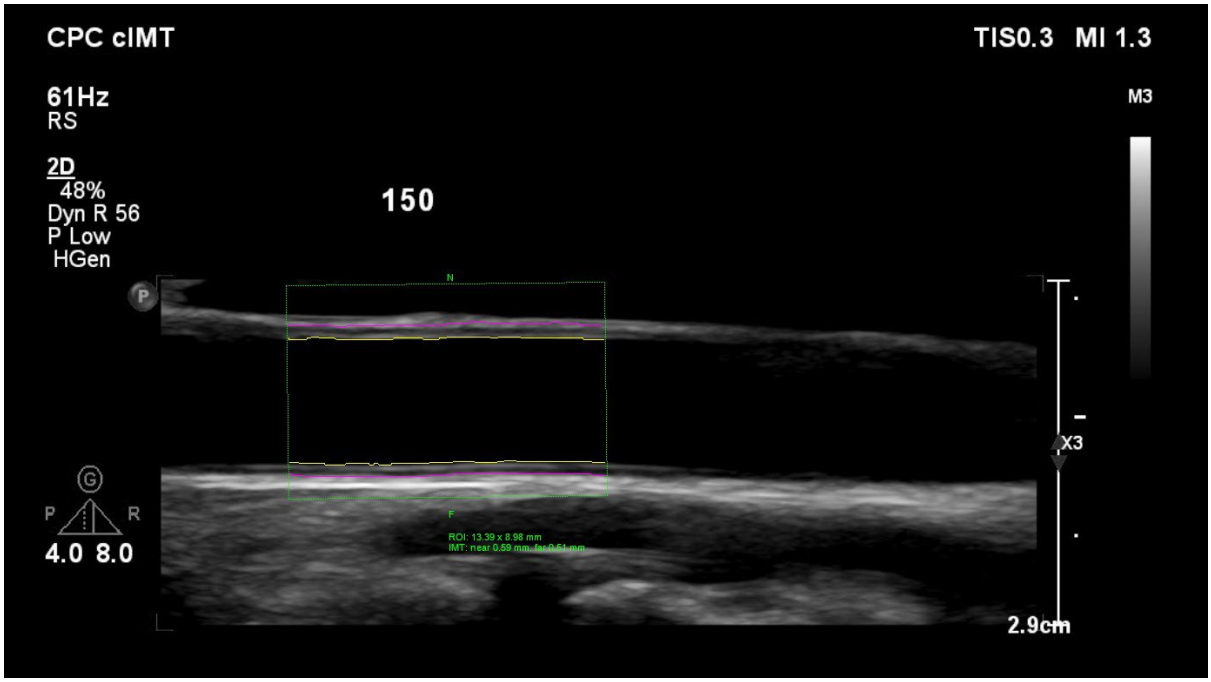
	CRBI score		Blood pressure		TC:HDL ratio		HbA1c	
Levels	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value	β (95% CI)	P-value
Optimal	-	-	-	-	-	-	-	-
Low	10.37 (5.00, 15.74)	<0.001	0.73 (-5.26, 6.72)	0.811	8.186 (5.34, 11.03)	<0.001	4.91 (1.17, 8.65)	0.010
Moderate	19.89 (14.63, 25.15)	<0.001	6.52 (0.46, 12.58)	0.035	16.68 (13.09, 20.28)	<0.001	9.92 (-3.04, 22.88)	0.134
High	32.47 (26.98, 37.97)	<0.001	20.18 (15.25, 25.15)	<0.001	28.02 (22.96, 33.07)	<0.001	11.23 (-4.03. 26.09)	0.151
Very high	44.38 (38.25, 50.51)	<0.001	37.50 (32.94, 42.06)	<0.001	34.53 (26.99, 42.07)	<0.001	12.85 (-5.52. 31.23)	0.170

Analyses adjusted for age, sex, ethnicity, C-reactive protein, Townsend deprivation index, sleep duration, physical activity derived from IPAQ, dietary consumption, CIMT, smoking, alcohol consumption, and body weight.

Appendix B

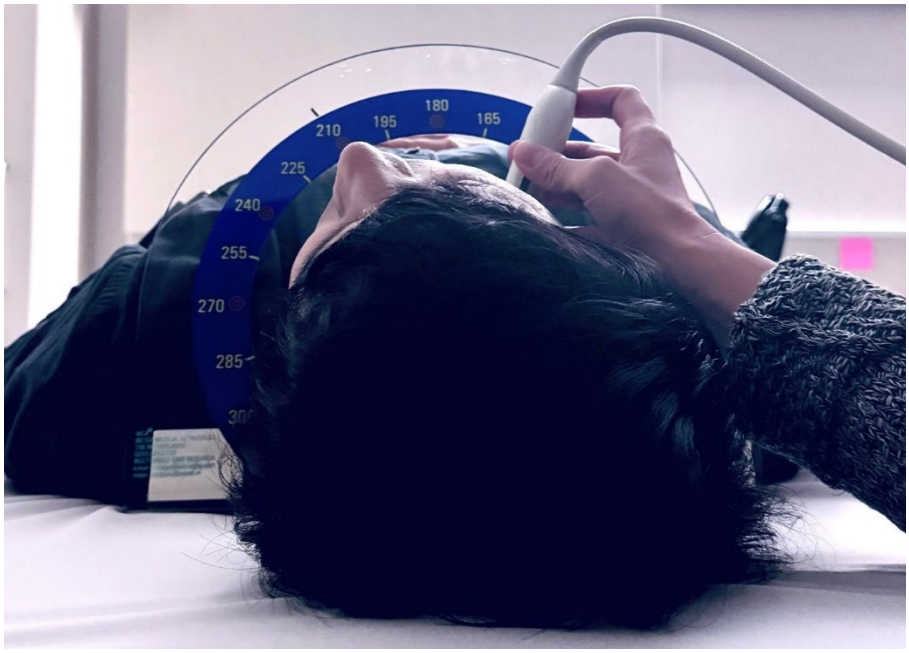
Supplementary material for Chapter 4

Supplementary Table of Contents for Chapter 4

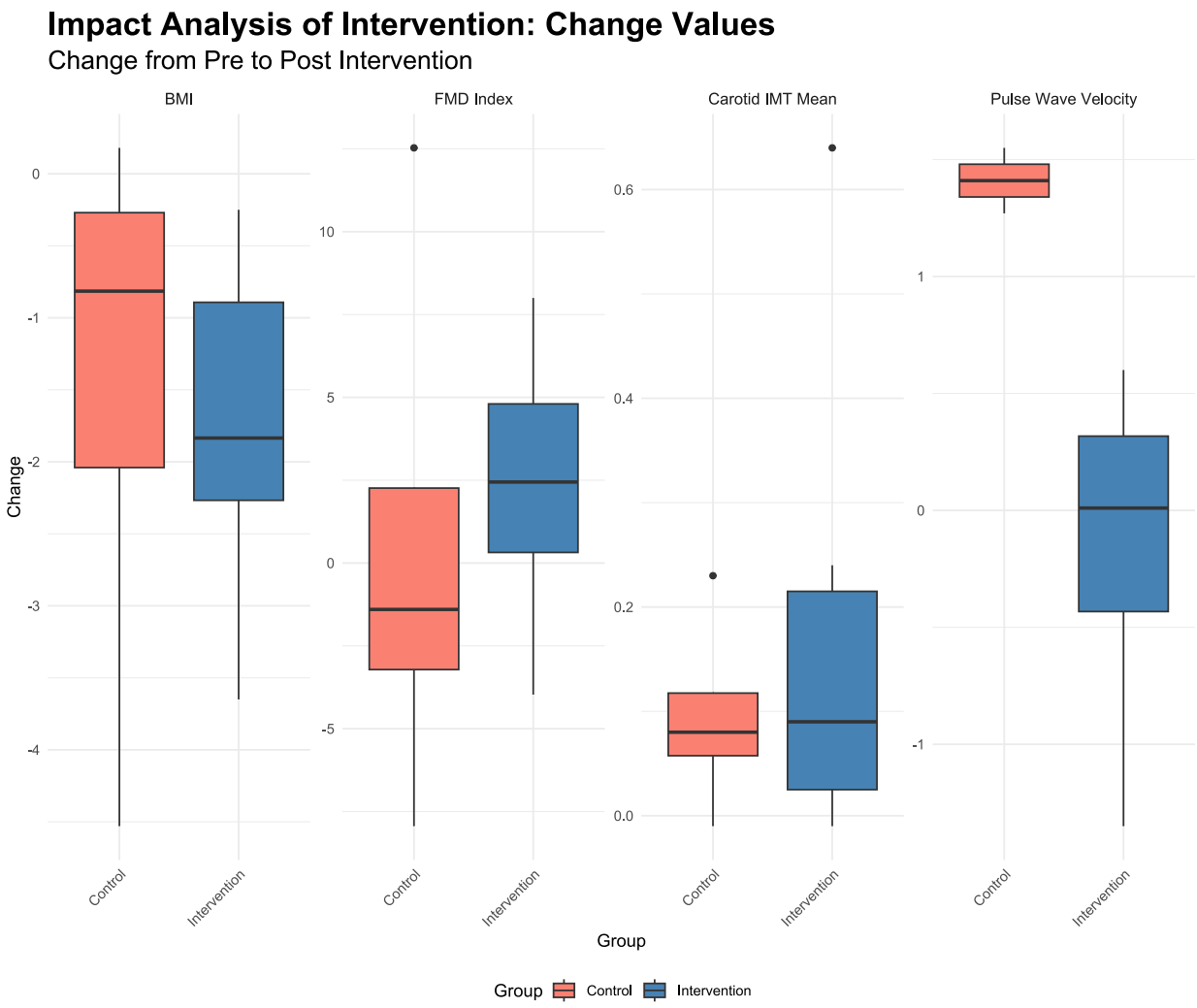


Supplementary Figure 4.1 Screenshot from “Carotid Analyzer for Research 6” software used for data analysis.

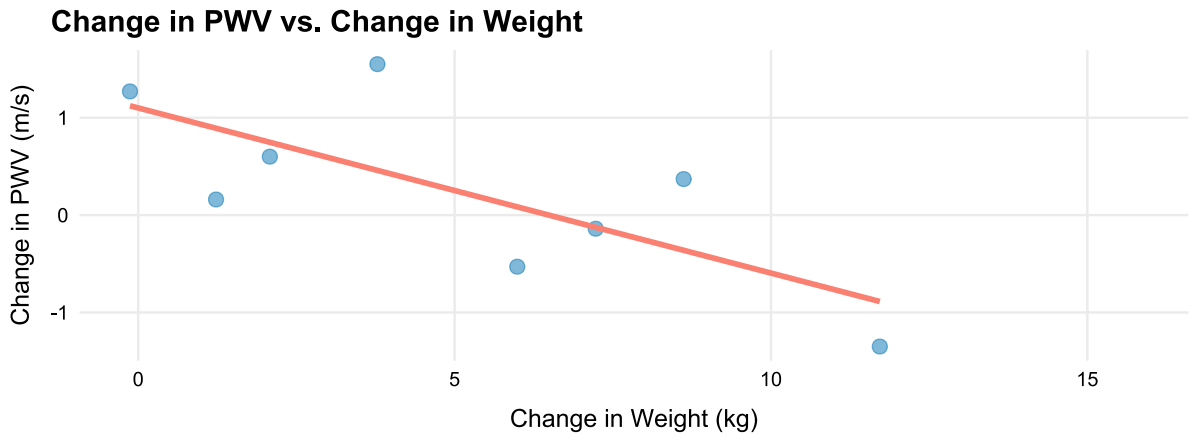
The dashed green line/box shows the ROI (region of interest) within which the software identifies the intima and media layers to perform the semi-automated analysis. 150 denotes 150º angle (towards the right side of the neck, the angle at which we place the probe, as shown in **Figure 1.10** in **Chapter 1**).



Supplementary Figure 4.2 Meijer's Carotid Arc
Used for standardising specific angles during probe placement ensuring consistent scans of both the left and right carotid arteries.[425]



Supplementary Figure 4.3 Impact analysis of intervention.



Supplementary Figure 4.4 Scatter plot for PWV vs. Weight Change.

Supplementary Table 4.1 Individual health conditions and medication history.

				Baseline		Month 6		Changes in Medications
Record ID	**Age**	**Group**	**Sex**	**Conditions**	**Medications**	**Conditions**	**Medications**	
LP-1	72	Intervention	Male	Arthritis, clinical depression, knee operations, appendix removal, weight fluctuation	Crestor 5mg/day, Enalapril 5mg/day, Aspirin 100mg/day	Mild sleep apnoea, constipation, TIA in 2010, knee and hip pain, non-recent depression	Crestor 20mg/day, Enalapril 5mg/day, Aspirin 100mg/day, Circadian (occasionally)	Crestor dosage increased, Circadian added
LP-2	70	Control	Male	Mild sleep apnoea, knee operations, car accident, atrial ablation, hernia operation	None reported	Same knee problems	Aspirin 100mg/day	Aspirin introduced
LP-3	60	Intervention	Male	Neck pain	Metformin 1mg/day, Simvastatin 20mg/day, Aspirin 100mg/day, Proflavanol C100	No changes	Metformin 1mg/day, Simvastatin 20mg/day, Aspirin 100mg/day, Proflavanol C100	No changes
LP-4	50	Intervention	Male	Borderline sleep apnoea, knee operation, stroke, heart PFO device surgery, weight loss	Idaprex 8, Atorvastatin 40mg, Natrilix 2.5mg, Zircol 20mg, Doxycycline 50mg	No new conditions reported	Idaprex 8, Atorvastatin 40mg, Zircol 20mg, Doxycycline 50mg	Natrilix stopped
LP-5	67	Control	Female	Mild sleep apnoea, various medical issues including asthma, hay fever, skin cancer, left bundle branch block, major depression, anxiety	Phenergan, Clopidogrel 75mg/day, Crestor 2.5mg/every second day, Ezetrol 10mg/day, Norvasc 5mg/day, Ventolin, vitamins, Melatonin, Temazepam	Worsened sleep, basal cell carcinoma, abnormal pap smear, broken metacarpals, resolved plantar fasciitis	Crestor 2.5mg/day, antihistamines (Zyrtec/Fenugen), Ventolin, Clopidogrel 75mg/day, Ezetrol 10mg/day, Norvasc 5mg/day, vitamins	Increased use of antihistamines and Ventolin
LP-6	52	Intervention	Female	Eczema, hay fever, Hashimoto's, weight gain	Claritin, Crestor 10mg, Ezetrol 10mg, Eltroxin 25mg, CoQ10 300mg, Ambrotose	No updates	Claritin, Crestor 10mg, Ezetrol 10mg, Eltroxin 25mg, CoQ10 300mg, Ambrotose	No changes
LP-7	73	Intervention	Female	Bowel infection, eczema, hepatitis, melanoma, surgeries, osteoporosis, weight gain	Pradaxa 150mg, Sevikar 20/5, Rosuvastatin 10mg, Sotalol HCL 80mg	No new conditions reported	Pradaxa 150mg, Sevikar 20/5, Rosuvastatin 10mg, Sotalol HCL 80mg, Vitamin Calcium, Vitamin D3, Fosamax Plus	Added Vitamin Calcium, Vitamin D3, Fosamax Plus
LP-8	43	Control	Male	Childhood asthma, dermatitis, fatty liver, orthopaedic surgeries	Capra 1500mg 2x/day, Tegretol 200mg 2x/day, Atorvastatin 40mg/day, Vitamin D	No changes since month 1	Capra 1500mg 2x/day, Tegretol 200mg 2x/day, Atorvastatin 40mg/day, Vitamin D	No changes
LP-9	62	Control	Male	Previous melanoma	Ezetimibe/Rosuvastatin 10mg;40mg 1x/day, Sevikar HCT 40/10/12.5 half tablet	Knee injury, circumstantial anxiety	Ezetimibe/Rosuvastatin 10mg;40mg 1x/day, Sevikar HCT 40/10/12.5 half tablet	No changes
LP-10	54	Intervention	Male	Moderate sleep apnoea, childhood hypothyroidism, L5S1 microdiscectomy	Progout 100mg 3x/day, Ezetimibe/Rosuvastatin 10mg/40mg 1x/day, Cartia low dose Aspirin 100mg, Apo-Candesartan 8mg 1x/day	No specific conditions reported	No specific medications reported	Unclear if there were changes

Intervention group consisting of App access and following a 5:2 pescatarian diet; Control group consisting of No app access and following American Heart Association dietary guidelines.

Supplementary Table 4.2 Impact of body weight (≤5% & >5%) on outcome measures.

	Weight loss ≤5% (N=5)			**Weight loss >5%** (N=5)			**P value**‡
	Pre	**Post**	***p* value**†	**Pre**	**Post**	***p* value**†	
Age	62.60 ± 6.23	-	-	58.00 ± 13.70	-	-	-
Sex	4M, 1F	-	-	3M, 2F	-	-	-
BMI	29.08 ± 5.33	28.60 ± 5.23	0.11	28.10 ± 4.01	25.27 ± 3.51	0.06	<0.01**
Flow mediated dilation							
FMD index (%)	5.59 ± 3.89	8.35 ± 7.11	0.48	6.68 ± 3.00	7.10 ± 5.09	0.80	0.67
Carotid IMT							
Carotid IMT_{Mean}	0.54 ± 0.28	0.73 ± 0.12	0.18	0.68 ± 0.17	0.78 ± 0.22	0.09	0.88
Carotid IMT_{Max}	0.70 ± 0.36	0.96 ± 0.18	0.11	0.91 ± 0.24	0.96 ± 0.27	0.34	0.41
Pulse wave analysis							
Aortic augmentation (mmHg)	6.80 ± 3.86	7.80 ± 3.96	0.15	8.13 ± 6.69	9.47 ± 7.25	0.59	0.83
Augmentation index (%)	16.00 ± 14.37	20.07 ± 9.26	0.79	18.07 ± 11.44	19.40 ± 7.80	1.00	0.71
SEVR	185.54 ± 38.08	182.87 ± 32.54	0.62	164.17 ± 11.10	159.20 ± 12.47	0.35	0.37
Pulse wave velocity (N=8)							
PWV (m/s)	7.29 ± 0.82	8.29 ± 0.98	0.07	7.90 ± 0.92	7.49 ± 0.89	0.34	0.08
Pulse transit time (ms)	69.25 ± 10.84	66.67 ± 6.92	0.37	65.42 ± 14.84	72.34 ± 14.85	0.18	0.20

Values are Mean ± SD

† Wilcoxon rank test

‡ Adjusted for baseline value for ANCOVA

* p<0.05

** p<0.01

p value = within group

P value = between group

IMT = intima media thickness; FMD = flow mediated dilation; PWV = pulse wave velocity; SEVR = sub endocardial viability ratio; Carotid IMT reported from Far wall measurements for more accuracy of results as per literature. M = male, F = female.

Supplementary Table 4.3 Impact of weight loss on body composition and biomarkers.

	Weight loss ≤5% (N=5)			**Weight loss >5%** (N=5)			**P value**‡
	Pre	**Post**	***p* value**†	**Pre**	**Post**	***p* value**†	
Age	62.60 ± 6.23	-	-	58.00 ± 13.70	-	-	-
Sex	4M, 1F	-	-	3M, 2F	-	-	-
Weight (kg)	85.02 ± 20.73	83.71 ± 20.68	0.11	89.56 ± 21.08	80.38 ± 17.76	0.06	<0.01**
BMI (kg/m^2)	29.08 ± 5.33	28.60 ± 5.23	0.11	28.10 ± 4.01	25.27 ± 3.51	0.06	<0.01**
Waist to Hip ratio	0.96 ± 0.09	0.90 ± 0.06	0.11	0.89 ± 0.09	0.85 ± 0.11	0.36	0.98
Fasting glucose (mmol/L)	6.00 ± 1.29	5.90 ± 1.52	0.27	5.20 ± 0.16	5.16 ± 0.25	0.79	0.46
HbA1c (%)	5.25 ± 0.30	5.45 ± 0.54	0.42	5.42 ± 0.08	5.43 ± 0.15	1.00	0.39
HbA1c (mmol/L)	36.60 ± 4.98	35.33 ± 7.09	1.00	36.00 ± 1.22	36.00 ± 2.00	1.00	0.85
Total Chol to HDL-C ratio	2.52 ± 1.04	2.65 ± 0.93	0.79	2.68 ± 0.29	2.50 ± 0.50	0.42	0.40
SBP (mmHg)	116.90 ± 9.63	120.13 ± 4.77	1.00	130.20 ± 34.38	127.50 ± 28.59	1.00	0.94
DBP (mmHg)	74.00 ± 5.49	77.63 ± 5.11	0.20	77.50 ± 9.53	74.90 ± 6.90	0.79	0.38
White cell count (x10^9/L)	4.98 ± 0.95	4.45 ± 0.70	0.36	5.62 ± 1.24	5.55 ± 0.92	0.79	0.23
Neutrophil (x10^9/L)	2.92 ± 0.77	2.45 ± 0.76	0.20	3.40 ± 0.90	3.58 ± 0.62	1.00	0.18
Cholesterol (mmol/L)	4.36 ± 1.93	4.85 ± 1.93	0.85	3.90 ± 0.33	3.70 ± 0.50	0.58	0.44
Triglycerides (mmol/L)	0.92 ± 0.24	0.98 ± 0.17	0.79	1.20 ± 0.31	0.98 ± 0.52	0.20	0.51
HDL-C (mmol/L)	1.77 ± 0.61	1.86 ± 0.60	1.00	1.46 ± 0.12	1.53 ±0.33	0.58	0.97
LDL-C (mmol/L)	2.24 ± 1.59	2.65 ± 1.63	1.00	1.88 ± 0.36	1.75 ± 0.39	0.85	0.39
Non-HDL-C (mmol/L)	2.60 ± 1.75	3.00 ± 1.74	1.00	2.44 ± 0.34	2.18 ± 0.53	0.57	0.35

Values are Mean ± SD

† Wilcoxon rank test

‡ Adjusted for baseline value for ANCOVA

* p<0.05

** p<0.01

p value = within group

P value = between group

BMI = body mass index; Chol = cholesterol; DBP = diastolic blood pressure; HbA1c = haemoglobin A1c; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; SBP = systolic blood pressure. M = male, F = female.

Supplementary Table 4.4 Correlation of weight change on outcome measures.

	ρ	*p* value
Flow mediated dilation		
FMD index (%)	-0.12†	0.73
Carotid IMT		
Carotid IMT_{Mean}	0.04‡	0.92
Carotid IMT_{Max}	-0.52‡	0.13
Pulse wave analysis		
Aortic augmentation (mmHg)	0.20†	0.57
Augmentation index (%)	-0.12†	0.74
SEVR	-0.17†	0.67
Pulse wave velocity (N=8)		
PWV (m/s)	-0.73†	0.04*
Pulse transit time (ms)	0.63†	0.10

†Pearson's product-moment correlation
‡Spearman's rank correlation
* p<0.05
** p<0.01
IMT = intima media thickness; FMD = flow mediated dilation; PWV = pulse wave velocity; SEVR = sub endocardial viability ratio; Carotid IMT reported from Far wall measurements for more accuracy of results as per literature.

Appendix C

Supplementary material for Chapter 5

Supplementary Table of Contents for Chapter 5

Gamification - further explained

The growing significance of digital interventions in healthcare is highlighted by their expanding clinical validation in diagnostics, their transformative effect on drug discovery and the personalisation of digital therapeutics through artificial intelligence. Gamified digital platforms also hold promise for enhancing adherence to lifestyle changes and reducing CVD risk. These developments align with the World Health Organisation's guidelines on leveraging digital health interventions to strengthen health systems.[1,2] In the context of this review, gamification is defined as the integration of game-design elements—such as points, rewards, and challenges—into non-game healthcare settings. This form of digital health intervention aims to motivate and engage individuals in adopting healthier behaviours and enhancing treatment compliance.[3]

In cardiovascular care, gamification has been employed to improve health behaviour and offers potential benefits for physical health and mental well-being.[4] Gamification elements shape both the structure of a game and the engagement of its players. These elements include: game mechanics (i.e., the rules and procedures that govern how the game operates), game dynamics (i.e., the behaviours that emerge from these mechanics, such as competition), objectives (i.e., the goals that players strive to achieve), challenges and rewards (i.e., mechanisms that guide player progress and motivation), feedback mechanisms (i.e., systems that update players on their performance), progression (i.e., adjustments to the difficulty level as players advance), interactivity (i.e., the ways players interact with the game environment), narrative elements (i.e., story layers that, though not always present, can enhance the experience), aesthetics (i.e., visual and auditory aspects that enrich user experience), and social features (i.e., capabilities for player-to-player interaction). Collectively, these elements contribute to a game's design and its psychological impact on players.[5] Gamification has significantly influenced various fields, including healthcare, education, and business. Originating in digital media, the concept of "gamification" has evolved to distinguish itself from serious games, which have a longer history and are intended for non-entertainment purposes. While serious games provide immersive experiences through game mechanics and rules, gamification focuses on modifying user behaviour through game-like experiences. Common gamification strategies include point systems, badges, leaderboards, and social network integration to boost engagement and interaction. While many studies have evaluated the impact of digital health technologies on CVD outcomes, often focusing on text-messaging programs, research specifically addressing the effectiveness of gamified smartphone apps for CVD risk populations remains limited. Existing reviews tend to focus on general digital interventions, often overlooking the unique aspects and potential benefits of gamification.

Several smartphone apps are available for managing CVD, including My Cardiac Coach™, Smart Blood Pressure (Smart BP), and CardioSmart® Heart Explorer. My Cardiac Coach™, a free app developed by the American Heart Association, provides a personalised recovery toolkit for heart attack survivors.[6] Despite growing interest in the potential applications of gamification for behavioural change and treatment adherence in healthcare, there is currently a lack of conclusive evidence regarding the efficacy of its core elements.[7] This uncertainty highlights the need for further research to pinpoint the most effective uses and potential limitations of gamification in healthcare and beyond. Gamification has the potential to improve outcomes such as body weight, blood pressure, and glycated haemoglobin (HbA1c) by leveraging psychological principles that drive engagement and motivation. Incorporating game-like elements —such as points, badges, leaderboards, and challenges— into healthcare apps may encourage individuals to maintain healthy behaviours, including regular exercise, proper diet, and medication adherence. These elements provide immediate positive reinforcement for completing health-related tasks, making the process of lifestyle modification more rewarding. Additionally, they can foster a sense of competition and achievement, which may enhance long-term engagement with the app. This sustained interaction may lead to better monitoring and self-management, ultimately resulting in more significant and lasting improvements in key health metrics like body weight, blood pressure, and HbA1c levels.

Textbox 1. Some popular apps used as/in digital health interventions.

1. MyFitnessPal[8]: Used for tracking diet and exercise, this app aims to help users lose weight or maintain a healthy lifestyle.
2. Headspace[9]: A mindfulness and meditation app designed to improve mental well-being.
3. Fitbit[10, 11]: While primarily a fitness tracker, it also provides insights into sleep patterns and other health metrics.
4. Calm[12]: Focuses on stress reduction and mental well-being through meditation and sleep stories.
5. Omada Health[13]: A comprehensive program that provides personal health coaching to manage conditions like diabetes and hypertension.
6. Smoke Free[14]: Designed to help users quit smoking, offering craving management tips and health improvement indicators.
7. Noom[15]: Combines calorie tracking with behaviour change strategies to help users lose weight and improve their health.
8. MySugr[16]: A diabetes management app that helps users keep track of their blood sugar levels, medication, and carb intake.
9. Apple Health[17]: A comprehensive app that consolidates various health data points such as physical activity, nutrition, measured biomarkers, and sleep for an overarching view of one's well-being.

Gamification in healthcare: theoretical pros and cons

Gamification in healthcare refers to the application of game design elements such as scoring, competition, and achievement badges to non-game contexts like healthcare management, medical training, and patient engagement. It is an approach that aims to make healthcare more engaging, efficient, and effective.[18]
Pros
Increased Engagement: The element of fun and competition often results in higher levels of engagement among both healthcare providers and patients.
Behavioural Change: Gamification can motivate patients to adhere to treatment plans, take medication on time, or follow a healthy lifestyle, thus improving health outcomes.
Data Collection: The use of gamified apps and platforms often comes with the added advantage of data collection, which can provide valuable insights into patient behaviour and treatment efficacy.
Education and Training: Gamified simulations can provide healthcare workers with a risk-free environment to practice procedures, improve their skills, and even familiarise themselves with new medical technology.
Stress Reduction: Light-hearted games and activities can ease the stress and anxiety often associated with healthcare environments.
Cost-Efficiency: In the long term, better patient compliance and engagement could lead to less frequent hospital visits, thus reducing healthcare costs.
Accessibility: Digital gamification platforms can make healthcare services and information accessible to people who might otherwise have geographical or logistical constraints.
Peer Support: Some gamified platforms offer social features, allowing users to share experiences, tips, and encouragement, thereby fostering a sense of community and support.
Cons
Not One-Size-Fits-All: What motivates one person might not motivate another; thus, the gamification model needs to be flexible enough to cater to individual differences.
Data Privacy Concerns: With digital platforms collecting health data, there are legitimate concerns over the security and privacy of this sensitive information.
Overemphasis on Rewards: There is a risk that users may become focused solely on earning rewards rather than the actual health benefits, which could lead to unintended negative behaviours.
Cost of Implementation: The initial cost of developing a gamified platform can be high, requiring a long-term investment before benefits are realised.
User Dropout: Engagement rates might decline over time if users find the gamified elements monotonous or unchallenging.
Accessibility Issues: Those who are not tech-savvy, particularly the elderly, might find it difficult to engage with gamified digital platforms.
Quality Assurance: The efficacy of gamified healthcare interventions isn't always well-studied, due to a lack of a universal rubric, which could lead to the implementation of ineffective or even harmful elements.
Distraction Risk: In a medical training setting, the fun aspects of gamification could potentially distract from the gravity and seriousness of healthcare work.

Supplementary Methods

Full search strategy

This study evaluates the impact of gamified versus traditional smartphone app-based approaches on cardiovascular health, specifically aiming to determine whether gamification enhances behavioural changes and improves app retention. Cardiovascular diseases (CVDs) are the leading cause of global mortality, responsible for approximately 17.9 million deaths annually. These include conditions such as coronary heart disease, cerebrovascular disease, and rheumatic heart disease. Individuals at risk for CVD often present with elevated blood pressure, glucose, and lipid levels, as well as overweight or obesity. Digital health technologies are increasingly being integrated into modern medicine to manage these risk factors, with smartphone apps playing a significant role due to their widespread use.

This systematic review focuses on evaluating smartphone apps that utilise gamification techniques, such as virtual points or badges, to promote healthy behavioural changes and improve cardiometabolic health in populations with or at risk of CVD. The review will include adults with CVD or those at risk with at least one risk factor (e.g., high blood pressure, high cholesterol, elevated waist circumference, reduced HDL-C, elevated fasting glucose) and exclude individuals under 18 or over 80 years of age, as well as those without a CVD diagnosis or risk profile.

The study will assess mobile apps that incorporate gamification elements, such as reward points or achievement badges, in comparison to standard mobile apps without these features and usual care without smartphone app involvement. Only Randomised Controlled Trials (RCTs) will be included to evaluate differences between the intervention and control groups. The scope is limited to studies involving smartphone or mobile apps within the context of CVD, excluding games played on computers or gaming consoles.

The primary outcomes will involve describing gamification techniques (e.g., points, badges, leaderboards, performance graphs, narrative journeys, virtual avatars) and measuring changes in health indicators (such as body weight, systolic blood pressure, LDL cholesterol, and HbA1c) between groups. Gamification techniques will be qualitatively characterised, while changes in health indicators will be reported as mean differences with 95% confidence intervals. Additional outcomes will include changes in health behaviour stages (precontemplation, contemplation, preparation, action, maintenance), including activity tracking and self-assessment of behaviour change, as well as changes in app retention rates, assessed by daily engagement time and interaction with in-app components. Exploratory outcomes will be qualitatively characterised, and statistically significant differences between intervention and control groups will be described qualitatively.

Data extraction

Titles and abstracts were independently screened by two reviewers (SM and SC, CMK, or TW), with full-text articles of potentially eligible studies reviewed in duplicate to confirm eligibility. Covidence was used to manage blinding and resolve conflicts, ensuring that reviewers were unaware of each other's decisions. The study selection process adhered to PRISMA guidelines and was illustrated in a PRISMA flow diagram, detailing the steps of identification, screening, and inclusion of studies. If articles lacked sufficient information to determine eligibility, additional details were sought from companion articles or by contacting the authors. Studies for which further information could not be obtained were excluded. All research data were securely stored on Microsoft OneDrive, an encrypted and password-protected repository used by the University of Sydney. In the event of disagreements between individual assessments, a third reviewer mediated to reach a resolution. If consensus could not be achieved, unresolved conflicts were escalated to NL or LF for final resolution. The quality assessment and data extraction for included studies were conducted by two independent reviewers. The risk of bias for each study was evaluated using the Cochrane Risk of Bias Assessment Tool 2.0 (RoB 2). This tool assesses five domains of risk: selection bias, performance bias, attrition bias, detection bias, and reporting bias. RoB 2, recommended for assessing bias in randomised trials included in Cochrane Reviews, is structured

into specific domains addressing various aspects of trial design, conduct, and reporting. Each domain includes a series of signalling questions designed to gather information relevant to risk of bias. An algorithm then generates a proposed judgment regarding the risk of bias for each domain, with possible outcomes of 'Low', 'High', or 'Some concerns'.

Strategy for data synthesis

A data extraction form will be created to characterise studies based on participants' clinical status, study arms, intervention duration, intervention frequency, intervention intensity, controls, and a description of the gamification intervention. The impact of the gamification intervention will be determined by comparing the mean difference in outcomes between the intervention and control groups. The meta-analyses will be performed using R software and the "metafor" package. Multiple meta-analyses will be conducted to assess the overall effect of gamification on primary outcomes (LDL, systolic blood pressure, and HbA1c), with subsequent forest plots generated. Heterogeneity will be tested using a chi-square test of the Q statistic, and the degree of heterogeneity will be evaluated using the I2 statistic (considered as: ~25% low, ~50% moderate, ~75% high). A sensitivity analysis will also be conducted in the meta-analysis to assess the effect of each study. Funnel plots will be examined for asymmetry to detect potential publication bias. A statistically significant difference will be considered if the p-value is less than 0.05. For meta-analyses, we will limit study durations to 8 weeks for CVD outcomes including body weight, systolic blood pressure, LDL, and HbA1c. For studies examining the effect of intervention on HbA1c, only those with a study duration of at least 12 weeks will be included to allow for detection of changes in HbA1c. In cases where information is missing, we will attempt to back-calculate required values from other reported data or contact authors to obtain missing information. If we are unable to obtain the necessary information, those papers will be excluded from our final analyses.

Qualitative analysis

Evaluating Apps Using the MARS

The Mobile Application Rating Scale (MARS)[19], a widely recognised tool, used for the comprehensive evaluation of mobile health apps.[20, 21] It scrutinises the quality of an app across four pivotal dimensions: engagement, functionality, aesthetics, and information quality. Each dimension, along with the overall app quality, is rated on a scale from 1 (signifying inadequacy) to 5 (signifying excellence). In detail, MARS consists of an app quality rating scale (sections A-D), an app subjective quality scale (section E), and an app-specific scale (section F). The app quality rating scale assesses various dimensions of app quality, including engagement (section A), functionality (section B), aesthetics (section C), and information (section D). The 19 items of the scale were rated on a 5-point scale from inadequate to excellent. Sections A to D have an internal consistency of α=.90 and an interrater reliability intraclass correlation coefficient of 0.79. The app subjective quality scale has 4 items with different rating scales that assess whether one would recommend apps to others, how many times apps may be used for a 12-month period, whether one would pay for apps, and overall star ratings. The app-specific scale has 6 items that assess the perceived impact of apps on the user's awareness, knowledge, attitudes, intention to change, help-seeking behaviours, and actual behaviour change. MARS has been validated and proven to possess good reliability and objectivity.[22, 23] It is a valuable instrument that enhances transparency about the quality of mobile health apps among healthcare stakeholders[24] and patients.[25]

Collection of App Technical and Descriptive Information

The App Classification section of the MARS[19] was completed for each mobile app evaluated. Two reviewers (SM and PH) downloaded and evaluated available apps from the AppStore, on an iPhone. MARS was first trialled on one app, to achieve consensus with the ratings before proceeding with the others. We will perform a correlation analysis to assess the strength and direction of the relationship between the different MARS dimensions and subjective ratings to study how they contribute to the overall quality and user perception of various apps.

App Quality Evaluation

Two raters (SM and PH) with training in using the MARS[19] independently evaluated the six apps (**Supplementary Table 5.5**). This involved downloading, registering if necessary, and using each app for at least 20 minutes, reviewing information about the apps on the App store, and then completing both the app quality rating scale and the app subjective quality scale. Individual app scores of SM and PH for the app quality rating scale and the app subjective quality scale were manually entered into separate Excel spreadsheets. Scores were averaged overall for each dimension of the app quality rating scale and items of the app subjective quality scale.

Supplementary Results

Inclusion and exclusion criteria of studies

The included studies focused on a diverse range of health conditions and interventions, adhering various inclusion and exclusion criteria (**Supplementary Table 5.19**). Generally, inclusion criteria emphasised specific age ranges, diagnosed medical conditions such as hypertension, diabetes, obesity, or cardiovascular diseases, and the ability to use mobile devices or applications. Some studies also required participants to have certain lifestyle risk factors or to be fluent in specific languages. Exclusion criteria commonly aimed to eliminate participants with severe comorbidities, cognitive or physical impairments, recent participation in similar studies, or conditions that would interfere with the study's requirements. These exclusions often included severe psychiatric disorders, pregnancy, recent significant medical events, and inability to use the required technology or adhere to the study protocol. Overall, the criteria were designed to ensure participant safety, reliable data collection, and adherence to study protocols.

Medication usage

Variations in participants' medication usage were observed across multiple studies (**Supplementary Table 5.11**). One study[26] specifically excluded participants who had experienced a cardiovascular event within the six months leading up to recruitment. In contrast, another study[27] exclusively focused on patients already receiving anti-hypertensive medications. Yet another study[28] set forth exclusion criteria that encompassed individuals using medications for sleep aid or weight management. Moreover, medication adherence presented as a noteworthy variable in several investigations. For instance, in one study[29], the intervention group initially demonstrated higher medication adherence compared to the control group. By the sixth month, both groups showed improvements in medication adherence, adding complexity to the narrative around treatment outcomes by making it more difficult to attribute changes in outcomes to intervention instead of change in medication. In a different study[30], the three-month mark indicated a slight decrease in medication usage within the intervention group, whereas usage increased in the control group. By the twelfth month, however, both groups exhibited elevated levels of medication usage, indicating a longitudinal shift in treatment modalities. The rigor of medication protocols also varied. In one specific study[31], all participants had previously been prescribed anti-diabetic medications, and there was no change in medication regimens throughout the intervention period. Other studies[26, 32] set exclusion criteria based on medication type; for example, two studies disqualified participants if they were on medications that could affect weight. Another study[33] provided a more granular view of medication adjustments. At the study's commencement, 69 patients were taking beta-blockers, 55 were on antihypertensives, 96 were prescribed statins, and 75 were using acetylsalicylic acid and platelet inhibitors. Throughout the follow-up period, various adjustments to medication dosages were observed, further emphasising the fluidity and individuality of medication management strategies.

It is worth noting that ten studies[34-43] did not report any information related to medication usage (**Supplementary Table 5.10**).

Gamification

A considerable number of studies have focused on 'Rules/goals' and 'Assessment' attributes with 18[26-30, 32-35, 37, 42, 44-50] and 15[26, 28, 31-33, 38-41, 47-52] studies respectively, indicating their significance in gamification research. However, other attributes such as 'Control', 'Game fiction', 'Goals', and 'Immersion' have been less frequently studied, suggesting potential gaps in the research landscape. In terms of game elements, 'Feedback' was the most researched element with 20 studies[26-28, 31-34, 37-40, 44-46, 48-53], indicating its importance in gamified systems for user engagement and learning outcomes. The second most commonly studied game element is 'Progress (task-related)' with 18 studies[26, 29-34, 38-40, 42, 45, 47-50, 52, 53], suggesting that tracking and displaying progress is another key factor in gamification. Elements like 'Challenge', 'Competition', 'Difficulty adjustment', 'Goal setting', and 'Rewards' are studied but not as extensively. This variety indicates a broad interest in different game elements but may also suggest that these areas are not as deeply explored. 'Social interaction'[52] and 'Follow-up'[41] have only one study each, which could point to an under-researched area in the gamification field. Overall, the focus on 'Rules/Goals' and 'Assessment' attributes, and 'Feedback' and 'Progress (task-related)' game elements suggests that researchers are primarily interested in the mechanics that directly affect user performance and engagement (**Supplementary Table 5.7**). The distribution of game elements across different game attributes is shown in **Supplementary Table 5.8**. Game attributes and game elements are described in the dendrogram (**Supplementary Figure 5.2**), which visualises the hierarchical clustering of game elements based on their association with different game attributes.

App Technical and Descriptive Information

A total of 9 apps (**Supplementary Table 5.20**) were found to still be available on the App Store and were free to download. Of which two apps[27] required participant login to access in-app content, and one app[35] was in German, therefore the remaining six apps[28, 32, 40, 47, 48], which were in English, were evaluated using the MARS[19]. We evaluated two apps from Duncan *et al.*, 2020[28]. However, only four apps[32, 40, 47, 48] were found to still be available on the Play Store. The updated version numbers and exact production dates were available for all six apps. We evaluated these app in July of 2023 and found most apps to have been updated between 2019 and 2023. At the time of download, all apps were affiliated with commercial developers, as opposed to not-for-profit organisations. All apps were rated by app users, with an overall mean rating of 4.6 out of 5 stars (SD 0.4). Lose it![32] Had a rating of 4.6 as rated by 9842 users on the AppStore. Two apps[28, 32] targeted all age groups, with four apps[28, 40, 47, 48] targeting both adolescents, young adults, and adults. Three apps[32, 40, 48] had in-app purchases available for certain upgrades. Although the six apps were similar in their focus towards behaviour change, they each differed on their primary focus. Two apps[32, 48] had multiple components allowing users to improve health behaviours, including losing weight, and one app[40] was for medication management. All apps allowed for goal setting and provided feedback, with two apps[32, 47] providing further tips and skills training. The technical and descriptive information for each app, including content focus, theoretical background, and therapeutic strategies, are listed in **Supplementary Table 5.21**.

Supplementary Table 5.1 PICOS description.

PICOS criteria	Description

Population	Adults living in the community setting aged ≥18 years with a current or previous CVD diagnosis or at risk of CVD.
	Risk factors are defined as [54-57]:
	• Overweight: BMI ≥ 25
	• High blood pressure (systolic ≥130mmHg; diastolic ≥ 80mmHg) [58]
	• Blood lipid [59]: TC ≥ 200mg/dL; or LDL ≥ 100mg/dL; or TG ≥ 150mg/dL
	• Glycated haemoglobin (HbA1c) ≥ 5.7% [60]
	• Metabolic syndrome (if ≥ 3 met) [61]:
	  • Waist circumference: > 40 inches (men) or > 35 inches (women)
	  • Blood pressure over 130/85 mmHg
	  • TG ≥ 150 mg/dL
	  • Fasting HDL < 40 mg/dL (men) or 50 mg/dL (women)
	Fasting blood sugar ≥ 100 mg/dL

Intervention	Gamified smartphone apps.
Comparison	Standard smartphone apps. Other controls including usual care.
Outcome	Cardiovascular health including body weight, systolic blood pressure, LDL, and HbA1c. Individual behaviour change.
Study design	Randomised Controlled Trials (RCTs) ≥ 8 weeks.

BMI, body mass index; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HDL, high-density lipoprotein cholesterol; LDL, low-density

The keywords and their associated search terms are as follows:

- For "cardiovascular disease," the search terms included (cardiovascular) OR (cardiovascular disease) OR (cardiovascular abnormalities) OR (vascular diseases) OR (heart disease) OR (coronary heart disease) OR (coronary artery disease) OR (myocardial infarction).
- The search terms for "cardiovascular disease risk factors" were (plasma lipids) OR (cholesterol) OR (triglycerides) OR (hyperlipidaemia) OR (blood pressure) OR (high blood pressure) OR (hypertension) OR (fasting glucose) OR (HbA1c) OR (Type 2 Diabetes) OR (overweight) OR (obesity).
- For "applied game design," the relevant search terms were (gamification) OR (mobile health gamification) OR (game theory) OR (game techniques) OR (game elements) OR (computer game) OR (video game) OR (exergame) OR (game learning) OR (applied game design) OR (gameplay) OR (game app).
- For "mobile application," the search terms included (app) OR (application) OR (program OR programme) OR (software) OR (phone application) OR (mobile application) OR (mobile software).

Supplementary Table 5.2 Search strategies per database.

	MEDLINE	EMBASE	CENTRAL	Scopus	CINAHL	PsycINFO
#	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)
1	exp Cardiovascular Abnormalities/ (201307)	exp Cardiovascular Abnormalities/ (220529)	exp Cardiovascular Abnormalities/ (2591)	(((TITLE-ABS-KEY (cardiovascular*	(MH "Cardiovascular Abnormalities+")	exp Cardiovascular Abnormalities/ (0)
2	exp Cardiovascular Diseases/ (2463916)	exp Cardiovascular Diseases/ (4453334)	exp Cardiovascular Diseases/ (108780)	OR "Heart Diseas*" OR	(MH "Cardiovascular Diseases+")	exp Cardiovascular Diseases/ (0)
3	exp Cardiovascular Infections/ (23743)	exp Cardiovascular Infections/ (52209)	exp Cardiovascular Infections/ (133)	"Myocardial Infarction*"))	"Cardiovascular Infections"	exp Cardiovascular Infections/ (0)
4	Cardiovascular System/ (33946)	cardiovascular system/ (164593)	Cardiovascular System/ (702)	AND ("Mobile* app*"	(MH "Cardiovascular System+")	exp Cardiovascular System/ (10381)
5	Cardiovascular*.mp. (597917)	Cardiovascular*.mp. (1099109)	Cardiovascular*.mp. (78955)	OR gamificat*	Cardiovascular*	Cardiovascular*.mp. (38230)
6	exp Heart Diseases/ (1154801)	exp Heart Diseases/ (2002589)	exp Heart Diseases/ (52989)	OR "digital app*"	(MH "Heart Diseases+") OR "Heart Disease*"	exp Heart Diseases/ (0)
7	Heart Diseas*.mp. (247934)	Heart Diseas*.mp. (436475)	Heart Diseas*.mp. (23739)	OR "Video game*"	(MH "Coronary Disease+")	Heart Diseas*.mp. (11305)
8	exp Coronary Disease/ (221479)	exp Coronary Disease/ (344594)	exp Coronary Disease/ (13800)	OR "Computer game*"	Coronary* diseas*	exp Heart Disorders/ (14772)
9	Coronary Artery Disease/ (64903)	coronary artery disease/ (202796)	Coronary Artery Disease/ (6595)	OR "Game Theor*"	(MH "Myocardial Infarction+") OR "Myocardial Infarction*"	exp Cardiovascular Disorders/ (64075)
10	Coronary* diseas*.mp. (139778)	Coronary* diseas*.mp. (28203)	Coronary* diseas*.mp. (13596)	OR "game learn*"	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	Heart Diseas*.mp. (11305)
11	exp Myocardial Infarction/ (178932)	exp Myocardial Infarction/ (405449)	exp Myocardial Infarction/ (10918)	OR "Game design*"	(MH "Mobile Applications")	exp Coronary Disease/ (0)
12	Myocardial Infarction*.mp. (254432)	Myocardial Infarction*.mp. (312743)	Myocardial Infarction*.mp. (32630)	OR "Game app*"	Mobile app*	Coronary Artery Disease/ (0)
13	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (2781929)	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (4772123)	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (187878)	OR "Game play"	Digital app*	Coronary* diseas*.mp. (3476)
14	plasma lipid*.mp. (13915)	plasma lipid*.mp. (18237)	plasma lipid*.mp. (2816)	OR "Mobile health gamif*"	"Gamification*"	exp Myocardial Infarctions/ (2931)
15	exp Cholesterol/ (162507)	exp Cholesterol/ (334904)	exp Cholesterol/ (10268)	OR exergame* OR	(MH "Video Games+") OR "Video game*"	Myocardial Infarction*.mp. (5426)

	MEDLINE	EMBASE	CENTRAL	Scopus	CINAHL	PsycINFO
#	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)
16	Cholesterol*.mp. (297326)	Cholesterol*.mp. (463820)	Cholesterol*.mp. (39131)	smartphone* OR	"computer game*"	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (96520)
17	exp Triglycerides/ or Triglyceride*.mp. (151519)	exp Triglycerides/ or Triglyceride*.mp. (258194)	exp Triglycerides/ or Triglyceride*.mp. (23457)	"Cell" phone*" OR	"Game Theor*"	Hyperlipid*.mp. (1408)
18	Hyperlipid*.mp. (49383)	Hyperlipid*.mp. (93826)	Hyperlipid*.mp. (6680)	smartphone*))	"Game learn*"	exp Hypertension/ (7486)
19	exp Hypertension/ (293148)	exp Hypertension/ (792982)	exp Hypertension/ (18186)	AND (TITLE-ABS-KEY	Applied game design*	hypertension*.mp. (18922)
20	hypertension*.mp. (506207)	hypertension*.mp. (960732)	hypertension*.mp. (65247)	("plasma lipid*" OR cholesterol*	"Game play*"	Fasting glucose.mp. (1006)
21	Fasting glucose.mp. (17886)	Fasting glucose.mp. (31344)	Fasting glucose.mp. (4892)	OR triglyceride* OR	"Game app*"	Blood Glucose/ (1237)
22	Blood Glucose/ (167865)	Blood Glucose/ (213069)	Blood Glucose/ (16252)	hyperlipid* OR	Gamification* N3 mobile*	blood glucose.mp. (6676)
23	blood glucose.mp. (206360)	blood glucose.mp. (135281)	blood glucose.mp. (31469)	hypertension* OR	Mobile health gamification*	Glycated Hemoglobin A/ or HbA1C.mp. (1874)
24	Glycated Hemoglobin A/ or HbA1C.mp. (57302)	Glycated Hemoglobin A/ or HbA1C.mp. (97906)	Glycated Hemoglobin A/ or HbA1C.mp. (21577)	"fasting glucose*" OR	exergame*	exp Diabetes Mellitus, Type 2/ (0)
25	exp Diabetes Mellitus, Type 2/ (139119)	exp Diabetes Mellitus, Type 2/ (273095)	exp Diabetes Mellitus, Type 2/ (18084)	"blood glucose*" OR	(MH "Smartphone") or smartphone*	Type 2 Diabet*.mp. or T2D.tw. or T2DM.tw. (7906)
26	Type 2 Diabet*.mp. or T2D.tw. or T2DM.tw. (145538)	Type 2 Diabet*.mp. or T2D.tw. or T2DM.tw. (229377)	Type 2 Diabet*.mp. or T2D.tw. or T2DM.tw. (38579)	hba1c OR "Glycosylated Hemoglobin A"	(MH "Cellular Phone+") OR "Cell* phone*"	Overweight.mp. or Overweight/ (16649)
27	Overweight.mp. or Overweight/ (78546)	Overweight.mp. or Overweight/ (255399)	Overweight.mp. or Overweight/ (18258)	OR "Type 2 Diabet*"	((Mobile* or phone* or smart phone* cell phone*) N3 "gam* app*")	exp Obesity/ (25479)
28	exp Obesity/ (221595)	exp Obesity/ (556921)	exp Obesity/ (14251)	OR t2d OR t2dm OR	S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27	Obes*.mp. (46316)
29	Obes*.mp. (375790)	Obes*.mp. (624122)	Obes*.mp. (46910)	overweight* OR obes*)))	"plasma lipid*"	plasma lipid*.mp. (283)
30	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (1424744)	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (2313886)	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 (191964)		(MH "Cholesterol+") OR "Cholesterol"	exp Cholesterol/ (2256)
31	Mobile Applications/ (7253)	mobile application/ (13681)	Mobile Applications/ (730)		(MH "Triglycerides") OR "Triglyceride*"	Cholesterol*.mp. (9058)
32	Mobile app*.mp. (10994)	Mobile app*.mp. (15275)	Mobile app*.mp. (2763)		(MH "Hyperlipidemia+") OR "Hyperlipid*"	exp Triglycerides/ or Triglyceride*.mp. (3542)

	MEDLINE	EMBASE	CENTRAL	Scopus	CINAHL	PsycINFO
#	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)
33	Gamification*.mp. (729)	Gamification*.mp. (793)	Gamification*.mp. (200)		(MH "Hypertension+") OR "Hypertension""	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 (84150)
34	Video Games/ (5844)	video game/ (4135)	Video Games/ (717)		"Fasting glucose"	exp Mobile Applications/ (1122)
35	Video game*.mp. (7659)	Video game*.mp. (7220)	Video game*.mp. (1866)		(MH "Blood Glucose") OR "Blood Glucose"	Mobile app*.mp. (2635)
36	computer game*.mp. (1338)	computer game*.mp. (1887)	computer game*.mp. (527)		(MH "Blood Glucose") OR "Blood Glucose""	Gamification*.mp. (710)
37	Game Theory/ (3416)	game/ (7380)	Game Theory/ (30)		(MH "Hemoglobin A, Glycosylated") OR "HbA1C"	computer game*.mp. (8826)
38	Game Theor*.mp. (4708)	Game Theor*.mp. (2633)	Game Theor*.mp. (41)		(MH "Diabetes Mellitus, Type 2")	exp Game Theory/ (3363)
39	Game learn*.mp. (20)	Game learn*.mp. (21)	Game learn*.mp. (18)		Type 2 Diabete*	Game Theor*.mp. (5211)
40	Applied game design*.mp. (1)	Applied game design*.mp. (2)	Applied game design*.mp. (0)		AB (T2D OR T2DM) OR TI (T2D OR T2DM)	Game learn*.mp. (89)
41	Game play*.mp. (1568)	Game play*.mp. (1800)	Game play*.mp. (340)		"Overweight""	(Gamification* adj3 mobile*).mp. (11)
42	Game app*.mp. (164)	Game app*.mp. (188)	Game app*.mp. (63)		(MH "Obesity+") OR "Obesity""	Mobile gamification*.mp. (3)
43	(Gamification* adj3 mobile*).mp. (14)	(Gamification* adj3 mobile*).mp. (13)	(Gamification* adj3 mobile*).mp. (6)		S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42	exergame*.mp. (294)
44	Mobile health gamification*.mp. (1)	Mobile health gamification*.mp. (0)	Mobile health gamification*.mp. (0)		S10 AND S28 AND S43	exp Smartphones/ (1888)
45	exergame*.mp. (593)	exergame*.mp. (608)	exergame*.mp. (311)			Cell* phone*.mp. (3152)
46	Smartphone/ (5488)	smartphone/ (15685)	Smartphone/ (447)			smartphone*.mp. (4823)
47	Cell* phone*.mp. (11192)	Cell* phone*.mp. (5938)	Cell* phone*.mp. (1432)			((Mobile* or phone* or smart phone* cell phone*) adj3 "gam* app*").mp. (20)
48	smartphone*.mp. (15169)	smartphone*.mp. (22368)	smartphone*.mp. (4271)			34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 (24021)
49	((Mobile* or phone* or smart phone* cell phone*) adj3 "gam* app*").mp. (18)	((Mobile* or phone* or smart phone* cell phone*) adj3 "gam* app*").mp. (18)	((Mobile* or phone* or smart phone* cell phone*) adj3 "gam* app*").mp. (11)			16 and 33 and 48 (79)

	MEDLINE	EMBASE	CENTRAL	Scopus	CINAHL	PsycINFO
#	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)	Searches (Results)
50	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (45516)	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (55298)	31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 (9949)			
51	13 and 30 and 50 (566)	13 and 30 and 50 (1337)	13 and 30 and 50 (326)			

Supplementary Table 5.3 Studies excluded at stage 2 with reasons.

Author, year	Journal	Volume (Issue):pages	Title	Exclusion reason
Abu-El-Noor *et al.*, 2021[62]	European Journal of Cardiovascular Nursing	20 (5):428-435	Impact Of A Mobile Phone App On Adherence To Treatment Regimens Among Hypertensive Patients: A Randomised Clinical Trial Study	No relevant outcomes
Adams *et al.*, 2018[63]	Health Psychology	37 (9):850-860	Meditation Smartphone Application Effects On Prehypertensive Adults' Blood Pressure: Dose-Response Feasibility Trial	Wrong comparator
Adhikary *et al.*, 2020[64]	Journal of the American College of Cardiology	75 (11):3583	Effectiveness Of Digital Therapeutics To Improve Blood Pressure Control Among Patients With Hypertension And Diabetes In India	Not a manuscript
Aschbrenner *et al.*, 2019[65]	Schizophrenia Bulletin	45 (Suppl. 2):S135	Randomized Trial Of A Lifestyle Intervention For Young Adults With Serious Mental Illness In Community Mental Health Centers	Not a manuscript
Bender *et al.*, 2017[66]	JMIR diabetes	2 (2):e30	A Feasible And Efficacious Mobile-Phone Based Lifestyle Intervention For Filipino Americans With Type 2 Diabetes: Randomized Controlled Trial	Wrong intervention
Block *et al.*, 2016[67]	Health informatics journal	22 (4):897-910	Effects Of An Evidence-Based Computerized Virtual Clinician On Low-Density Lipoprotein And Non-High-Density Lipoprotein Cholesterol In Adults Without Cardiovascular Disease: The Interactive Cholesterol Advisory Tool	Wrong intervention
Caro *et al.*, 2018[68]	NURE Investigación	15 (92):45139	Utilización De Una Aplicación Móvil Para El Fomento De La Adherencia Terapéutica En La Hipertensión Arterial En Atención Primaria	Not in English
Chandler *et al.*, 2019[69]	International Journal of Environmental Research and Public Health	16 (7):1226	Impact Of A Culturally Tailored Mhealth Medication Regimen Self-Management Program Upon Blood Pressure Among Hypertensive Hispanic Adults	Wrong intervention
Chandler *et al.*, 2020[70]	Int J Environ Res Public Health	17 (6)	Impact Of 12-Month Smartphone Breathing Meditation Program Upon Systolic Blood Pressure Among Non-Medicated Stage 1 Hypertensive Adults	Wrong study design
Cho *et al.*, 2020[71]	Journal of medical Internet research	22 (10):e17435	Effect Of Smartphone-Based Lifestyle Coaching App On Community-Dwelling Population With Moderate Metabolic Abnormalities: Randomized Controlled Trial	Wrong intervention
Choi *et al.*, 2018[72]	FASEB Journal	32 (1)	Improving Cardiac Function And Body Composition Through Incentive-Based Smartphone Application In Sedentary Overweight Adults	Not a manuscript
Contreras *et al.*, 2019[73]	Current Medical Research & Opinion	35 (1):167-173	Specific Hypertension Smartphone Application To Improve Medication Adherence In Hypertension: A Cluster-Randomized Trial	Wrong intervention
DeKluiver *et al.*, 2019[74]	European Heart Journal	40 (Suppl. 1):1217	A European Randomised Controlled Trial For M-Health Guided Cardiac Rehabilitation In The Elderly; Results Of The EU-Care RCT Study	Not a manuscript
Dorsch *et al.*, 2019[75]	Hypertension	74 (Suppl. 1)	A Randomized Controlled Trial Evaluating A Novel Just-In-Time Contextual Mobile Application Intervention To Reduce Sodium Intake In Hypertension: The Low Salt 4 Life Trial	Not a manuscript
Dorsch *et al.*, 2020[27]	JMIR mhealth and uhealth	8 (8):e16696	The Effects Of A Novel Contextual Just-In-Time Mobile Application Intervention On Sodium Intake In Adults With Hypertension: Results From The Lowsalt4life Pilot Study	No additional data to extract
Du *et al.*, 2017[76]	European Heart Journal	38 (Suppl.1):60	Ehelp China, A Randomised Trial Evaluating The Effect Of A Smart Phone-Based Patient Support Tool On Treatment Duration In Patients Prescribed Rosuvastatin In China	Not a manuscript
Eastwood *et al.*, 2014[77]	Circulation	130:A19005	Staying Connected: A CVD Risk Intervention For Young Black Women	Not a manuscript
Eisenhauer *et al.*, 2021[78]	BMC Public Health	21 (1):1568	Mobile Health Assisted Self-Monitoring Is Acceptable For Supporting Weight Loss In Rural Men: A Pragmatic Randomized Controlled Feasibility Trial	Wrong comparator
Falkenhain *et al.*, 2021[79]	Obesity (Silver Spring, Md.)	29 (10):1606	Keyto App And Device Versus WW App On Weight Loss And Metabolic Risk In Adults With Overweight Or Obesity: A Randomized Trial	Wrong comparator
Fenton *et al.*, 2021[80]	Nutrients	13 (7)	Efficacy Of A Multi-Component M-Health Diet, Physical Activity, And Sleep Intervention On Dietary Intake In Adults With Overweight And Obesity: A Randomised Controlled Trial	No relevant outcomes
Foley *et al.*, 2016[81]	Contemporary clinical trials	48:44166	Track: A Randomized Controlled Trial Of A Digital Health Obesity Treatment Intervention For Medically Vulnerable Primary Care Patients	No additional data to extract
Frias *et al.*, 2017[82]	Journal of Medical Internet Research	19 (7):42005	Effectiveness Of Digital Medicines To Improve Clinical Outcomes In Patients With Uncontrolled Hypertension And Type 2 Diabetes: Prospective, Open-Label, Cluster-Randomized Pilot Clinical Trial	Wrong intervention
Ghezeljeh *et al.*, 2018[83]	Contemporary nurse	54 (45050):362-373	Comparing The Effects Of Education Using Telephone Follow-Up And Smartphone-Based Social Networking Follow-Up On Self-Management Behaviors Among Patients With Hypertension	Wrong intervention

Author, year	Journal	Volume (Issue):pages	Title	Exclusion reason
Ghose *et al.*, 2021[84]	Forthcoming at MIS Quarterly, NYU Stern School of Business Forthcoming	NA	Empowering Patients Using Smart Mobile Health Platforms: Evidence From A Randomized Field Experiment	No relevant outcomes
Gill *et al.*, 2013[85]	Journal of Diabetes	5 (Suppl. 1):80	A Randomized Clinical Trial Of Mhealth Supported Exercise Intervention In Patients With Metabolic Syndrome	Not a manuscript
Guo *et al.*, 2017[86]	American Journal of Medicine	130 (12):1388	Mobile Health Technology For Atrial Fibrillation Management Integrating Decision Support, Education, And Patient Involvement: Maf App Trial	No relevant outcomes
Haufe *et al.*, 2020[87]	Frontiers in Psychiatry	11:562	Employers With Metabolic Syndrome And Increased Depression/Anxiety Severity Profit Most From Structured Exercise Intervention For Work Ability And Quality Of Life	No relevant outcomes
Indraratna *et al.*, 2021[88]	European Heart Journal	42 (Suppl. 1):3083	A Randomised Control Trial Of Tele Clinical Care-A Smartphone-App Based Model Of Care For Heart Failure And Acute Coronary Syndromes	Not a manuscript
Ionov *et al.*, 2021[89]	Blood Pressure	30 (1):20-30	Value-Based Approach To Blood Pressure Telemonitoring And Remote Counseling In Hypertensive Patients	Wrong intervention
Johnston *et al.*, 2016[90]	American Heart Journal	178:85-94	Effects Of Interactive Patient Smartphone Support App On Drug Adherence And Lifestyle Changes In Myocardial Infarction Patients: A Randomized Study	Wrong comparator
Kario *et al.*, 2021[91]	European heart journal	42(40):4111-412	Efficacy Of A Digital Therapeutics System In The Management Of Essential Hypertension: The HERB-DH1 Pivotal Trial	No additional data to extract
Khunti *et al.*, 2021[92]	Health Technology Assessment	25 (77):i-189	Behavioural Interventions To Promote Physical Activity In A Multiethnic Population At High Risk Of Diabetes: PROPELS Three-Arm RCT	Wrong intervention
Kim *et al.*, 2019[93]	European Journal of Preventive Cardiology	26 (Suppl. 1):S96	Application For Cardiac Self-Improvement (ANSIM), A Randomized Controlled Trial: 9-Month Clinical Outcome	Not a manuscript
Kirwan *et al.*, 2013[94]	Journal of medical Internet research	15 (11):e235	Diabetes Self-Management Smartphone Application For Adults With Type 1 Diabetes: Randomized Controlled Trial	Wrong population
Krackhardt *et al.*, 2019[95]	Journal of the American College of Cardiology	74 (13):B542	TCT-549 The "Me & My Heart" (Emocial) Study: A Randomized Evaluation Of A New Smartphone-Based Support Tool To Increase Therapy Adherence Of ACS Patients	Not a manuscript
Lee *et al.*, 2017[96]	Journal of Korean Academy of Nursing	47 (6):756-769	The Effects Of Smart Program For Patients Who Underwent Percutaneous Coronary Intervention (SP-PCI) On Disease-Related Knowledge, Health Behavior, And Quality Of Life: A Non-Randomized Controlled Trial	Not in English
Lee *et al.*, 2019[97]	Circulation	139 (Suppl.1)	The Weight Loss By Using The Smartphone Application For People With Metabolic Abnormalities: A Randomized Controlled Trial	Not a manuscript
Lee *et al.*, 2020[98]	International Journal of Hypertension	2020:8275945	Addition Of The Electronic Educational Material To Doctor's Face-To-Face Education Has No Additive Effects On Hypertension Control: A Randomized Single Blind Study	Wrong intervention
Lewey *et al.*, 2021[99]	Journal of the American College of Cardiology	77 (18):3059	Effectiveness Of A Digital Health Intervention To Improve Physical Activity Among Postpartum Women With Hypertensive Disorders Of Pregnancy	Not a manuscript
Li *et al.*, 2019[100]	International Journal of Environmental Research and Public Health	16 (21):4058	A Wechat-Based Self-Management Intervention For Community Middle-Aged And Elderly Adults With Hypertension In Guangzhou, China: A Cluster-Randomized Controlled Trial	Wrong intervention
Li *et al.*, 2020[101]	Journal of Medical Internet Research	22 (12):e19452	Mobile Health App With Social Media to Support Self-Management for Patients With Chronic Kidney Disease: Prospective Randomized Controlled Study	No relevant outcomes
Li *et al.*, 2021[102]	JMIR mHealth and uHealth	10 (2):e32251	The Effects On Adherence Of A Mobile Application-Based Self-Management Digital Therapeutics Among Coronary Heart Disease Patients: Pilot Randomized Controlled Trial	Wrong intervention
Lin *et al.*, 2018[103]	JMIR mHealth and uHealth	6 (10):e10471	The Association Between Engagement and Weight Loss Through Personal Coaching and Cell Phone Interventions in Young Adults: Randomized Controlled Trial	No relevant outcomes
Liu *et al.*, 2015[104]	International journal of environmental research and public health	12 (12):15993-6004	Mobile Phone-Based Lifestyle Intervention For Reducing Overall Cardiovascular Disease Risk In Guangzhou, China: A Pilot Study	Wrong intervention
Liu *et al.*, 2019[105]	Stud Health Technol Inform	264:1712-1713	Smartphone-Based Self-Empowerment App On Secondary Prevention Of Patients With Cardiovascular Disease	Wrong intervention
Martin *et al.*, 2015[106]	Journal of the American Heart Association	4 (11):e002239	Mactive: A Randomized Clinical Trial Of An Automated Mhealth Intervention For Physical Activity Promotion	Study duration < 8 weeks
Martinez-Rodriguez *et al.*, 2022[107]	Sensors	22 (3)	New App-Based Dietary And Lifestyle Intervention On Weight Loss And Cardiovascular Health	Wrong intervention

Author, year	Journal	Volume (Issue):pages	Title	Exclusion reason
McGillicuddy *et al.*, 2015[108]	Progress in transplantation (Aliso Viejo, Calif.)	25 (3):217-223	Sustainability Of Improvements In Medication Adherence Through A Mobile Health Intervention	Wrong intervention
Mendelson *et al.*, 2014[109]	Sleep	37 (11):1863-70	CPAP Treatment Supported By Telemedicine Does Not Improve Blood Pressure In High Cardiovascular Risk OSA Patients: A Randomized, Controlled Trial	Wrong intervention
Morawski *et al.*, 2017[110]	Circulation: Cardiovascular Quality and Outcomes	10 (Suppl. 3)	The Accuracy Of Self-Reported Blood Pressure In The Medication Adherence Improvement Support App For Engagement-Blood Pressure (Medisafe-BP) Trial	Not a manuscript
Morawski *et al.*, 2018[111]	JAMA Internal Medicine	178 (6):802-809	Association Of A Smartphone Application With Medication Adherence And Blood Pressure Control: The Medisafe-BP Randomized Clinical Trial	Wrong intervention
Muralidharan *et al.*, 2021[112]	Digital health	7:20552076211039032	Change In Cardiometabolic Risk Factors Among Asian Indian Adults Recruited In A Mhealth-Based Diabetes Prevention Trial	Wrong intervention
Murphy *et al.*, 2019[113]	Heart Lung and Circulation	28 (Suppl. 4):S373-S374	Suboptimal Secondary Prevention Post Acute Coronary Syndromes: Insights From The SMART-REHAB Trial	Not a manuscript
Murphy *et al.*, 2019[114]	Heart Lung and Circulation	28 (Suppl. 4):S367	Impact Of Gender On Meeting Secondary Prevention Targets And Depression Post Acute Coronary Syndromes: Insights From The SMART-REHAB Trial	Not a manuscript
Ni *et al.*, 2022[115]	Journal of medical Internet research	24 (3):e27202	An Mhealth Intervention To Improve Medication Adherence And Health Outcomes Among Patients With Coronary Heart Disease: Randomized Controlled Trial	Wrong intervention
Nicklas *et al.*, 2021[116]	Journal of general internal medicine	36 (Suppl. 1):S178	Feasibility Of An Mhealth Postpartum Lifestyle Intervention For Women With Cardiometabolic Risk Pre-And Mid-Covid: The Fit After Baby Pilot Randomized Controlled Trial	Not a manuscript
Norton *et al.*, 2015[117]	Alzheimer's and Dementia	11 (7) Suppl 1:P246	Improvements Over Six Months In Stress Management, Diet Quality, And Moderate Physical Activity Are Associated With Changes In Biomarkers Of Vascular Health And Inflammation: The Gray Matters Study	Not a manuscript
Oddsson *et al.*, 2017[118]	Diabetes	66 (Suppl. 1):A42	Effects Of A Gamified Mobile Application To Support A Lifestyle-Change Program In Adults: A Controlled Pilot	Not a manuscript
Patel *et al.*, 2017[119]	JAMA Intern Med	177 (11):1586-1593	Effect Of A Game-Based Intervention Designed To Enhance Social Incentives To Increase Physical Activity Among Families: The BE FIT Randomized Clinical Trial	Wrong intervention
Payne Riches *et al.*, 2021[120]	JMIR mHealth and uHealth	9 (10):e26233	A Mobile Health Salt Reduction Intervention For People With Hypertension: Results Of A Feasibility Randomized Controlled Trial	Study duration < 8 weeks
Persell *et al.*, 2019[121]	Circulation	140 (Suppl. 1)	Home Blood Pressure Monitoring Plus A Mobile Phone-Based Hypertension Health Coaching App Or A Blood Pressure Tracking App: A Randomized Controlled Clinical Trial	Not a manuscript
Petrella *et al.*, 2014[122]	BMC Public Health	14 (1):1082	Mobile Health, Exercise And Metabolic Risk: A Randomized Controlled Trial	Wrong intervention
Prendergast *et al.*, 2020[123]	Journal of the National Medical Association	112 (5):S16-S17	Preliminary Data From A Randomized Controlled Trial For A Hypertension Education And Empowerment Intervention (TOUCHED) In An Urban, Academic Emergency Department: Opportunities In The Era Of COVID-19	Not a manuscript
Redfern *et al.*, 2020[124]	npj Digital Medicine	3 (1):117	A Digital Health Intervention For Cardiovascular Disease Management In Primary Care (CONNECT) Randomized Controlled Trial	Wrong intervention
Riches *et al.*, 2020[125]	Journal of Human Hypertension	34 (Suppl. 1):15-16	Salt Swap: A Feasibility Randomised Controlled Trial Of A Behavioural Intervention To Reduce Salt Intake Among People With Raised Blood Pressure	Not a manuscript
Sankaran *et al.*, 2019[126]	JMIR mHealth and uHealth	7 (4):e10874	Evaluating the Impact of the HeartHab App on Motivation, Physical Activity, Quality of Life, and Risk Factors of Coronary Artery Disease Patients: Multidisciplinary Crossover Study	No additional data to extract
Santo *et al.*, 2018[127]	European Heart Journal	39 (Suppl. 1):226	Medication Reminder Apps To Improve Medication Adherence In Coronary Heart Disease Patients (Medapp-CHD): A Randomised Clinical Trial	Not a manuscript
Santo *et al.*, 2019[128]	Medical Sciences	7 (6):68	Evaluating Reach, Acceptability, Utility, and Engagement with An App-Based Intervention to Improve Medication Adherence in Patients with Coronary Heart Disease in the MedApp-CHD Study: A Mixed-Methods Evaluation	No additional data to extract
Sarfo *et al.*, 2018[129]	Stroke	49 (1):236-239	PINGS (Phone-Based Intervention Under Nurse Guidance After Stroke) Interim Results Of A Pilot Randomized Controlled Trial	Wrong intervention
Sarfo *et al.*, 2019[130]	International Journal of Stroke	14 (6):630-638	Phone-Based Intervention For Blood Pressure Control Among Ghanaian Stroke Survivors: A Pilot Randomized Controlled Trial	Wrong intervention
Sears *et al.*, 2021[131]	Circulation	144(Suppl. 1)	One Drop Digital App And Coaching Improves Lifestyle Risks, Glycemic Control And Psychological Wellbeing In People With Hypertension And Type 2 Diabetes	Wrong population

Author, year	Journal	Volume (Issue):pages	Title	Exclusion reason
Sepulveda *et al.*, 2019[132]	Journal of Hypertension	37 (Suppl. 1):e224-e225	Transmedia Psychoeducational Program To Improve Pharmacological Adherence To Antihypertensive Treatment Among Elderly People	Not a manuscript
Sim *et al.*, 2020[133]	Obesity Reviews	21 (Suppl. 1)	A Smartphone Application For Medication Adherence In Patients With Obesity-Related Chronic Conditions	Not a manuscript
Sit *et al.*, 2016[134]	The Lancet	388 (SPEC.ISS 1):64	A Smartphone-Based Exercise Adherence Intervention For People With Metabolic Syndrome: A Feasibility Pilot Study	Not a manuscript
Song *et al.*, 2020[135]	Journal of Cardiovascular Translational Research	13 (4):659-667	Effect Of Smartphone-Based Telemonitored Exercise Rehabilitation Among Patients With Coronary Heart Disease	Wrong intervention
Sowell *et al.*, 2021[136]	Current Developments in Nutrition	5 (Suppl. 2):183-183	Impact Of Weight Matters And Use Of App-Based Technology On Changes In Eating Behavior In African Americans	Not a manuscript
Steinberg *et al.*, 2020[137]	JMIR Mhealth Uhealth	8 (12):e17536	Feasibility Of A Digital Health Intervention To Improve Diet Quality Among Women With High Blood Pressure: Randomized Controlled Feasibility Trial	Wrong intervention
Still *et al.*, 2020[138]	Patient Preference and Adherence	14:2301-2313	A Community And Technology-Based Approach For Hypertension Self-Management (Coachman) To Improve Blood Pressure Control In African Americans: Results From A Pilot Study	Wrong intervention
Stuckey *et al.*, 2013[139]	Diabetes	62 (Suppl. 1):A629	Health Supported Exercise Intervention In Patients With Metabolic Syndrome: A Randomized Clinical Trial	Not a manuscript
Stuckey *et al.*, 2013[140]	Circulation	128 (22) Suppl. 1	Does Prescriptive Exercise With Mobile Health Tracking Improve Self-Efficacy And Health Status In Individuals With Metabolic Syndrome?	Not a manuscript
Stuckey *et al.*, 2013[141]	Circulation	128 (22) Suppl. 1	Does A Prescriptive Exercise Program With Mobile Health Tracking Improve Cardio-Metabolic Risk Factors To A Greater Extent Than Exercise Prescription Alone?	Not a manuscript
Su *et al.*, 2021[142]	The journal of nursing research: JNR	29 (6):e176	Effectiveness Of A Nurse-Led Web-Based Health Management In Preventing Women With Gestational Diabetes From Developing Metabolic Syndrome	Wrong intervention
Sunil Kumar *et al.*, 2020[143]	Diabetes and Metabolic Syndrome: Clinical Research and Reviews	14 (5):1327-1332	An Android Smartphone-Based Randomized Intervention Improves The Quality Of Life In Patients With Type 2 Diabetes In Mysore, Karnataka, India	No relevant outcomes
Thatthong *et al.*, 2020[144]	Journal of Public Health	28 (4):437-443	Innovative Tool For Health Promotion For At-Risk Thai People With Hypertension	Wrong intervention
Thurston *et al.*, 2020[145]	JACCP Journal of the American College of Clinical Pharmacy	3 (1):149	Assessing The Use Of A Novel Mobile Application To Improve Blood Pressure And Medication Adherence In Patients The Hypertension	Not a manuscript
Tian *et al.*, 2015[146]	Circulation	132 (9):815-824	A Cluster-Randomized, Controlled Trial Of A Simplified Multifaceted Management Program For Individuals At High Cardiovascular Risk (Simcard Trial) In Rural Tibet, China, And Haryana, India	Wrong intervention
Torkabad *et al.*, 2020[147]	Journal of Nursing & Midwifery Sciences	7 (4):219-225	Effectiveness Of Smartphone-Based Medication Reminder Application On Medication Adherence Of Patients With Essential Hypertension: A Clinical Trial Study	Wrong intervention
Toro-Ramos *et al.*, 2017[148]	Metabolic Syndrome and Related Disorders	15 (9):465-473	Effectiveness Of A Smartphone Application For The Management Of Metabolic Syndrome Components Focusing On Weight Loss: A Preliminary Study	Wrong study design
Treskes *et al.*, 2020[149]	JAMA network open	3 (4):e202165	Effect Of Smartphone-Enabled Health Monitoring Devices Vs Regular Follow-Up On Blood Pressure Control Among Patients After Myocardial Infarction: A Randomized Clinical Trial	Wrong intervention
VanHorn *et al.*, 2018[150]	American Journal of Preventive Medicine	55 (5):603-614	Dietary Approaches To Stop Hypertension Diet And Activity To Limit Gestational Weight: Maternal Offspring Metabolics Family Intervention Trial, A Technology Enhanced Randomized Trial	Wrong intervention
Widmer *et al.*, 2017[151]	American Heart Journal	188:65-72	Digital Health Intervention During Cardiac Rehabilitation: A Randomized Controlled Trial	Wrong intervention
Wungrath *et al.*, 2021[152]	International Journal of Pharmaceutical Research	13 (1):5805-5812	The Effect Of Nutritional Education Using Line Application In Conjunction With Tele-Counseling On Nutritional Knowledge And Behavior Among The Elderly With Chronic Diseases	Wrong study design
Yadav *et al.*, 2021[153]	IJC Heart and Vasculature	35:100832	'Routine' Versus 'Smart Phone Application Based – Intense' Follow Up Of Patients With Acute Coronary Syndrome Undergoing Percutaneous Coronary Intervention: Impact On Clinical Outcomes And Patient Satisfaction	Wrong intervention
Yan *et al.*, 2021[154]	PLoS Medicine	18 (4)	Effectiveness Of A Primary Care-Based Integrated Mobile Health Intervention For Stroke Management In Rural China (SINEMA): A Cluster-Randomized Controlled Trial	Wrong population
Yang *et al.*, 2018[155]	Journal of Obstetrics & Gynaecology Research	44 (7):1228-1234	Medical Nutrition Treatment Of Women With Gestational Diabetes Mellitus By A Telemedicine System Based On Smartphones	Wrong study design

Author, year	Journal	Volume (Issue):pages	Title	Exclusion reason
Yudi *et al.*, 2017[156]	Heart Lung and Circulation	26 (Suppl. 2):S349	Smartphone-Based, Early Cardiac Rehabilitation In Patients With Acute Coronary Syndromes [Smart-Rehab Trial]: A Randomised Controlled Trial	Not a manuscript
Zhang *et al.*, 2020[157]	Internal & Emergency Medicine	15 (2):241-250	Cost-Effectiveness Analysis Of Different Hypertension Management Strategies In A Community Setting	No relevant outcomes

Supplementary Table 5.4 Ongoing clinical trials which met the eligibility criteria.

Author, year	Country	Trial registration number	Recruitment status	Study arms (target sample size)	Population condition	mHealth description		Study design; Intervention duration; Length of follow up
						Intervention	Comparison	
Berger *et al.*, 2017	United States	NCT03329079	Active, not recruiting	(1) MT+ (40) (2) MT (40)	Male, aged 40-69 with BMI≥28 kg/m^2	Experimental arm will receive a 3-month MT+ intervention using the premium mobile phone app version with social comparison group, behaviour change text messaging, and daily self-weighing via Wi-Fi scale.	Comparison group will receive the basic version of the mobile phone app only.	6 months, Randomized, Parallel Assignment Masking: None (Open Label)
Ho *et al.*, 2021	Hong Kong	NCT04875780	Recruiting	(1) Experimental (94) (2) Active Comparator (94) (3) Wait-list control (94)	Pre-diabetes	16-week core program consisting of 16 online weekly interactive lessons on diet and physical activity for weight loss. After the completion of the core program, participant can proceed to the 36-week post-core phase. The post-core program provides 8 monthly lessons focusing on maintaining lifestyle habits and weight loss.	Participants in the control group will be invited to have an annual review and blood test at baseline, 4 and 12 months and received general lifestyle advice from a registered nurse at a community clinic.	12-month Parallel Assignment 3-arm randomised controlled trial
Fukuoka *et al.*, 2020	United States	NCT03969056	Unknown status	(1) Artificial Intelligence (AI) Activity (20) (2) 10,000 steps (20)	Hypertension (SBP 130-180mmHg, or/and DBP 80-100mmHg)	The intervention provides participants with an automated and personalised daily step goal intervention involving a sophisticated activity analytics algorithm using advanced statistics and machine learning.	Participants in this group receive a standardised and fixed 10,000 daily steps goal intervention.	Allocation: Randomised Interventional Model: Parallel Assignment Masking: None (Open Label) Primary Purpose: Treatment

SBP, systolic blood pressure; DBP, diastolic blood pressure. Unknown status, A study on ClinicalTrials.gov whose last known status was recruiting; not yet recruiting; or active, not recruiting but that has passed its completion date, and the status has not been verified within the past 2 years.

Supplementary Table 5.5 Studies grouped by disease/condition.

Disease/Condition	Author, year
CAD	Broers *et al.*, 2020[44]; Yudi *et al.*, 2020[49]
CKD	Li *et al.*, 2021[48]
CVD	Li *et al.*, 2021[48]
CVD risk	Bennett *et al.*, 2018[26]; Gonzalez-Sanchez *et al.*, 2019[30]; Ilejka *et al.*, 2020[32]; Lunde *et al.*, 2020[33]; Santo *et al.*, 2019[40]; Tekkesin *et al.*, 2021[41]; Vaz *et al.*, 2021[52]; Yun *et al.*, 2020[50]
HF	Broers *et al.*, 2020[44]
HTN	Bozorgi *et al.*, 2021[34]; Broers *et al.*, 2020[44]; Dorsch *et al.*, 2020[27]; Echeazarra *et al.*, 2021[45]; Gong *et al.*, 2020[29]; Kario *et al.*, 2021[36]; Logan *et al.*, 2012[53]; Manigault *et al.*, 2020[37]; Persell *et al.*, 2020[39]; Yun *et al.*, 2020[50]; Zha *et al.*, 2020[43]
Metabolic syndrome	Haufe *et al.*, 2019[35]; Wong *et al.*, 2021[42]
Obese	Bennett *et al.*, 2018[26]; Duncan *et al.*, 2020[28]; Höchsmann *et al.*, 2019[31]; Vaz *et al.*, 2021[52]
Overweight	Duncan *et al.*, 2020[28]; Höchsmann *et al.*, 2019[31]; Vaz *et al.*, 2021[52]
T2DM	Alonso-Domínguez *et al.*, 2019[51]; Gunawardena *et al.*, 2018[46]; Hilmarsdóttir *et al.*, 2021[47]; Höchsmann *et al.*, 2019[31]; Li *et al.*, 2021[48]; Logan *et al.*, 2012[53]; Oh *et al.*, 2022[38]; Yun *et al.*, 2020[50]; Zhai & Yu, 2020[158]

CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; HTN, hypertension; T2DM, type 2 diabetes mellitus
For the purpose of grouping, we pooled the following under CVD risk: ASCVD risk score ≥7.5%, cardiac rehabilitation patients, hypercholesterolemia, diagnosis of CHD, prediabetes, and stroke.

Supplementary Table 5.6 Number of studies reporting each disease/condition.

Disease/Condition	Number of Studies	Percentage of Total Studies (%)	Cumulative Percentage (%)
HTN	11	26.2	26.2
T2DM	9	21.4	47.6
CVD risk	8	19	66.7
Obese	4	9.5	76.2
Overweight	3	7.1	83.3
CAD	2	4.8	88.1
Metabolic syndrome	2	4.8	92.9
HF	1	2.4	95.2
CVD	1	2.4	97.6
CKD	1	2.4	100

CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; HTN, hypertension; T2DM, type 2 diabetes mellitus
For the purpose of grouping, we pooled the following under CVD risk: ASCVD risk score ≥7.5%, cardiac rehabilitation patients, hypercholesterolemia, diagnosis of CHD, prediabetes, and stroke.

Supplementary Table 5.7 Number of studies grouped by game attributes & game elements.

Game Attribute	Number of Studies
Action language	3
Assessment	15
Control	2
Game fiction	1
Immersion	1
No information	1
Rules/goals	19
Game Element Used	
Challenge	3
Competition	2
Difficulty adjustment	2
Feedback	20
Follow-up	1
Goal setting	2
Progress (task-related)	18
Rewards	2
Social interaction	1

Supplementary Table 5.8 Distribution of game elements across different game attributes.

	Game element				
Game attribute	*Challenge*	*Feedback*	*Follow-up*	*Goal setting*	*Progress (task-related)*
Action language	0	3	0	0	0
Assessment	1	6	1	0	6
Control	0	1	0	0	1
Rules/goals	2	6	0	1	8

Supplementary Table 5.9 Game attributes and game elements of included studies.

		Gamification details				
Study/Title	**Author, Year**	**Game attribute**	**Game element used**	**Outcome measures**	**Learning focus**	**Behaviour change theory implemented (if any)**
EMID Study	Alonso-Domínguez *et al.*, 2019[51]	Assessment	Feedback	Change in total score of the Mediterranean. Diet Adherence Screener (MEDAS) questionnaire. Total score of the Diet Quality Index.	Habit/behaviour change by means of displaying nutritional deviations in terms of both diet composition and the number of calories, with the aim of encouraging a change of habits.	Self-monitoring. Feedback.
Track	Bennett *et al.*, 2018[26]	Rules/goals Assessment	Feedback Progress (task-related)	Daily entering of an outcome (weight).	Weight loss related behaviour change goals.	Social cognitive theory (Foley paper) iOTA - interactive obesity treatment approach. (Taken from sister study 10.1016/j.cct.2016.03.006 https://www.jmir.org/2013/11/e244/)
-	Bozorgi *et al.*, 2021[34]	Rules/goals	Progress (task-related) Feedback	Adherence to antihypertensive medication, and adherence to the DASH diet, reduced sodium and fat intake, regular blood pressure monitoring, physical activity.	Healthy diet (DASH and low-salt diet) and weight loss plans. Knowledge-based information on the nature, control, and treatment of the disease. Motivational and supportive programs for smoking cessation.	Feedback Goal setting
Do CHANGE 2	Broers *et al.*, 2020[44]	Rules/goals	Feedback Difficulty adjustment	Usability and acceptance Satisfaction	Improve steps and healthy meals.	Feedback Self-monitoring
-	Dorsch *et al.*, 2020[27]	Rules/goals Action language	Challenge Feedback	Change in urinary sodium	Improving confidence in following a low-sodium diet. i.e., To decrease salt intake	Goal setting Action planning The Theory of Planned Behaviour, self-regulation, and mindful decision making are the theories used in the intervention to illicit a behavioural change. Taken from sister study: 10.2196/11282
Move, Eat and Sleep study	Duncan *et al.*, 2020[28]	Assessment Rules/goals	Feedback	Daily minutes of moderate-to-vigorous intensity physical activity, steps, resistance training, Light Intensity Activity (mins.d), Daily Sitting Time (mins.d), Sedentary Time (mins.d); and the number of food goals achieved, energy intake (kilojoules/day); bed times/wake times.	Weight and target behaviours focus on physical activity, diet, and sleep	Education Goal setting Action planning Providing feedback Progress comparison Self-monitoring
-	Echeazarra *et al.*, 2021[45]	Rules/goals	Progress (task-related) Feedback	Self-measured BP	Good BP measurement practice: How to measure BP correctly, when to measure.	Education Feedback Planned behaviour
-	Gong *et al.*, 2020[29]	Rules/goals	Progress (task-related)	SBP and DBP % Controlled blood pressure Medication adherence (questionnaire)	NR	Goal setting Feedback
EVIDENT II study	Gonzalez-Sanchez *et al.*, 2019[30]	Rules/goals	Progress (task-related)	Adherence in logging food	Changing CV risk factors. Mediterranean diet compliance. Increase physical activity.	Goal setting Prompt self-monitoring
The ABCD trial	Gunawardena *et al.*, 2018[46]	Rules/goals	Feedback	App usage	Improving overall diabetes self-care/management.	Self-monitoring

Study/Title	Author, Year	Gamification details				Behaviour change theory implemented (if any)
		Game attribute	Game element used	Outcome measures	Learning focus	
	Haufe *et al.*, 2019[35]	Rules/goals		Adherence	General facts on exercise, healthy nutrition, and mental health.	Goal setting Action planning
SidekickHealth	Hilmarsdóttir *et al.*, 2020[47]	Rules/goals Assessment	Goal setting Progress (task-related) Competition	Awards healthy behaviours with accumulated health points (which can result in water donations to UNICEF).	Help people increase their frequency of health behaviours through goal setting, self-monitoring, and the completion of health-related tasks.	Goal setting Action planning
-	Höchsmann *et al.*, 2019[31]	Assessment Control Game fiction Immersion	Feedback Progress (task-related)	Physical activity time (steps/day). Time spent in-game training.	Improving Physical Activity Behaviour	Action planning/goal setting Feedback/rewards The CALO-RE taxonomy
Swipe out Stroke	Ifejika *et al.*, 2020[32]	Assessment Rules/Goals	Feedback Challenges Progress (task-related)	Weight loss Self-management strategies Health behaviours	Changing dietary patterns post-stroke for weight loss.	Goal setting Action planning
-	Kario *et al.*, 2021[36]	N/A	N/A	Mean change from baseline to 24 weeks in SBP.	Lifestyle modification (improve management of hypertension) . Reduce blood pressure	Action planning Self-monitoring
-	Li *et al.*, 2021[48]	Rules/goals Assessment	Feedback Progress (task-related) Rewards	Medication adherence over 12 months.	Medication adherence	Goal setting, reminders, self-monitoring, action planning, feedback, gamification.
-	Logan *et al.*, 2012[53]	Not enough information	Progress (task-related) Feedback	Change in BP measurements	BP measurement	Prompt self-monitoring of (BP)
-	Lunde *et al.*, 2020[33]	Assessment Rules/goals	Progress (task-related) Feedback	Examine whether individualized follow-up with an app for one-year post-cardiac rehabilitation could improve VO_2peak.	Improving exercise habits. Improving self-perceived goal achievement.	Self-monitoring Specific goal setting Action planning
-	Manigault *et al.*, 2020[37]	Rules/goals	Feedback	Both intervention and control group: Logging BP	Medication adherence	Agreed behavioural contract Goal setting
-	Oh *et al.*, 2022[38]	Action language Assessment	Feedback Progress (task-related)	Change in HbA1c	Smartphone app gathered and transferred data on the participant's lifestyle and provided feedback, health, and drug information, and reminders of their medication schedule.	Goal setting; action planning; prompt self-monitoring; compare progress
Smart Hypertension Control Study	Persell *et al.*, 2020[39]	Goals Action language Assessment	Progress (task-related) Feedback	Self-reported • full adherence to antihypertensive medications • sleep duration • physical activity Self-efficacy score • Confidence in using home monitor • Confidence in controlling BP	Boost self-confidence and improve self-monitoring (adherence).	Action planning Goal setting
MedApp-CHD	Santo *et al.*, 2019[40]	Assessment Control	Progress (task-related) Feedback	Medication adherence Interactive medication logging feature.	Not sure this applies in this case	Goal setting

Study/Title	Author, Year	Gamification details				Behaviour change theory implemented (if any)
		Game attribute	Game element used	Outcome measures	Learning focus	
-	Tekkesin *et al.*, 2021[41]	Assessment	Follow-up	1-year ASCVD risk score		Reminders, self-monitoring
-	Vaz *et al.*, 2021[52]	Assessment	Challenge Competition Difficulty adjustment Feedback Progress (task-related) Rewards Social interaction	Change in weight measurement	To enhance behaviour modification with the goal of increasing energy expenditure and reducing energy intake. The intervention was designed to objectively track physical activity, weight, and diet as automatically and seamlessly as possible.	Goal setting Action planning Prompt self-monitoring Reinforcement Social connectivity
-	Wong *et al.*, 2021[42]	Rules/goals	Progress (task-related)	Self-input of body weight, blood pressure, (optional blood glucose and lipid levels), goal setting capacity.	Improve lifestyle behaviour, diet, and exercise	Health belief model
SMART-REHAB	Yudi *et al.*, 2020[49]	Assessment Rules/goals	Feedback Progress (task-related) Goal setting	Change in six-minute walk distance	Improve cardiac education and knowledge	Reminders, self-monitoring, encouragement, feedback, education.
-	Yun *et al.*, 2020[50]	Assessment Rules/goals	Feedback Progress (task-related)	Percentage of subjects that met the target clinical indicators (HbA1c <7.0%, SBP<140 mmHg in clinic, or LDL cholesterol <130 mg/dL).	Habit change	Action planning
-	Zha *et al.*, 2020[43]	N/A	N/A	Blood pressure measurement	Self-monitoring BP measurements Blood pressure monitoring and management	Self-monitoring Feedback; Goal setting
-	Zhai & Yu, 2020[158]	N/A	N/A	Change in HbA1c	Diabetes self-management	Prompt self-monitoring Unclear

Supplementary Table 5.10 Summary of behavioural change interventions.

Author, year	Tracked behaviour	Change in diet	Change in physical activity	Reported effectiveness
Alonso-Dominguez *et al.*, 2019[51]	Diet, Physical Activity	Improved adherence to Mediterranean diet.	Heart-healthy walks	Effective in improving adherence to diet and promoting physical activity.
Bennett *et al.*, 2018[26]	Diet, Physical Activity	Improved adherence to Mediterranean diet.	Increased moderate to vigorous physical activity.	Effective in promoting moderate to vigorous physical activity and diet adherence.
Bozorgi *et al.*, 2021[34]	Diet, Physical Activity	Significant adherence to dietary recommendations.	Increased levels of moderate and vigorous physical activity.	Effective in promoting adherence to dietary and physical activity recommendations.
Broers *et al.*, 2020[44]	Diet, Physical Activity	Improved dietary habits.	Increased physical activity levels.	Effective in improving dietary habits and increasing physical activity levels.
Dorsch *et al.*, 2020[27]	None	Not specified	Not specified	Insufficient data
Duncan *et al.*, 2020[28]	Diet, Physical Activity	Improved diet quality and reduced energy intake.	Increased physical activity levels and adherence to resistance training guidelines.	Effective in improving diet quality, reducing energy intake, and increasing physical activity.
Echeazarra *et al.*, 2021[45]	None	Not targeted	Not targeted	Insufficient data
Gong *et al.*, 2020[29]	None	Not targeted	Not targeted	Insufficient data
Gonzalez-Sanchez *et al.*, 2019[30]	Diet, Physical Activity	Significant improvements in adherence to Mediterranean diet.	Increased levels of physical activity.	Effective in improving adherence to Mediterranean diet and increasing physical activity.
Gunawardena *et al.*, 2018[46]	Diet, Physical Activity	Improved glycaemic control, suggesting better dietary management.	Encouraged regular physical activity.	Effective in improving glycaemic control and promoting physical activity.
Haufe *et al.*, 2019[35]	Diet, Physical Activity	Participants were provided with healthy food choices and dietary counselling.	Significant increase in physical activity levels.	Effective in promoting healthy food choices and increasing physical activity levels.
Hilmarsdóttir *et al.*, 2021[47]	Diet, Physical Activity	Nutrition goals and tips to promote healthy eating habits.	Goals and recommendations to increase physical activity.	Effective in promoting healthy eating habits and increasing physical activity.
Höchsmann *et al.*, 2019[31]	Physical Activity	Not addressed	Significant increase in daily physical activity and aerobic capacity.	Effective in increasing daily physical activity and aerobic capacity.
Ifejika *et al.*, 2020[32]	Diet, Physical Activity	Included dietary counselling for better management of stroke recovery.	Promoted physical activity through a structured program.	Effective in promoting dietary and physical activity changes.
Kario *et al.*, 2021[36]	Diet, Physical Activity	Improved dietary habits and adherence to DASH diet.	Increased physical activity levels and adherence to exercise recommendations.	Effective in improving dietary habits and increasing physical activity
Li *et al.*, 2021[48]	Diet, Physical Activity	Significant improvement in diet quality and adherence.	Enhanced physical activity through tailored exercise plans.	Effective in improving diet quality and increasing physical activity.
Logan *et al.*, 2012[53]	Diet, Physical Activity	Healthy diet promoted via self-care messages.	Promoted regular physical activity and monitored BP.	Effective in promoting healthy diet and BP control.
Lunde *et al.*, 2020[33]	Diet, Physical Activity	Enhanced dietary habits through personalised counselling.	Improved physical activity through guided exercises.	Effective in enhancing dietary habits and physical activity.
Manigault *et al.*, 2020[37]	Diet, Physical Activity	Dietary habits improved with structured program.	Physical activity improved with tailored interventions.	Effective in improving dietary habits and physical activity.
Oh *et al.*, 2022[38]	Diet, Physical Activity	Improved dietary habits and adherence to recommendations.	Increased physical activity levels	Effective in improving dietary habits and increasing physical activity.
Persell *et al.*, 2020[39]	Diet, Physical Activity	Promoted healthier dietary choices.	Encouraged regular physical activity	Effective in promoting healthier dietary choices and regular physical activity.
Santo *et al.*, 2019[40]	Diet, Physical Activity	Significant improvements in diet quality.	Increased levels of physical activity	Effective in improving diet quality and increasing physical activity.
Tekkesin *et al.*, 2021[41]	Diet, Physical Activity	Encouraged healthier eating habits.	Promoted physical activity	Effective in encouraging healthier eating habits and regular physical activity.
Vaz *et al.*, 2021[52]	Diet, Physical Activity	Adherence to diet recommendations improved.	Encouraged regular physical activity	Effective in improving adherence to diet and physical activity recommendations.
Wong *et al.*, 2021[42]	Diet, Physical Activity	Promoted healthier dietary choices.	Promoted regular physical activity	Effective in promoting healthier dietary choices and regular physical activity.

Author, year	Tracked behaviour	Change in diet	Change in physical activity	Reported effectiveness
Yudi *et al.*, 2020[49]	Physical Activity	Not addressed	Significant improvement in exercise capacity.	Effective in improving exercise capacity.
Yun *et al.*, 2020[50]	None	Not targeted	Not targeted	Insufficient data
Zha *et al.*, 2020[43]	Diet, Physical Activity	Significant improvements in diet quality.	Encouraged regular physical activity	Effective in improving diet quality and increasing physical activity.
Zhai & Yu, 2020[158]	Diet, Physical Activity	Improved dietary management.	Improved physical activity levels	Effective in improving dietary management and physical activity levels.

Supplementary Table 5.11 Baseline and post-intervention medication usage.

Author, year	Baseline Medication	Post-intervention Medication	P-value or Effect Size
Alonso-Dominguez *et al.*, 2019[51]	Various antihypertensive, antidiabetic meds etc.	No change	Mostly > 0.05
Bennett *et al.*, 2018[26]	NI	NI	NA
Bozorgi *et al.*, 2021[34]	NI	NI	NA
Broers *et al.*, 2020[44]	Antiplatelet, Statins, β-Blockers etc. in both groups	NR	Mixed p-values
Dorsch *et al.*, 2020[27]	Antihypertensive medications	NI	NA
Duncan *et al.*, 2020[28]	NI	NI	NA
Echeazarra *et al.*, 2021[45]	NI	NI	NA
Gong *et al.*, 2020[29]	Mean antihypertensive medication 1.86-1.89	Improved adherence in intervention group	p=0.004
Gonzalez-Sanchez *et al.*, 2019[30]	Various antihypertensive, antidiabetic meds etc.	Slight change in %	Mostly > 0.05
Gunawardena *et al.*, 2018[46]	0-1 medications, 2-4 oral meds, Insulin in both groups	NA	NA
Haufe *et al.*, 2019[35]	Various antihypertensive, antidiabetic meds etc.	NI	NA
Hilmarsdóttir *et al.*, 2021[47]	6.1±2.6 meds in intervention group	NI	NA
Höchsmann *et al.*, 2019[31]	Various antihypertensive, antidiabetic meds etc.	NR	NA
Ifejika *et al.*, 2020[32]	Diabetes, hypertension, or hyperlipidaemia meds	NR	NA

Supplementary Table 5.12 Approach to medication.

Author, year	Approach to Medication
Alonso-Dominguez *et al.*, 2019[51]	Participants continued current medication regimens.
Bennett *et al.*, 2018[26]	Excluded participants based on certain medications and recent cardiovascular events.
Broers *et al.*, 2020[44]	Provided statistics on types of medications used (e.g., Antiplatelet, Statins, β-Blockers, etc.).
Gong *et al.*, 2020[29]	Focused on medication adherence; reported that the intervention group had higher medication adherence than the control group.
Gonzalez-Sanchez *et al.*, 2019[30]	Examined changes in medication usage over time; noted a statistically significant increase in the control group.
Gunawardena *et al.*, 2018[46]	Medications adjusted as per standard diabetes care guidelines.
Duncan *et al.*, 2020[28]	Excluded individuals using medication for sleep or weight management.
Höchsmann *et al.*, 2019[31]	Participants continued current anti-diabetic medication regimens.
Ifejika *et al.*, 2020[32]	Excluded individuals using weight loss medications in the past 6 months.
Logan *et al.*, 2012[53]	Medications adjusted by the patients' primary care physician.
Lunde *et al.*, 2020[33]	Detailed statistics on medication types and adjustments (e.g., beta-blockers, antihypertensive medication, statins, etc.).
Yudi *et al.*, 2020[49]	Medication list reviewed through an app to ensure evidence-based pharmacotherapy has been prescribed.
Yun *et al.*, 2020[50]	Control group encouraged to continue their usual care and routine medications.
Zha *et al.*, 2020[43]	Mentioned HTN medications.
Others[34-43]	No information or not reported regarding medication.

Supplementary Table 5.13 Detailed risk of bias assessment of included studies.

Author, year	Alonso-Dominguez, 2019[28]	Bennett, 2018[35]	Bozorgi, 2021[34]	Brown, 2020[48]	Dorsch, 2020[37]	Dumcau, 2020[38]	Echezarreta, 2021[45]	Gong, 2020[44]	Gonzalez-Sanchez, 2019[39]	Gunawardena, 2018[46]	Hanlie, 2019[36]	Hinnasóttir; 2021[47]	Höckelmann, 2019[33]	Hejtka, 2020[32]	Kario, 2021[30]	Li, 2021[43]	Logan, 2012[53]	Lunde, 2020[33]	Mansigani, 2020[37]	Ola, 2022[29]	Persell, 2020[31]	Saatio, 2019[49]	Telitesina, 2021[41]	Vaz, 2021[42]	Wong, 2021[52]	Yadi, 2020[40]	Yan, 2020[50]	Zha, 2020[51]	Zhai & Yu, 2020[54]
Domain 1: Bias arising from the randomisation process																													
1.1	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	NI	Y
1.2	Y	PY	Y	Y	NI	Y	PY	PY	Y	PY	Y	Y	Y	NI	PY	PY	NI	Y	NI	PY	Y	Y	NI	Y	Y	Y	PY	NI	PY
1.3	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N	PY	PN	N	N	PN	N	N	N	N	N	N
ROB	L	L	L	L	SC	L	L	L	L	L	L	L	L	SC	L	L	SC	L	L	L	L	L	SC	L	L	L	L	SC	L
Domain 2: Bias due to deviations from intended intervention																													
2.1	Y	Y	Y	Y	Y	Y	Y	Y	Y	PY	Y	PY	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
2.2	Y	Y	Y	Y	Y	Y	PY	Y	Y	PY	Y	PY	N	PY	Y	Y	Y	Y	PY	PY	PY	Y	Y	Y	PY	Y	Y	Y	Y
2.3	NI	PN	NI	N	N	PN	PN	N	N	NI	NI	PN	N	N	PN	PN	PN	N	PN	PN	NI	N	PN	PN	PN	NI	PN	NI	PN
2.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
2.6	Y	PY	NI	PY	N	Y	PY	PN	PY	PY	PY	PY	Y	N	Y	Y	PY	Y	PY	PY	PY	Y	Y	N	Y	Y	NA	Y	PY
2.7	NA	NA	NA	NA	PY	NA	NA	PY	NA	NA	NA	NA	NA	PN	NA	NA	NA	NA	NA	NA	NA	NA	NA	Y	NA	NA	NA	NA	NA
ROB	SC	L	SC	L	SC	L	L	H	L	SC	SC	L	L	SC	L	L	L	L	L	L	SC	L	L	H	L	SC	L	SC	SC
Domain 3: Bias due to missing outcome data																													
3.1	N	Y	Y	Y	PY	N	N	N	N	Y	Y	N	Y	N	N	N	Y	N	N	Y	PN	N	N	N	N	N	N	N	Y
3.2	PN	NA	NA	NA	NA	PY	N	N	N	NA	NA	PN	NA	N	N	PY	NA	Y	N	NA	N	Y	PN	N	N	Y	PN	N	NA
3.3	N	NA	NA	NA	NA	NA	NI	NI	PY	NA	NA	N	NA	Y	NI	NA	NA	NA	Y	NA	NI	NA	Y	NI	PY	NA	PN	N	NA
3.4	NA	NA	NA	NA	NA	NA	NI	NI	PN	NA	NA	NA	NA	PN	N	NA	NA	NA	Y	NA	PN	NA	PN	Y	PN	NA	NA	NA	NA
ROB	L	L	L	L	L	L	H	H	SC	L	L	L	L	SC	SC	L	L	L	H	L	SC	L	SC	H	SC	L	L	L	L
Domain 4: Bias in measurement of the outcome																													
4.1	PN	N	PN	N	N	PN	PN	N	N	PN	N	N	N	N	N	N	N	N	N	PN	N	N	N	PN	PN	N	NA	N	N
4.2	PN	N	PN	N	N	N	PN	N	N	N	N	PN	N	PN	N	PN	PN	N	N	PN	N	PN	PN	PN	PN	PN	NA	N	N
4.3	Y	Y	Y	PN	Y	NI	Y	PY	N	NI	N	PN	N	N	Y	N	NI	N	NI	Y	PY	PY	NI	Y	N	N	NA	NI	NI
4.4	N	N	PY	NA	N	PN	PN	N	NA	N	NA	NA	NA	PN	N	NA	PN	N	N	PN	PN	PN	PN	N	NA	NA	NA	PN	N
4.5	NA	NA	PY	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ROB	L	L	H	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L	L
Domain 5: Bias in selection of the reported result																													
5.1	PY	N	NI	Y	Y	N	NI	Y	Y	PY	PY	Y	Y	N	N	PY	NI	Y	NI	NI	PN	PY	N	N	NI	N	NA	PN	NI
5.2	PN	PN	PN	N	N	N	N	N	N	N	N	PN	N	PN	N	NA	N	N	N	NI	N	PN	N	Y	N	N	NA	N	N
5.3	PN	PN	PN	PN	Y	PY	NI	N	N	PN	NI	PN	N	PN	PY	NA	PN	N	Y	NI	NI	PN	PY	PY	Y	PY	NA	PN	N
ROB	L	SC	L	L	H	H	SC	L	L	L	SC	L	L	SC	H	L	SC	L	SC	SC	SC	L	H	H	SC	H	SC	SC	SC
Overall ROB	SC	SC	H	L	H	H	H	H	SC	SC	SC	L	L	SC	H	L	SC	L	H	SC	SC	L	H	H	SC	H	L	SC	SC

H, high; L, low; N, no; NA, not applicable; NI, no information; PN, probably no; PY, probably yes; ROB, risk of bias; SC, some concerns; Y, yes

Supplementary Table 5.14 Primary and secondary outcomes of included studies.

Author, year	Primary Outcomes	Secondary Outcomes
Alonso-Dominguez *et al.*, 2019[51]	Change in total score of the Mediterranean Diet Adherence Screener (MEDAS) questionnaire.	Total score of the Diet Quality Index (DQI) questionnaire. Clinical variables.
Bennett *et al.*, 2018[26]	The primary outcome was 12-month weight change.	Secondary outcomes included ≥ 5% weight loss, waist circumference, blood pressure, fasting lipids, glucose, and HbA1c over 12 months.
Bozorgi *et al.*, 2021[34]	Adherence to hypertensive drug use.	Clinical and behavioural outcomes, such as adherence to the DASH diet, reduced sodium and fat intake, regular blood pressure monitoring, physical activity, and predisposing, enabling, and reinforcing factors in adherence to treatment.
Broers *et al.*, 2020[44]	Lifestyle [Time Frame: 0-6 months]. The Health Promoting Lifestyle Questionnaire (HPLP-II) will be administered to evaluate whether patients' subjective perception of lifestyle change has changed. Behavioural flexibility [Time Frame: 6 months]. Whether the patients' behavioural flexibility (having a bigger behavioural repertoire which makes it easier to perform alternative behaviours) has increased and thus whether behaviour change (as conceptualised by Do Something Different program) has occurred will be assessed using purpose designed questions by the Do Something Different program. Quality of life [Time Frame: 6 months]. Changes in quality of life will be assessed using the WHOQOL-Bref questionnaire. As this is a widely used instrument it will allow the integration of data from different partners.	Usability, acceptance, satisfaction with intervention / tools [Time Frame: 3 months]. Unified Theory of Acceptance and Use of Technology (UTAUT2) questionnaire will be used to assess the usability, acceptance, and satisfaction of the care portal. Cost-effectiveness [Time Frame: 6 months]. Whether the intervention arm will be cost-effective as compared to the care as usual will be evaluated using the EQ-5D questionnaire. It could be expected that the intervention arm will experience a lower disease burden and be less likely to use additional health care resources.
Dorsch *et al.*, 2020[27]	Change in the 24-hour urinary sodium excretion estimated from spot urine by using the Kawasaki equation, which was analysed using unpaired two-sided t tests.	Change in the sodium intake measured by the food frequency questionnaire (FFQ), the 24-hour urinary sodium excretion, blood pressure levels, and the self-reported confidence in following a low-sodium diet.
Duncan *et al.*, 2020[28]	Body weight (kg) Height (cm) Waist circumference HbA1c	Weekly minutes of moderate- and vigorous-intensity physical activity. Weekly frequency of resistance training Daily sitting time Daily energy intake and dietary quality Sleep quality Insomnia symptom severity Sleep timing
Echeazarra *et al.*, 2021[45]	Behavioural outcome. Knowledge and skills about BP checking. Effectiveness of TensioBot with regards to the BP checking in-site. Satisfaction survey about app.	None
Gong *et al.*, 2020[29]	The primary outcomes of this clinical trial were systolic blood pressure (SBP) and diastolic blood pressure (DBP) changes in all participants. The mean SBP and DBP at the baseline and end of this trial were calculated from the first and last 3 days' BP respectively. The other outcome was the change in percentage of participants in the 2 groups with controlled blood pressure.	The Modified Morisky Scale 8 (MMS-8), which was comprised of 8 questions, was used to measure medication adherence.
Gonzalez-Sanchez *et al.*, 2019[30]	Mediterranean diet compliance [Time Frame: 1 year]. Measurement by Mediterranean diet questionary from PREDIMED study. The main result was the effect on CVRFs and CVR at 3 and 12months of post-intervention follow-up in the IG compared to the CG.	Increase physical activity [Time Frame: 1 year]. Measurement by accelerometer and evaluate bay counts/minute. Lipids, glucose, insulinemia and HbA1, information regarding drugs used for hypertension and hyperlipidaemia.
Gunawardena *et al.*, 2018[46]	Effectiveness of the smart phone-based diabetes management application, SGM on overall control of diabetes mellitus. Improvement of glycaemic control as determined by HbA1c. Number of harmful blood glucose fluctuations according to pre-determined criteria using a questionnaire. [At baseline and every 12 weeks for a total of 52 weeks.]	Effect of SGM on blood glucose levels, lipid profile and occurrence and progression of complications such as dyslipidaemia, nephropathy, neuropathy, and micro-vascular complications by following biochemical and physical investigations. Lipid panel (Cholesterol, HDL Cholesterol, LDL Cholesterol, Triglycerides). Fasting blood glucose. Comprehensive Metabolic panel (Alkaline phosphatase, ALT, AST, Blood urea nitrogen, Potassium, Sodium, Calcium, Chloride, Creatinine, Albumin, Total protein).

Author, year	Primary Outcomes	Secondary Outcomes
		Urine for micro albumin. Foot examination (for foot ulcers, callus formation, fungal infection) . Dilated eye examination.
Haufe *et al.*, 2019[35]	Change in metabolic syndrome Z score following a 6-month exercise intervention in the exercise group compared with the waiting-list control group.	Work ability, exercise capacity, health-related quality of life, body composition, and adherence to the intervention.
Hilmarsdóttir *et al.*, 2021[47]	HbA1c	HRQoL
Höchsmann *et al.*, 2019[31]	Change from baseline daily physical activity at 24 weeks [Time Frame: Baseline and 24 weeks] Measured as steps per day.	Adherence to the intervention [Time Frame: 24 weeks] Measured as usage log entries (intervention group) and self-reported exercise log entries (control group).
Ifejika *et al.*, 2020[32]	Reduced total body weight.	Compliance with the weight loss intervention, improvement in depression, and, if abnormal, normalisation of systolic blood pressure, serum low-density lipoprotein value, proportion of total haemoglobin, and proportion of serum coagulation factor VIII
Kario *et al.*, 2021[36]	Mean change from baseline to 24 weeks in 24-hour systolic BP (SBP) measured by ambulatory blood pressure monitoring (ABPM).	Mean change in 24-hr SBP by ABPM at 16 weeks [Evaluated at both 16 and 24 weeks]. Mean changes by ABPM in 24-hr DBP. Mean changes by ABPM in daytime/nighttime SBP and DBP. Mean changes by ABPM in pulse pressure. Mean changes in home awake SBP and DBP. Mean changes in office SBP and DBP. Mean changes in weight, BMI, and waist circumference. Smartphone app-related variables (app usage rate, progress of app educational programs, etc.). Any adverse events including device-related adverse events.
Li *et al.*, 2021[48]	The primary outcome was overall medication adherence rate, defined as: number of dosage units taken/ (number of dosage units prescribed per day × number of prescribed days between two visits) for each individual, measured at months 1, 2, 3, 6, 9 and 12.	The secondary outcomes were changes in clinical outcomes (HbA1c, total cholesterol, HDL-C, LDL-C, triglycerides, FBG/NFBG, creatinine, TFT, systolic and diastolic blood pressure and weight) at baseline, months 3, 6, 9 and 12.
Logan *et al.*, 2012[53]	Change in mean daytime ambulatory systolic BP.	Changes in 7 days of home BP readings, psychological questionnaire responses, and prescribed antihypertensive medications.
Lunde *et al.*, 2020[33]	Difference in VO_2 peak. Change in Maximal oxygen consumption [Time Frame: Change from baseline to 12 months]. Physical capacity will be evaluated with maximal oxygen consumption. Cardiorespiratory fitness test on a treadmill with a standardised ramp-protocol. Direct measurement of oxygen consumption.	Change in Quality of Life [Time Frame: Change from baseline to 12 months]. Heart-Quality of Life (HeartQoL) will be used to assess quality of life. Change in Quality of Life. Euro Quality of life questionnaire (EQ-5D). Change in Health Literacy. European Health Literacy Survey questionnaire (HLS-EU-Q47). Type D personality [Time Frame: Baseline]. Standard assessment of Negative Affectivity, Social Inhibition, and Type D personality (DS14). Change in Endurance Fitness [Time Frame: Change from baseline to 12 months]. Time to exhaustion, incline and speed at the treadmill test. Other Pre-specified Outcome Measures Chang in Blood pressure [Time Frame: Change from baseline to 12 months]. Systolic and diastolic blood pressure, measured manually in resting sitting position before treadmill test. Change in Exercise habits [Time Frame: Change from baseline to 12 months]. The patients will be asked weekly exercise for the last year.
Manigault *et al.*, 2020[37]	The primary outcomes were median CMG and systolic and diastolic BP at the 3-month follow-up visit. Medication adherence [Time Frame: 6 months]. Blood pressure [Time Frame: 6 months].	The secondary outcome was the proportion of subjects with uncontrolled blood pressure at the 3-month follow-up visit. As a secondary outcome, the impact of the intervention on the ability of patients to meet their target BP was investigated.
Oh *et al.*, 2022[38]	Body fat BP Blood glucose	App usage: - The input rates of food intake and exercise to the smartphone app. - The input rate of medicine intake.
Persell *et al.*, 2020[39]	Systolic blood pressure (mmHg) at 6 months (adjusted for baseline systolic blood pressure).	Diastolic blood pressure (mmHg) at 6 months (adjusted for baseline diastolic blood pressure). Proportion with controlled blood pressure at 6 months (defined as BP <140/<90 mmHg).

Author, year	Primary Outcomes	Secondary Outcomes
		Medication adherence, measured as 4-day recall of antihypertensive medications. Number of antihypertensive agents used at 6 months. Number of antihypertensive medication changes (increases or substitution) at 6 months. Number of health system contacts (telephone, office, or mychart encounters) at 6months – derived from electronic health record (EHR). Frequency of home blood pressure measurements per month – derived from HBMD device. Proportion of months where a home blood pressure reading is obtained – derived from HBMD device. Self-efficacy to monitor and control high blood pressure. Weight at 6 months (lbs). Diet quality score. Self-reported physical activity. Self-reported sleep duration.
Santo *et al.*, 2019[40]	The primary outcome was medication adherence measured by the 8-item Morisky Medication Adherence Scale (MMAS-8) at 3 months.	Secondary outcomes included systolic and diastolic blood pressure (BP), total and low-density lipoprotein (LDL) cholesterol, number of pills missed in the last 7 days and medication knowledge.
Tekkesin *et al.*, 2021[41]	Atherosclerotic cardiovascular disease (ASCVD) risk score of individual patients at 12 months that is adjusted to baseline ASCVD risk score. [Time Frame: 12 months] Patients with ASCVD risk score of >7.5 % are considered to have a high risk for 10-year atherosclerotic cardiovascular diseases.	Smoke abstinence [Time Frame: 12 months]. Cessation of smoking habits including non-nicotine and electronic cigarettes during past 4 weeks will be measured at 12 months. Improvement in high sensitive C reactive protein levels (hs-CRP) (mg/L) (hs-CRP value at 12 months that is adjusted to baseline value) [Time Frame: 12 months]. Improvement in quality of life [Time Frame: 12 months]. Quality of life will be evaluated by filling World Health Organisation Quality of Life questionnaire. Minimum score is 122.77 and maximum score is 387.69 with higher values are considered as better quality of life. Peak oxygen consumption value at 12 months that is adjusted to baseline value [Time Frame: 12 months]. Peak VO_2 will be evaluated by cardio-pulmonary exercise testing. Major adverse cardiovascular events [Time Frame: 12 months]. Occurrence of death, myocardial infarction, Stroke, cardiovascular hospitalisation. Systolic and diastolic blood pressure values (mmHg) at 12 months that are adjusted to baseline values [Time Frame: 12 months]. Body mass index (BMI) (kg/m^2) level at 12 months that is adjusted to baseline level [Time Frame: 12 months]. HbA1c (%) level at 12 months that is adjusted to baseline level [Time Frame: 12 months]. Plasma fasting lipid levels (total cholesterol, low density lipoprotein, high density lipoprotein and triglycerides) (mg/dL) at 12 months that are adjusted to baseline levels [Time Frame: 12 months]. Carotid intima-media thickness (mm) value at 12 months that is adjusted to baseline value [Time Frame: 12 months]. Carotid intima-media thickness will be evaluated by ultrasonography (USG) .
Vaz *et al.*, 2021[52]	Change in body weight in kg [Time Frame: 6 months].	Change from baseline blood pressure [Time Frame: 6 months]. Change from baseline waist circumference [Time Frame: 6 months]. Change from baseline insulin resistance by homeostasis model assessment (HOMA-IR) [Time Frame: 6 months]. Change from baseline glycated haemoglobin (HbA1c) [Time Frame: 6 months]. Change from baseline plasma triglycerides [Time Frame: 6 months]. Change from baseline body weight in kg [Time Frame: 3 months]. Change from baseline body weight in kg [Time Frame: 12 months]. Change from baseline blood pressure [Time Frame: 12 months]. Change from baseline waist circumference [Time Frame: 12 months]. Change in Quality of Life [Time Frame: 6 months after receiving the intervention]. SF36 Questionnaire in wait-listed control group after the intervention. Change in insulin resistance by homeostasis model assessment (HOMA-IR).

Supplementary Table 5.15 Reported COI and source of funding of included studies.

Author, year	COI statement	Funding (e.g., industry/non-industry/both)	Funding details	COI exists
Alonso-Dominguez *et al.*, 2019[51]	The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript or in the decision to publish the results.	Non-industry	This study is supported by funding grants from the Regional Health Management through the 2016 grants to carry out research projects in biomedicine, health management and socio-health care (GRS 1276/B/16), the 2016 program for the professional development of nurses in their research activity (BOCYL-D-11022016-2) and the 2015 incentive program for nurses who have completed their residency (ORDER SAN / 360/2015). The study was also co-financed by the Carlos III Health Institute and the European Regional Development Fund (ERDF) (RD 16/0007/0003).	No
Bennett *et al.*, 2018[26]	Gary Bennett holds equity in Coeus Health and serves on the scientific advisory board of Nutrisystem. These organisations had no role in study design, data collection, data analysis and interpretation of data, in the writing of the report, or in the decision to submit the article for publication. The remaining authors declare that they have no conflicting interests.	Non-industry	This trial is funded by the NIH, National Institute of Diabetes and Digestive and Kidney Diseases (R01DK093829). The funder had no role in study design, data collection, data analysis and interpretation of data, in the writing of the report, and in the decision to submit the article for publication.	No
Bozorgi *et al.*, 2021[34]	NR	Industry	This study was supported by Tehran University of Medical Sciences in the form of a PhD thesis, taken up by Ms. Mahnaz Ashoorkhani, student of Health Education and Promotion, under grant no. 94-02-102-29524. It was conducted in association with the Tehran Heart Center.	No
Broers *et al.*, 2020[44]	Authors E.B., J.W., J.D., W.K., M.W., I.A., J.P.J., and M.H. declare no conflict of interests. The Do CHANGE team received funding for research and innovation from the European Union for the current project. Two small- and medium-sized enterprises (Do Something Different, Docobo Ltd.) and one start-up (Onmi) are financially supported to develop their products.	Industry	Funded by the European Commission's Horizon 2020 program (grant number: 463735).	No
Dorsch *et al.*, 2020[27]	None declared.	Non-industry	Funded by the Agency for Healthcare Research and Quality (R21 HS024567)	No
Duncan *et al.*, 2020[28]	The authors and principal investigators of this study declare no conflict of interest.	Both industry and non-industry	M.J.D. (APP1141606) is supported by funding from the National Health and Medical Research Council. T.L.B. is supported by an Investigator Grant from the National Health and Medical Research Council. C.E.C. is supported by an NHMRC Senior Research Fellowship and a University of Newcastle, Faculty of Health and Medicine, Gladys M Brawn Senior Research Fellowship. E.S. is supported by a National Health and Medical Research Council Senior Research Fellowship (AP1110526) and a University of Sydney SOAR Fellowship. This project is partly supported by Diabetes Australia General Grant (Y17G-DUNM) and the National Heart Foundation of Australia (101584; 100629).	No
Echeazarra *et al.*, 2021[45]	The authors declare that they have no conflict of interest.	Non-industry	NI	No
Gong *et al.*, 2020[29]	The application and the sphygmomanometers were provided by Shanghai O2O Care Company for free. We thank Xuejun Wang who is the president of the company, the APP study group which was constituted by 38 hospitals in Chongqing and the patients.	Industry	This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.	Yes

Author, year	COI statement	Funding (e.g., industry/non-industry/both)	Funding details	COI exists
Gonzalez-Sanchez *et al.*, 2019[30]	The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.	Non-industry	This work was supported by the Spanish Ministry of Science and Innovation (MICINN) and Carlos III Health Institute/European Regional Development Fund (ERDF) (FIS: PI13/00618, PI13/01526, PI13/ 00058, PI13/01635, PI13/02528, PI12/01474; RETICS: RD12/0005, RD16/0007); and the Regional Health Management of Castilla and León (GRS 1191/B/15, GRS 909/B/14, GRS 770/B/13). None of the funders were involved in the design, implementation, analysis, or interpretation of the data.	No
Gunawardena *et al.*, 2018[46]	The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.	Unclear	The author(s) received no financial support for the research, authorship, and/or publication of this article.	No
Haufe *et al.*, 2019[35]	We declare no competing interests. The funder of the study had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or decision to submit for publication. All authors had access to the raw data if needed. The corresponding author had full access to all study data and had final responsibility for the decision to submit for publication.	Both	This study was supported and funded by grants from Audi BKK health insurance and the German Research Foundation through the Cluster of Excellence REBIRTH.	No
Hilmarsdóttir *et al.*, 2021[47]	The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.	Non-industry	The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The study was supported by grants from the Akureyri Hospital Research Fund, the University of Akureyri Research Fund, and the Icelandic Nurse Association Science Fund.	No
Höchsmann *et al.*, 2019[31]	No financial disclosures were reported by authors of this paper.	Both	Novartis Pharma GmbH (for the financial support during the development of the game application). This research is funded by the Swiss National Science Foundation (SNSF grant no. 166214).	No
Ifejika *et al.*, 2020[32]	None declared.	Industry	NLI has received a University of Texas Southwestern Medical Center and Texas Health Resources Clinical Scholar Award (#4). NLI's and CCC's previous work at the Center for Clinical and Translational Sciences at the McGovern Medical School at University of Texas Health Science Center at Houston was funded by US National Institutes of Health (NIH)/National Center for Advancing Translational Sciences Clinical and Translational Award UL1 TR000371 and KL2 TR000370. NLI received the NIH/National Institute of Neurological Disorders and Stroke Diversity Supplement to P50 NS 044227, the University of Texas Specialized Program of Translational Research in Acute Stroke. The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work is funded by the UTHealth Center for Clinical and Translational Sciences via the National Center for Advancing Translational Sciences (Grant/Award Number: KL2 TR000370, UL1 TR000371) at the National Institutes of Health and National Institute of Neurological Disorders and Stroke (Grant/Award Number: P50 NS 044227).	No

Author, year	COI statement	Funding (e.g., industry/non-industry/both)	Funding details	COI exists
Kario *et al.*, 2021[36]	KK received research grants from A&D Co. (Tokyo) and Omron Healthcare (Kyoto, Japan). KK and AN received consulting fees from CureApp, Inc AN and KS are founders of the CureApp Institute. TT, AK, and RS are employees of CureApp, Inc SS and KS are founders of CureApp, Inc EH has a consultation contract as a biostatistician with CureApp, Inc. The other authors have nothing to disclose.	Industry	A&D Co. (Tokyo) and Omron Healthcare (Kyoto, Japan). CureApp, Inc provided funding and contributed to the development of the HERB software system and the design of this study.	Suspicious
Li *et al.*, 2021[48]	The authors declare no conflict of interest.	Both	This work was supported by funding from the Sydney Local Health District (BR17/1646). The app was provided by Perx Health.	No
Logan *et al.*, 2012[53]	A.G.L. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. None of the other authors has real or perceived conflicts of interest related to the study, J.A.C. has received funding from Research In Motion, Inc. (makers of the Blackberry mobile telephones) through the National Science and Engineering Research Council Strategic Network Grant Program. P.G.R. received reimbursement of expenses from Research In Motion, Inc, to attend a healthcare advisory meeting.	Non-industry	The Heart and Stroke Foundation of Ontario (ESA 5970) was the sole source of funding for this project and was not involved in any aspect of the study. Charitable Registration No. 106846942 RR0001. Samuel Lunenfeld Research Institute, Mount Sinai Hospital (from protocol on clinicaltrials.gov).	Yes
Lunde *et al.*, 2020[33]	The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.	Industry	Oslo Metropolitan University	No
Manigault *et al.*, 2020[37]	The views expressed in the submitted article are his or her own and not an official position of the institution or funder. The authors of this manuscript have nothing to disclose regarding financial or other conflicts of interest.	Non-industry	This research was funded by a Mercer University College of Pharmacy Faculty Development Grant and the Mercer University Seed Grant Program.	No
Oh *et al.*, 2022[38]	None declared.	Non-industry	This work was supported by a grant (19RERP-B090094-06) from the Residential Environment Research Program funded by the Ministry of Land, Infrastructure, and Transport of the Korean government (NRF-2017R1A6A3A11036413) and a grant from the National Research Foundation of Korea funded by the Korean government. The authors appreciate Huraypositive Co for providing the LIBIT app and GST Korea for supplying the Mediram app and nonhuman kiosks.	No
Persell *et al.*, 2020[39]	Dr Persell reported previously receiving research funding from Pfizer and reported receiving grants from Omron Healthcare Co. Ltd. during the conduct of the study. Dr Li reported receiving salary and reimbursement for travel from Omron Healthcare Co Ltd. Dr Sato reported receiving salary and reimbursement for travel from Omron Healthcare Co Ltd. No other disclosures were reported.	Industry	This work was funded by Omron Healthcare Co Ltd paid to Northwestern University. Analyses were conducted by Northwestern University employees. Employees from Lark Technologies, Inc and Omron Healthcare Co Ltd participated in discussing the results and revising the manuscript. Northwestern University investigators retained the right to publish and what content to publish independent of the funder.	Suspicious
Santo *et al.*, 2019[40]	None declared.	Industry	This study was supported by a Vanguard Grant (ID101464) funded by the National Heart Foundation of Australia (NHFA).	No

Author, year	COI statement	Funding (e.g., industry/non-industry/both)	Funding details	COI exists
			KS was funded by a University of Sydney International Postgraduate Research Scholarship. JC is a chief investigator on National Health and Medical Research Council (NHMRC) programme grant (ID1052555). CKC is funded by a Career Development Fellowship co-funded by NHMRC and NHFA (APP1105447). JR is funded by a Career Development and Future Leader Fellowship co-funded by the NHMRC and the NHFA (APP1061793).	
Tekkesin *et al.*, 2021[41]	The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.	Industry	This work was supported by Türk Telekomunikasyon A.S. The study was performed at Dr. Siyami Ersek Thoracic and Cardiovascular Surgery Training and Research Hospital, Turkey.	Suspicious
Vaz *et al.*, 2021[52]	Kevin Jon Williams reports an ownership interest in Hygieia, Inc., and in Gemphire Therapeutics, Inc., and recently served on the Medical and Scientific Advisory Board of Gemphire Therapeutics, Inc. The other authors have no conflict of interest to declare. Portions of this work were presented at the American Diabetes Association Scientific Sessions in 2018.	Non-industry	Temple University Department of Medicine Junior Faculty Research Development Award (C. L. Vaz) and the Obesity Treatment Foundation (C. L. Vaz). No commercial entity donated any funds, goods, or services to this research.	No
Wong *et al.*, 2021[42]	The authors report no conflicts of interest in this study.	Non-industry	Sincere thanks to the Start-up Fund, the Hong Kong Polytechnic University for the groundwork and Health and Medical Research Fund, Food and Health Bureau of Hong Kong SAR to support our research.	No
Yudi *et al.*, 2020[49]	There are no conflicts of interest.	Non-industry	M.B.Y. is supported by a combined National Health and Medical Research Council (NHMRC) and National Health Foundation Postgraduate Scholarship. The Victorian Cardiac Clinical Network and the National Heart Foundation of Australia, through a Vanguard Grant, have funded this study. They did not have any role in the design of this study protocol.	No
Yun *et al.*, 2020[58]	None declared.	Industry	Korea Health Technology R&D Project through the Korea Health Industry Development Institute and by the Ministry of Health and Welfare, Republic of Korea (grant number: HI16C0455)	No
Zha *et al.*, 2020[43]	The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.		The author(s) received no financial support for the research, authorship, and/or publication of this article.	Suspicious
Zhai & Yu *et al.*, 2020[158]	NR	Non industry	Funding from scientific research funding of Tianjin Medical University Chu Hisen-I Memorial Hospital (2019ZDKF09) for Dr Yangkui Zhai.	No

Supplementary Table 5.16 MARS App Quality Rating Subscale (Sections A-D).

		App name						
		Sidekick Health	Lose it!	Perx	Medisafe	Balanced	ControlMyWeight	Mean (SD)
Engagement	Entertainment	3.5	4.5	4	3	2.5	2	3.25 (0.94)
	Interest	4.5	5	4	3	2	2.5	3.50 (1.18)
	Customisation	4	5	4.5	5	3.5	2.5	4.08 (0.97)
	Interactivity	4.5	5	4.5	5	3.5	3	4.25 (0.82)
	Target group	5	5	5	4.5	3.5	4	4.50 (0.63)
Functionality	Performance	5	5	5	5	4.5	3.5	4.67 (0.61)
	Ease of use	5	5	5	5	4	5	4.83 (0.41)
	Navigation	5	5	5	5	4	4.5	4.75 (0.42)
	Gestural design	5	5	5	5	4	3.5	4.58 (0.66)
Aesthetics	Layout	5	5	5	5	4.5	3.5	4.67 (0.61)
	Graphics	5	4.5	4.5	5	3.5	3.5	4.33 (0.68)
	Visual appeal	5	4.5	3.5	4	3	2	3.67 (1.08)
Information	Accuracy of app description	5	5	5	5	4.5	4	4.75 (0.42)
	Goals	4	5	4.5	4.5	4	4.5	4.42 (0.38)
	Quality of information	4	5	5	5	4.5	4	4.58 (0.49)
	Quantity of information	4	5	4	5	4.5	3	4.25 (0.76)
	Visual information	5	5	4.5	4.5	4.5	4	4.58 (0.38)
	Credibility	3	2	4	3	4.5	3	3.25 (0.88)
	Evidence base	4	4	4	4	4	5	4.17 (0.41)

Supplementary Table 5.17 MARS App Subjective Quality Subscale (Section E).

		App name						
		Sidekick Health	Lose it!	Perx	Medisafe	Balanced	ControlMyWeight	Mean (SD)
Subjective	Recommend	4	4.5	3.5	4	2.5	3	3.58 (0.74)
	Relevance	5	5	4.5	5	3	4.5	4.50 (0.77)
	Would you pay	3	4	4	4	1	2	3.00 (1.26)
	Overall star rating	4	4.5	4	4	2.5	2.5	3.58 (0.86)
App-specific	Awareness	4	4.5	4	2.5	3	2.5	3.42 (0.86)
	Knowledge	3	5	3.5	2.5	3	3	3.33 (0.88)
	Attitudes	4	4.5	4.5	4.5	3.5	4	4.17 (0.41)
	Intention to change	4.5	5	5	4.5	3.5	4.5	4.50 (0.55)
	Help seeking	4	3	3.5	3	2.5	3	3.17 (0.52)
	Behaviour change	4	4.5	4.5	5	3.5	4	4.25 (0.52)

Supplementary Table 5.18 MARS grading of available apps from included studies.

Mobile Application Rating Scale (MARS)

App name	Engagement	Functionality	Aesthetics	Information	App quality mean Score	App subjective quality Score	App-specific
Sidekick Health[47]	4.30	5.00	5.00	4.14	4.61	4.00	3.92
Lose it![32]	4.90	5.00	4.67	4.43	4.75	4.50	4.42
Perx[48]	4.40	5.00	4.33	4.43	4.54	4.00	4.17
Medisafe[49]	4.10	5.00	4.67	4.43	4.55	4.25	3.67
Balanced[28]	3.00	4.13	3.67	4.36	3.79	2.25	3.17
ControlMyWeight[28]	2.80	4.13	3.00	3.93	3.46	3.00	3.50

The App Quality Ratings comprising Engagement, Functionality, Aesthetics, and Information informs the App quality mean Score.
The App subjective quality Score with subjectively evaluated each App for recommendation, rate of use, cost, and overall star rating.

Supplementary Table 5.19 Inclusion and exclusion criteria of included studies.

Author, year	Inclusion Criteria	Exclusion Criteria
Alonso-Dominguez *et al.*, 2019[51]	Age 25-70 years. T2DM (following ADA guidelines: FPG > 126 mg/dL or 2hr plasma glucose > 200 mg/dL during OGTT or HbA1c > 6.5%).	History of cardiovascular events. Musculoskeletal pathology that prevents walking. Clinically demonstrable neurological or neuropsychological disease.
Bennett *et al.*, 2018[26]	Obesity and elevated cardiovascular disease risk. At least two visits to the health centre in the last 12 months. Fluency in English. Ownership of a mobile phone. Willingness to send/receive three to nine text messages per week.	Pregnancy or ≤ 12 months postpartum. Cohabitation with another participant. Participation in a related trial or plans to move outside of the region within 2 years. Participants with a cardiovascular event in ≤ 6 months. A condition/medication that would affect weight. Profound cognitive, developmental, or psychiatric disorders; or psychiatric hospitalization in ≤ 12 months.
Bozorgi *et al.*, 2021[34]	The diagnosis of essential hypertension, without its complications, such as cardiovascular accidents etc. Being medically treated for hypertension. Age of patients between 30 and 60 years. Having a Smartphone and/or tablet. The ability to read Persian; Inclination to participate in the study. Intention to reside in the site of study for the next 6 month.	Presence of other cardiovascular diseases. Diabetes mellitus. Physical disability.
Broers *et al.*, 2020[44]	Age 18-75 years. Diagnosed with CAD, HF or HT. Having at least two of the following risk factors: smoking, positive family history, increased cholesterol, diabetes, sedentary lifestyle, psychosocial risk factors. Patients should also have access to the Internet and have a smartphone (and sufficient Knowledge on using personal computer or smartphone). Patients should have sufficient knowledge of the countries' native language. Additional inclusion criteria for HF patients only is to have a left ejection fraction of ≤35% and experience HF symptoms (e.g., shortness of breath, chest pain, exhaustion).	Significant cognitive impairments (e.g., dementia) . patients who are on the waiting list for heart transplantation. Life expectancy <1 year. Life threatening comorbidities (e.g., cancers) . History of psychiatric illness other than anxiety/depression. Patients who do not have access to internet. Patients with insufficient knowledge of the local pilot language (Dutch, Chinese and Catalonian).
Dorsch *et al.*, 2020[27]	>18 years age. Diagnosed with HTN on anti-HTN therapy for at least 3 months. Using an iPhone.	Chronic kidney disease (CKD), heart failure. Systolic blood pressure >180 mmHg, diastolic blood pressure >110 mmHg. Insulin-requiring diabetes mellitus, or taking loop diuretics, corticosteroids, or nonsteroidal anti-inflammatory medications.
Duncan *et al.*, 2020[28]	Aged 18–65 years. BMI between 25.0 and 40.0 kg/m^2. Possession of an iOS/Android smartphone/tablet with internet access.	Current use of an activity tracker for physical activity and/or sleep. Current pregnancy, reported presence of a doctor-diagnosed sleep disorder. Current use of medication to assist with sleep or weight management. Presence of a condition which precluded activity, diet and/or sleep behaviour modification, weight. Loss ≥4.5 kg in last 3 months, intention to participate in another weight loss trial. Previous weight loss surgery at any time. Current employment involving shift-work on a rotating roster.
Echeazarra *et al.*, 2021[45]	Patients attending the Nephrology outpatient clinic (CCEE) of the Araba University Hospital (HUA), with a diagnosis of hypertension or suspected primary or secondary hypertension. They must be at least 18 years old and have been previously instructed to perform BP checks at home with an information sheet available at the outpatient hospital. Patients must have an approved and calibrated tensiometer and a smartphone with Internet connection at home, and sufficient ability to send messages via WhatsApp or Telegram. Patients agreed to participate in the study by signing an informed consent form.	Previous diagnosis of severe psychiatric disorder. Severe illness suggesting a life expectancy of less than 6 months or high probability of needing haemodialysis or transplantation in less than 3 months. Severe clotting disorders that can cause bruising if frequent BP measurements are performed. Motor or visual disability that makes it difficult to perform self-measurements at home.
Gong *et al.*, 2020[29]	Age 18–79 yr. old. Primary hypertension according to the diagnostic criteria in 2010 Chinese Guidelines for Hypertension Prevention and Treatment. (1) Systolic blood pressure > 140mmHg and (or)	Age<18 yr. or Age ≥80 yr. Secondary hypertension Illiteracy and no ability to use smart phone

Author, year	Inclusion Criteria	Exclusion Criteria
	diastolic blood pressure > 90mmHg; 2) 24 hours ambulatory blood pressure >130/80mmHg) Owing a smart phone and the ability to use it, sufficient literacy, aspiration to participate in the trial. Life expectancy is more than 6 months.	Cerebral stroke in the past Complication of severe cardiopulmonary diseases, tumour. Life expectancy is less than 6 months.
Gonzalez-Sanchez *et al.*, 2019[39]	Healthy subjects since 20 to 70 years.	Older than 70 years are excluded, due to difficulties in the use of ICTs and those who cannot exercise or follow a diet Mediterranean diet.
Gunawardena *et al.*, 2018[46]	A diagnosis of diabetes (Type 1, Type 2 or unspecified). Age 18-80. HbA1c above 8%. Having fluctuations in blood glucose (standard deviation 60 mg/ dl and above). Duration of diabetes over one year. Must own a mobile device that supports Android or iOS (iPhone Operating System) applications. Agreed with study protocol and able to give a written consent for the study.	Pregnancy. Patients on haemodialysis. Steroid induced diabetes. Inability to be compliant with the study protocol. Presence of cognitive impairment.
Haufe *et al.*, 2019[35]	Female and male participants. Over the age of 18 years. At least three of the five metabolic syndrome components according to the AHA/NHLBI criteria. Who were not participating in an ongoing occupational health programme.	Acute or chronic infections. Oncological diseases. Joint replacements or any surgery within the previous 6 weeks. Pregnant or breastfeeding women. Any condition that precluded participation in an exercise intervention.
Hilmarsdóttir *et al.*, 2021[47]	Diagnosed with T2DM at least 6 months ago. Able to write and speak the Icelandic language. own a smartphone; able to use the SidekickHealth app. Aged 18-75 years. Not undergone or planned bariatric surgery during the trial period.	NR
Höchsmann *et al.*, 2019[31]	Physician-diagnosed and medically treated non−insulin-dependent diabetes mellitus. BMI ≥25. Aged 45−70 years. <150 minutes of moderate-intensity PA per week. Regular smartphone use during the year before the study to ensure that participants were familiar with the use of smartphones and would be able to play the PA-promoting smartphone game without additional assistance beyond the in-game tutorial.	Health risks that contraindicate exercise testing, impaired physical mobility, and acute infections or injuries. Other clinically significant concomitant disease states (e.g., renal failure, hepatic dysfunction, cardiovascular disease, etc.). Inability to follow the procedures of the study, e.g., due to language problems, psychological disorders, dementia, etc. of the participant. Previous enrolment into the current study. Participation in other studies in the last four weeks. Systolic blood pressure > 170mmHg, diastolic blood pressure > 100 mmHg. Regular physical activity before the study (≥150 min moderate intensity daily PA per week or >1 endurance or strength training session per week of more than 30 min in duration) .
Ifejika *et al.*, 2020[32]	Ischemic or haemorrhagic stroke. Age 18-85 years. African American or Hispanic ethnicity. Poststroke modified Rankin Scale (mRS) score 0-3. Poststroke body mass index >30 kg/m^2. Prescription medication for diabetes mellitus, hypertension or hyperlipidaemia. Willing to follow a healthy eating pattern and NOT use weight loss medications. Personal or caregiver ownership of a computer, smartphone or other smart device (iPhone or Android platform) with internet access. If patient has alexia, agraphia, acalculia, dementia or blindness, caregiver must be willing to complete the intervention.	Preexisting disability with mRS score ≥4. Contraindications to weight loss (planning to become pregnant, history of an eating disorder). Steroid use for suspected vasculitis. Current or recent (past 6 months) participation in a weight loss program or use of weight loss medication.
Kario *et al.*, 2021[36]	Age ≥ 20 years. Diagnosed with essential hypertension (office SBP 140-179 mmHg and/or DBP 90-109 mmHg). Antihypertensive medication-naïve or prescribed antihypertensive medication for > 30 days after initial use. Can use a smartphone daily (operating system: Android 6.0 and above or iOS 11.0 or above). Agree to follow the scheduled visits and to receive ABPM at both 16 and 24 weeks after registration.	Office SBP ≥ 180 and/or DBP ≥ 110. Suspected secondary hypertensions. Untreated for comorbidities in hypertension patients categorised as high cardiovascular risk group by the JSH2014 guideline. Female with pregnancy or expecting. Recent history of cardio- and cerebrovascular diseases, history of unstable angina, liver disease, renal disease, cancer, or heart failure. Difficulty with daily activities.

Author, year	Inclusion Criteria	Exclusion Criteria
		Participating in ongoing clinical trials. Relatives or cohabitant partners who have already participated in this trial. Judged by the investigator or clinical trial physicians to be unsuitable for participation in this study for any other reason (e.g., irregular clinic visits).
Li *et al.*, 2021[48]	Diagnosed with at least one of the following chronic conditions: type 2 diabetes mellitus (T2DM), heart failure, hypertension (HT), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD). Taking a minimum of three different medications. Able to visit the clinic monthly over a 12-month period. iPhone accessibility.	Absence of a chronic disease controlled with medication. Unable to correctly use the Penx app or an iPhone. Inability to read and write English. Participants may also be excluded, if in the opinion of the study Investigators, they have some other condition or disorder that may adversely affect the outcome of the study or the safety of the Participant (e.g., psychiatric illness, substance abuse) . Unable to commit to the appointment schedule or perform the tasks required in the study.
Logan *et al.*, 2012[53]	Diagnosis of type 2 diabetes mellitus (the onset of diabetes must have occurred on or after the age of 30 years and there is no history of diabetic ketoacidosis). Uncontrolled systolic hypertension (defined as a daytime systolic BP of 130 mm Hg or higher on 24-hour ambulatory).	Conditions making the patient unsuitable for study such as severe cognitive impairment, language difficulties (unable to speak and understand instructions in English), frequent (more than once per month for more than week) or prolonged (more than 2 months) trips away from home, homelessness, self-identified substance abuse, being pregnant, or unable to use home BP device. Life expectancy less than one year. Coexisting conditions that require frequent (more than once a month) office visits or repeated (more than once in the past year) hospitalizations Atrial fibrillation or other cardiac arrhythmias requiring drug treatment. Moderately severe chronic renal failure defined as estimated GFR less than 25 mL/min. Myocardial infarction, episode of heart failure requiring hospitalization, or paralyzing stroke in the past year. Having unstable angina. Severe valvular heart diseases such as severe aortic stenosis. Symptomatic orthostatic hypotension. Refusal to sign consent form or to carry out the demands made by the study.
Lunde *et al.*, 2020[33]	Finished Cardiac rehabilitation at NIMI or Feiring (one of 3 CR programs: 12-week outpatient CR, four-week inpatient CR and one-week inpatient CR). ≥ 40 years old. Owner and user of a Smartphone (Android or Apple). Understanding basic Norwegian or English.	Patients who experienced ischemia or arrhythmias during cardiopulmonary exercise testing that restricted them to less than 80% of their maximal heart rate or a BORG scale score below 15 during exercise. Patients with muscular or skeletal disorders impacting exercise capacity more than heart disease, as well as those with advanced cancer significantly affecting life expectancy.
Manigault *et al.*, 2020[37]	18 years of age. Diagnosed with hypertension as evidenced by diagnosis codes or chart documentation. Prescribed at least one antihypertensive for a minimum of three months prior to enrolment. Have access to an Android mobile device with data capabilities. Consent to using the application on their device.	Do not read or speak English. Unable to read and sign the informed consent or Health Insurance Privacy and Accountability Act (HIPAA) waiver. Too ill or cognitively impaired to participate.
Oh *et al.*, 2022[38]	Adults aged 40 to 70 years. Being treated for T2DM (without insulin) or hypertension. In stable status for at least the past 4 months. Recent HbA1c levels of participants measured in <4 months were >6.0%. Android phone with OS 4.3 (for self-measuring home devices).	A history of malignant diseases. Coronary artery obstructive disease. Stroke, organ transplantation. Drug abuse and alcohol dependence. Disability or respiratory disease limiting exercise. Hospitalisation in the past 6 months with major medical conditions.
Persell *et al.*, 2020[39]	Adults aged 18 years to <85 years at the time of screening. Standardised mean blood pressure≥135 mmHg systolic or≥85 mmHg at initial study visit. Have and use an iOS device(s) (iPhone generation 5S or newer). Able to provide written informed consent prior to participation in the study. Receive primary care from a Northwestern Medicine clinic site.	Current user of a Lark health coaching app. Baseline blood pressure≥180 mmHg (systolic) or≥110 mmHg (diastolic). Persistent atrial fibrillation. Pregnant or planning to become pregnant during the study period. Severe kidney disease, defined as estimated glomerular filtration rate < 30 per 1.73m^2 or currently on renal replacement therapy (i.e., haemodialysis or peritoneal dialysis). Hearing impaired and unable to respond to phone calls. Lack of fluency in English. History of a cardiovascular event (stroke, transient ischemic attack, myocardial infarction, coronary artery bypass grafting) in the past three months. Diagnosis of dementia. Diagnosis of psychosis. Terminal cancer diagnosis.

Author, year	Inclusion Criteria	Exclusion Criteria
		New York Heart Association class III or IV heart failure. Individuals requiring blood pressure monitor cuff size larger than 17 inches (42 cm).
Santo *et al.*, 2019[40]	Diagnosis of CHD. Over 18 years. Owned an active smartphone (iOS or Android). Had sufficient English skills.	Already using a medication reminder app or other electronic reminder systems, such as phone alarms. If their smartphones were not capable of downloading the apps.
Tekkesin *et al.*, 2021[41]	Presence of high risk for cardiovascular diseases (ASCVD risk score > 7.5%).	Patients with prior cardiovascular events including myocardial infarction, percutaneous coronary intervention, coronary artery by-pass grafting operation, stroke, and peripheral artery disease. Pregnancy. Patients with communication problems or severe neuropsychiatric problems. Patients with chronic kidney disease. Patients who are considered for being unable to use smart phone.
Vaz *et al.*, 2021[52]	BMI 25 to 42 kg/m^2. Age 18 to 65 years. Employed in sedentary occupations. Weight stability for last 4 weeks. Own a personal smartphone with >4 GB data per month or unlimited. Proficient with use of smartphone applications and technology with current daily usage. Home internet availability with personal computer. Ability to engage in moderate-intensity exercise. Ability to comply with all study-related procedures.	Current or planned pregnancy. Cardiovascular, pulmonary, renal, and/or joint disease. Uncontrolled thyroid disease. History of eating disorders, psychiatric disease. History of substance abuse or dependence in the last 1 year. Diabetes mellitus. Night shift work. Previous weight-loss surgery. Use of weight loss drugs/diet/program in the last 6 weeks.
Wong *et al.*, 2021[42]	Ethnic Chinese. Owned a smartphone. Aged 50 or above. Had metabolic syndrome,1 as defined by central obesity (waist circumference: male >90 cm, female >80 cm) and two of the following: • Triglyceride concentrations ≥150 mg/dL (1.7 mmol/L), or treatment for this lipid abnormality. • HDL cholesterol <40 mg/dL (1.03 mmol/L) in males and <50 mg/dL (1.29 mmol/L) in females. • Treatment for this lipid abnormality. • Systolic blood pressure ≥130 or diastolic blood pressure ≥85 mmHg, or treatment of previously diagnosed hypertension. • Fasting plasma glucose ≥100 mg/dL (5.6 mmol/L) or previously diagnosed type 2 diabetes.	Individuals with physical health problems; mental, visual, or cognitive impairments that compromised their use of a smartphone; or contraindications to walking or performing exercise were excluded.
Yudi *et al.*, 2020[49]	Age >18 years with a diagnosis of an ACS and documented CAD on angiography (coronary artery stenosis >50%), treated either medically or with percutaneous coronary intervention. Personal ownership of a smartphone.	Untreated ventricular tachycardia. Severe heart failure. Significant residual coronary artery disease requiring revascularisation. Treatment with coronary artery bypass surgery. Coexisting disease with a life expectancy less than 1 year or significant exercise limitations for reasons other than CHD.
Yun *et al.*, 2020[50]	Subject 19 years old and more. Subject who understands the purpose of the study and signs with informed consent form. Subject with chronic disease (hypertension, diabetes, dyslipidaemia) . Subject with more than one Poor Disease Control Indicator. HbA1c 7.0% or more. Systolic BP 140mmHg or more. LDL-cholesterol 130mg/dL or more. Subjects who use smart phones and PCs (those who can use ICT-based health care programs).	Inability to speak, understand, or write Korean. Inability to understand the contents of the provided materials due to poor eyesight and hearing. Medical conditions that would limit adherence to participation of the clinical trial (as confirmed by their referring physician, e.g., dyspnoea, severe depression, and other mental disorders).
Zha *et al.*, 2020[43]	Between 18 and 64 years of age. Resided in one of the four public housing units in the community. Had been diagnosed with uncontrolled hypertension (BP measured at 140/90 mmHg or higher for either systolic or diastolic pressure at five separate times during a 2-month period). On antihypertension medication. Owned and used a compatible Apple (iOS version 5.0 or higher) or Android (with operating system 3.0 or later) device.	Patients under the age of 18 years old. Pregnant women. Patient with serious arrhythmia. Patient with preeclamptic. Patient who cannot speak/read English. Patients using University Hospital or other clinical offices as their primary care service.

Author, year	Inclusion Criteria	Exclusion Criteria
	For the mHealth intervention, the application required a newer Apple or Android smartphone or tablet device for compatibility. In addition, as the application interface was only in English, participants needed to be able to read and speak English.	
Zhai & Yu, 2020[158]	Patients with type 2 diabetes diagnosed according to the Diagnostic Criteria for Type 2 Diabetes developed by the World Health Organisation in 1999 based on medical records. Diagnosed with diabetes 3 months. Aged between 18 and 60 years. No plans to relocate and travel in the next 6 months. Cell phone users.	Serious complications with kidney, eye, foot, and nervous system and acute complications such as diabetic ketoacidosis or lactic acidosis. Cognitive impairment, severe hearing and visual impairment. Type 1 diabetes or other unusual types of diabetes. Pregnancy and malignant tumours. Physically disabled. Surgery, pregnancy, and breastfeeding in the past 3 months. Patients who are participating in similar studies.

Supplementary Table 5.20 App availability on respective platforms (for MARS grading).

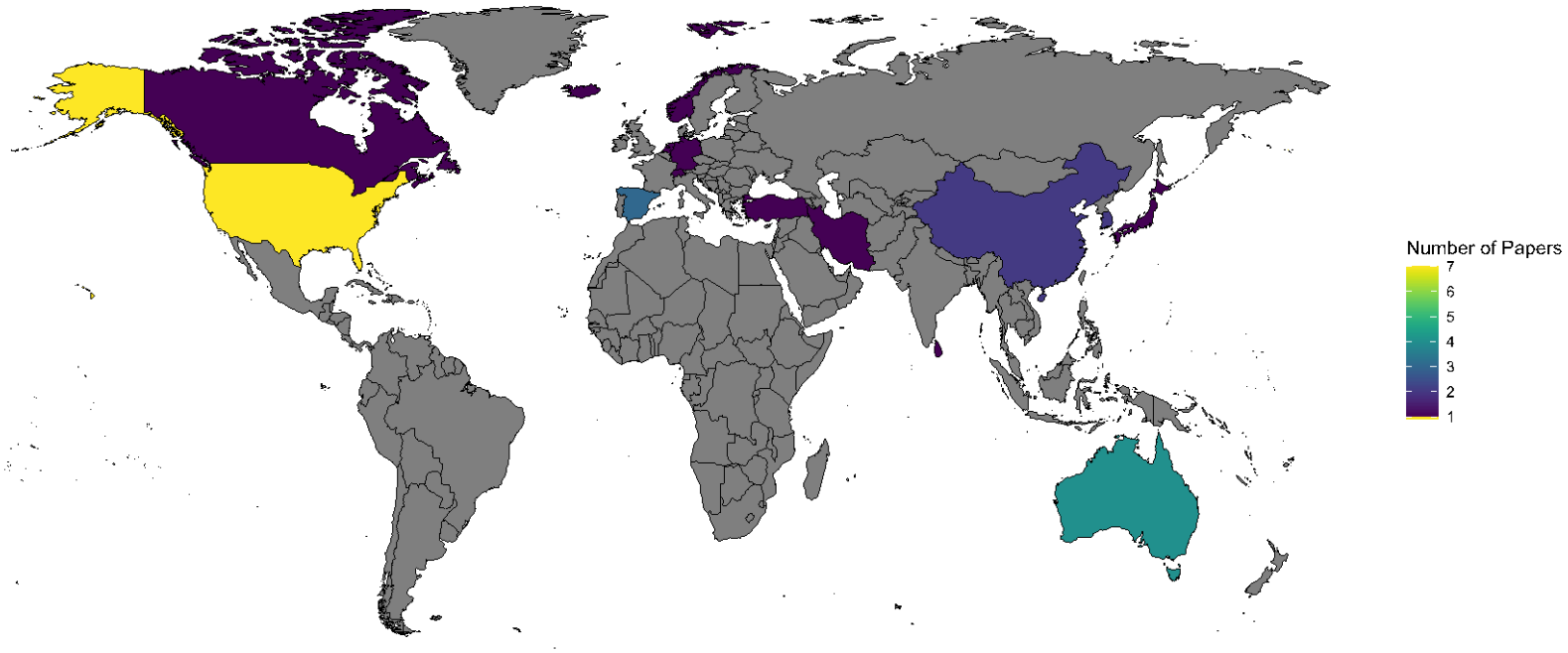
		App Availability	
Author, year	**App name (if any)**	**App Store**	**Play Store**
Dorsch *et al.*, 2020[27]	LowSalt4Life & Nutritionix	Yes (but requires participant login)	No
Duncan *et al.*, 2020[28]	Balanced app & ControlMyWeight app	Yes	No
Haufe *et al.*, 2019[35]	Rebirth Active	Yes (but in German)	No
Hilmarsdóttir *et al.*, 2021[47]	SidekickHealth app	Yes	Yes
Ifejika *et al.*, 2020[32]	Lose it!	Yes	Yes
Li *et al.*, 2021[48]	Perx	Yes	Yes
Santo *et al.*, 2019[40]	Advanced app: Medisafe; Basic app: My heart, my life	Yes (Medisafe)	Yes

As of 27 June 2023. App Store refers to Apple App Store. Play Store refers to Google Play Store.

Supplementary Table 5.21 App technical and descriptive information.

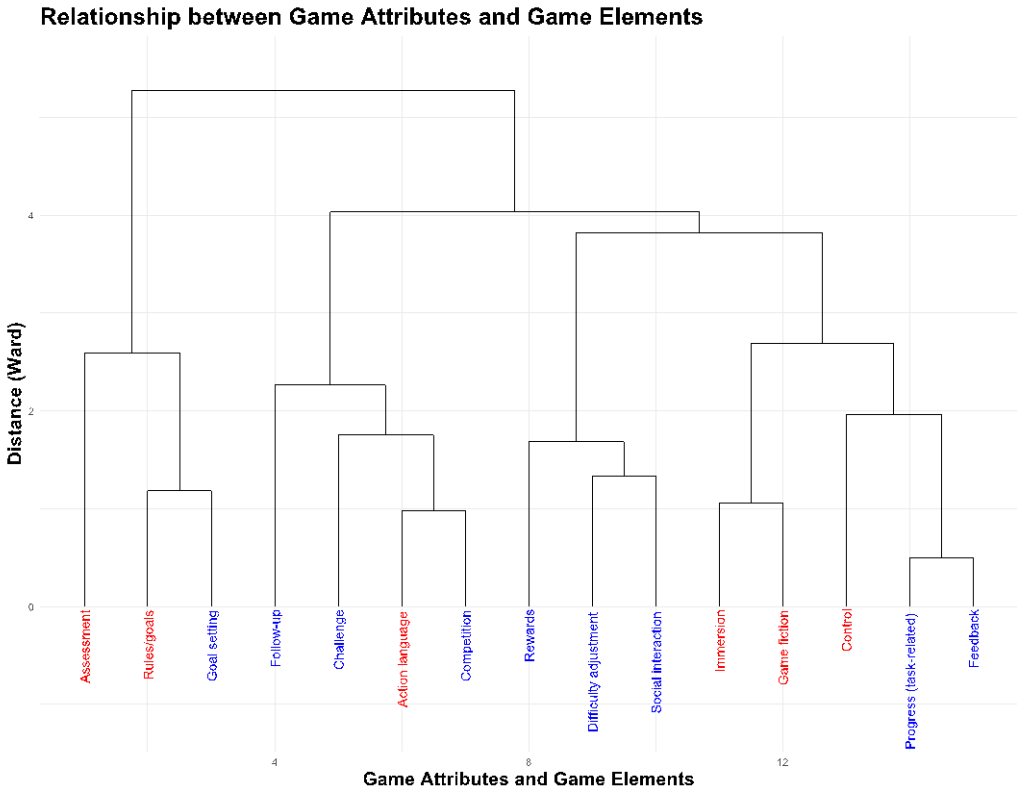
App name (Platform)	Version number	Developer name	Date updated (dd/mm/yyyy)	App cost ($AUD)	Age group	App rating (N)	App description	Technical aspects	App content focus	Theoretical background/ strategies
Sidekick Health[47] (iPhone)	3.5.12	Sidekick Health AB	01/07/2023	Basic: Free	Adolescents; young adults; adults	3.7 (3)	Helps people living with chronic illness (PSA, RA, IBD, CD, UC) manage the daily aspects of their lives to be healthier and feel better.	Has an App community; Requires login; Needs web access to function	Increase happiness/ wellbeing; mindfulness/ meditation/ relaxation; behaviour change; goal setting; physical health; Other - engagement	Assessment; feedback; monitoring/tracking; goal setting; advice/tips/strategies/skills training; CBT-behavioural (positive events); mindfulness/meditation; relaxation; gratitude
Lose it![32] (iPhone)	15.4 .300	FitNow	20/07/2023	Basic: Free Upgrade: 99.99	General	4.6 (9842)	Calorie counting, nutrition tracking, and intermittent fasting tool that helps users achieve their weight loss goals.	Allows sharing (Facebook, Twitter, etc.); has an app community; allows password-protection; requires login; sends reminders; needs web access to function	Behaviour change; goal setting; physical health	Feedback; information/education; monitoring/tracking; goal setting; advice/tips/strategies/skills training
Perx[48] (iPhone)	3.8.7	Lucky Health Pty. Ltd.	17/07/2023	Basic: Free Upgrade: 29.99	Adolescents; young adults; adults	4.7 (356)	Contains Uses behavioural science and consumer engagement tactics to help users improve heath behaviours.	Allows password-protection; requires login; sends reminders	Increase happiness/ wellbeing; Behaviour change; goal setting; physical health	Feedback; information/education; monitoring/tracking; goal setting; advice/tips/strategies/skills training; CBT-behavioural (positive events)
Medisafe[40] (iPhone)	8.3.32	Medisafe Inc.	18/07/2023	Basic: Free Upgrade: 62.99 per year	Adolescents; young adults; adults	4.7 (5799)	Visual and easy medication management with reminders and other biomarker tracking. Can generate progress reports to send to clinicians and can synchronise family's medication management.	Allows password-protection; requires login; sends reminders	Behaviour change; goal setting	Feedback; monitoring/tracking; goal setting
Balanced[28] (iPhone)	3.0.0	Headjam Pty. Ltd.	15/07/2022[A]	Basic: Free Upgrade: NA	General	5 (1)	App allows users to track self-behaviour to improve health including sleep quality, exercise, and sitting time.	Allows password-protection; requires login; needs web access to function	Increase happiness/ wellbeing; mindfulness/ meditation/ relaxation; reduce negative emotions; behaviour change; goal setting; physical health	Feedback; monitoring/tracking; goal setting
ControlMyWeight[28] (iPhone)	2.2.8	CalorieKing	21/11/2022	Free	Adolescents; young adults; adults	4.6 (8259)	Food and exercise diary for weight management curated with Australia's food database. Works offline.	Allows password-protection; requires login	Behaviour change; goal setting	Feedback; monitoring/tracking; goal setting

[A] Approximate date, since AppStore says last updated: 1 year ago

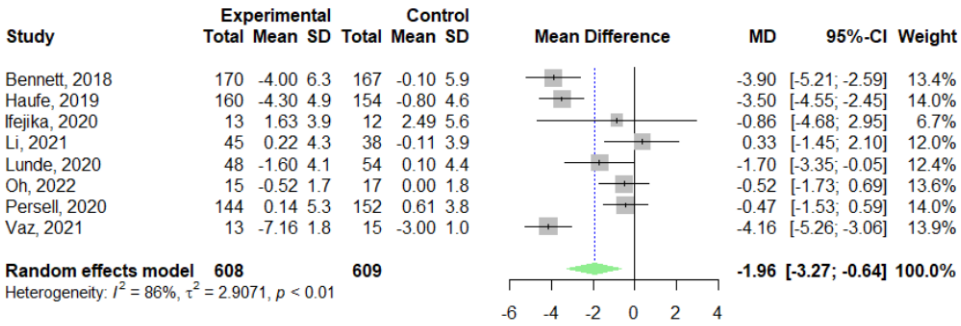


Supplementary Figure 5.1 Papers by country where studies were primarily conducted.

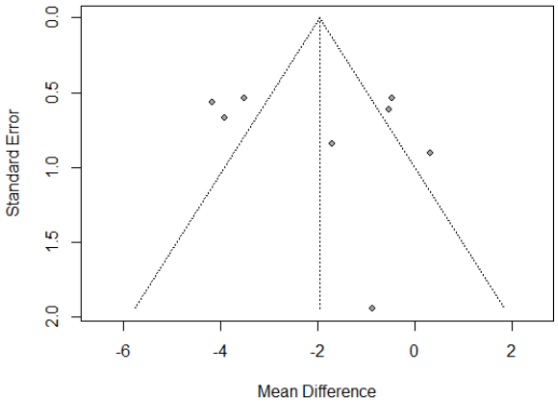
The total number of studies included from each region are as follows: 8 from Asia, 8 from Europe, 8 from North America, 4 from Australia, with number of papers per country shown on the figure with the USA contributing 7 studies, closely followed by Australia with 4 studies. Turkey was considered in Asia for this figure.



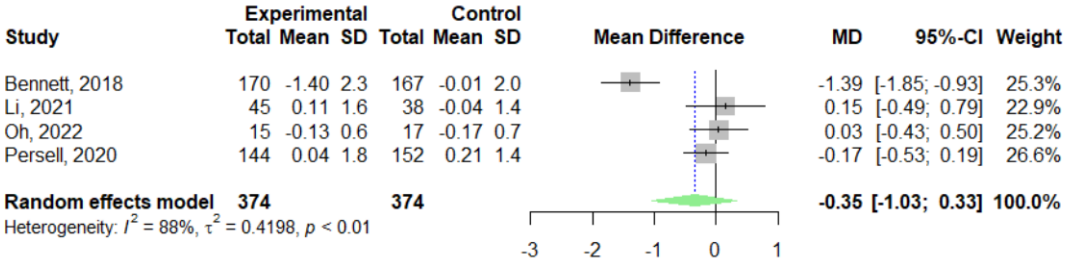
Supplementary Figure 5.2 Relationship between game attributes and game elements.
Game attributes are coloured in red, while game elements are in blue. In this graph, the Euclidean distance on the y-axis represents the dissimilarity between clusters, while each leaf on the x-axis represents a game element. Clusters of game elements that are close to each other (i.e., connected at a lower height on the dendrogram) are more similar in terms of their relationships with game attributes. For instance, the game elements grouped together at the lower heights are often used in similar contexts or for similar attributes in the studies.



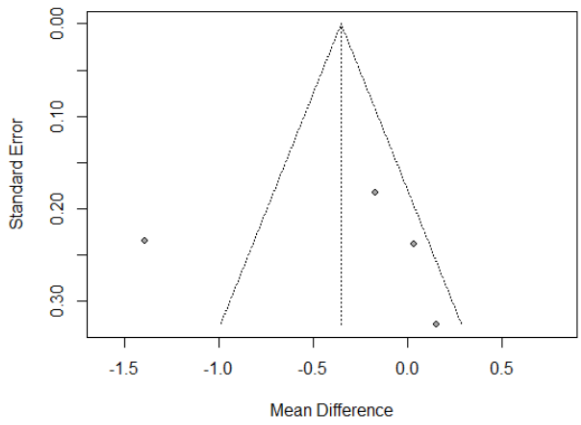
Supplementary Figure 5.3 Forest Plot of Body weight (kg) Sensitivity-Analysis Results.
A sensitivity-analysis of eight studies involving 1217 participants revealed a statistically significant reduction in body weight due to the intervention, with a pooled mean difference of -1.96 (95% CI: -3.27 to -0.64, p < 0.01). The analysis noted substantial heterogeneity (I^2 = 86%, τ^2 = 2.9071, p < 0.01), indicating considerable variability in effect sizes across studies. The effect estimates from individual studies were weighted between 6.7% and 14.3%, contributing evenly to the overall results.



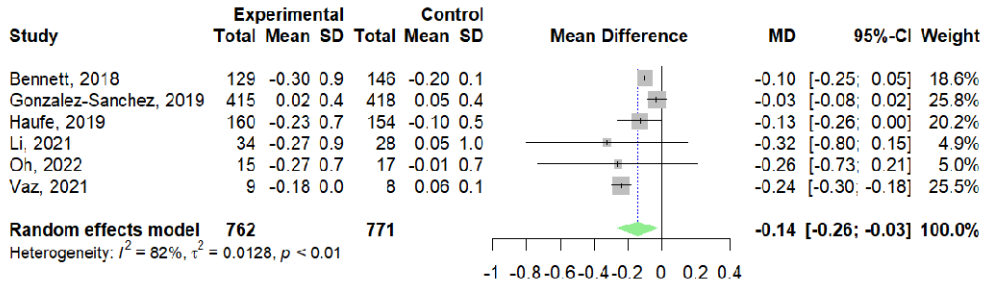
Supplementary Figure 5.4 Funnel plot of body weight for risk of publication bias (Sensitivity-analysis).
Mean change in body weight plotted against the SE of the mean change. The plot appears symmetrical.



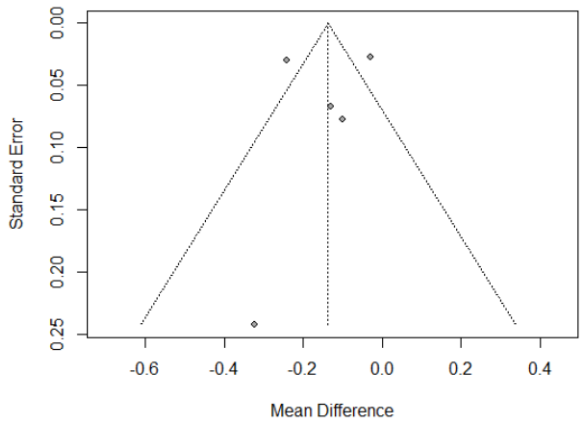
Supplementary Figure 5.5 Forest Plot of BMI (kg/m^2) Sensitivity-Analysis Results.
In this sensitivity-analysis comprising four studies with 748 participants, the intervention demonstrated a modest, non-significant reduction in BMI, with a mean difference of -0.35 (95% CI: -1.03 to 0.33, p < 0.01). Despite the overall effect being non-significant, substantial heterogeneity was present (I^2 = 88%, τ^2 = 0.4198), indicating variability in outcomes. The studies contributed relatively equally to the analysis, with individual study weights ranging from 22.9% to 26.6%.



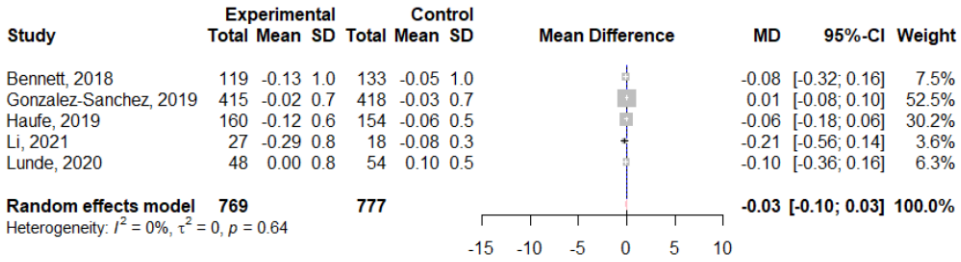
Supplementary Figure 5.6 Funnel plot of BMI for risk of publication bias (Sensitivity-analysis).
Mean change in BMI plotted against the SE of the mean change. The plot appears symmetrical.



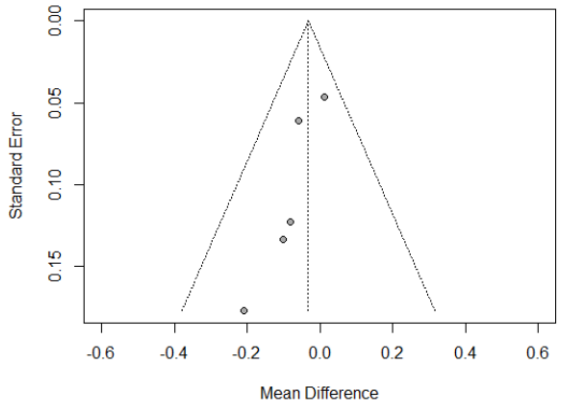
Supplementary Figure 5.7 Forest Plot of HbA1c (%) Sensitivity-Analysis Results.
In this sensitivity-analysis, which includes six studies with a combined total of 1533 participants, a small but statistically significant reduction in HbA1c was found with a mean difference of -0.14 (95% CI: -0.26 to -0.03). Despite the significance of the pooled results, there is a high degree of heterogeneity (I^2 = 82.2%, τ^2 = 0.0128), suggesting variations in the studies' results. The weight of individual studies within the analysis varied significantly, ranging from 4.9% to 25.8%.



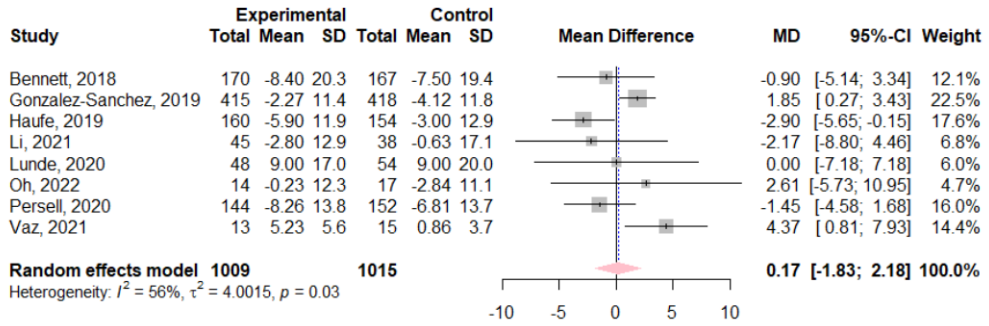
Supplementary Figure 5.8 Funnel plot of HbA1c for risk of publication bias (Sensitivity-analysis).
Mean change in HbA1c plotted against the SE of the mean change. The plot appears symmetrical.



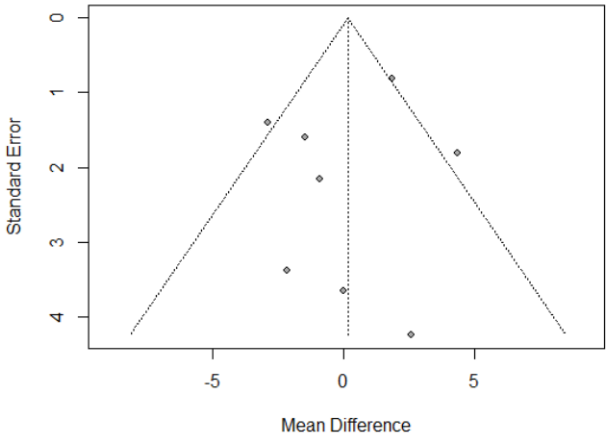
Supplementary Figure 5.9 Forest Plot of LDL (mmol/L) Sensitivity-Analysis Results.
This sensitivity-analysis of five studies, with a total of 1546 participants, shows a non-significant mean difference of -0.03 (95% CI: -0.10 to 0.03) for the intervention's effect, indicating no substantial impact on LDL. The heterogeneity among the included studies is negligible (I^2 = 0%, τ^2 = 0), suggesting a high level of consistency in the findings across different study samples and contexts. The contribution of each study to the overall effect size varies, with one study (Gonzalez-Sanchez, 2019) having a notably higher weight (52.5%) compared to the others.



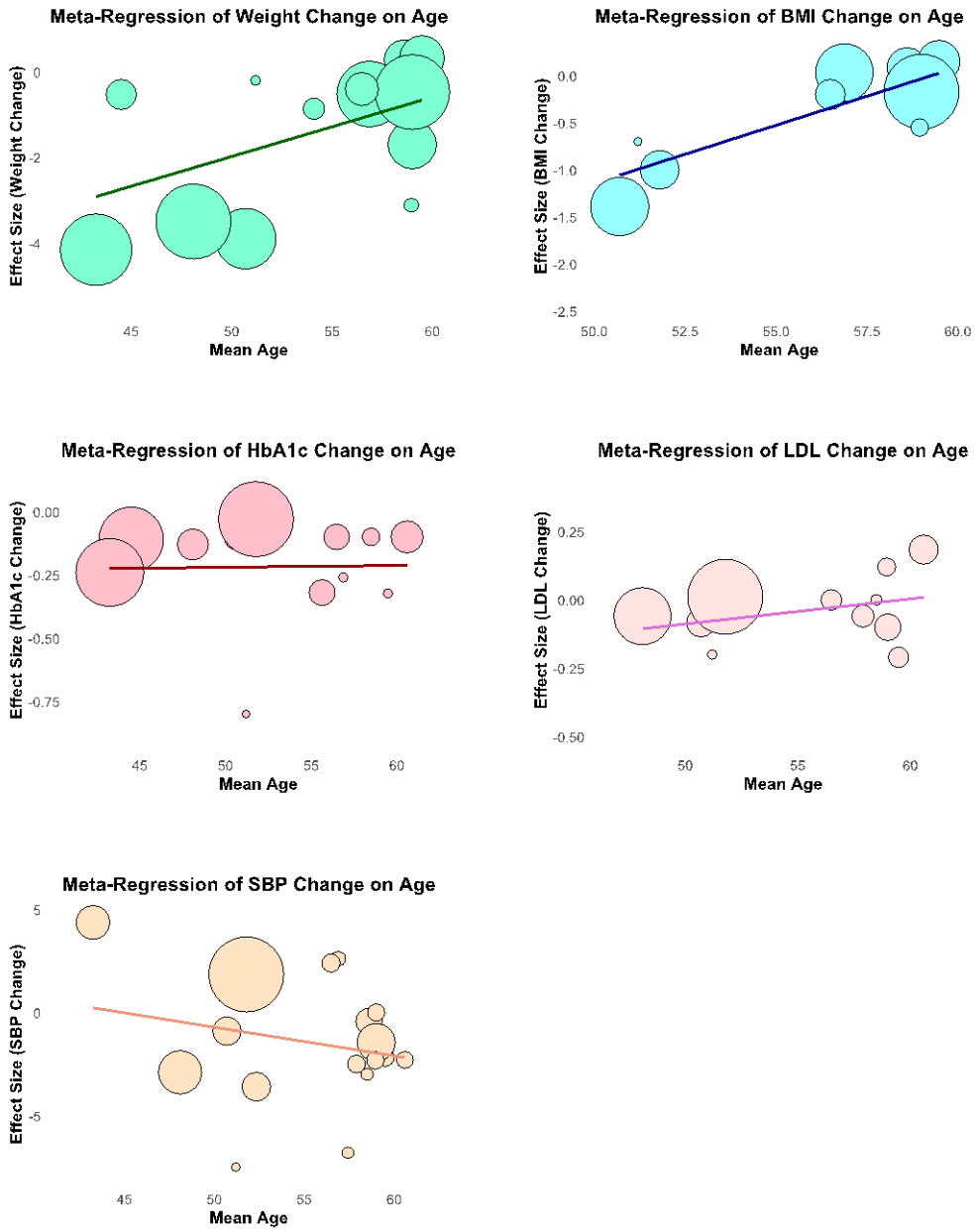
Supplementary Figure 5.10 Funnel plot of LDL for risk of publication bias (Sensitivity-analysis).
Mean change in LDL plotted against the SE of the mean change. The plot appears symmetrical.



Supplementary Figure 5.11 Forest Plot of SBP (mmHg) Sensitivity-Analysis Results.
In this sensitivity-analysis, data from seven studies with 2024 participants indicate a non-significant pooled mean difference of 0.17 (95% CI: -1.83 to 2.18) for SBP. There is moderate heterogeneity (I^2 = 56%, τ^2 = 4.0015, p = 0.03), suggesting some variability in outcomes between studies. The individual study contributions to the sensitivity-analysis are notably varied, with weights ranging from 4.7% to 22.5%, reflecting differences in study size and effect estimates.



Supplementary Figure 5.12 Funnel plot of SBP for risk of publication bias (Sensitivity-analysis).
Mean change in SBP plotted against the SE of the mean change. The plot appears symmetrical.



Supplementary Figure 5.13 Meta-regression plots for primary outcome vs age.
The bubble sizes in the meta-regression plots represent the precision of the effect size estimates, calculated as the inverse of the variance for each study. The variance was determined using the standard deviations and sample sizes of both the intervention and control groups, with larger bubbles indicating studies with smaller variances, more precise effect size estimates, and greater influence on the regression analysis.

Supplementary Figure 5.14 Comparison of App Dimension Ratings from included Apps using MARS.

References

1. Labrique A, Agarwal S, Tamrat T, Mehl G. WHO Digital Health Guidelines: a milestone for global health. npj Digital Medicine. 2020;3(1):120.
2. WHO Guidelines Approved by the Guidelines Review Committee. WHO guideline Recommendations on Digital Interventions for Health System Strengthening. Geneva: World Health Organization; 2019.
3. Deterding S, Dixon D, Khaled R, Nacke L. From game design elements to gamefulness: defining "gamification". Proceedings of the 15th International Academic MindTrek Conference: Envisioning Future Media Environments; Tampere, Finland: Association for Computing Machinery; 2011. p. 9–15.
4. Berglund A, Jaarsma T, Berglund E, Strömberg A, Klompstra L. Understanding and assessing gamification in digital healthcare interventions for patients with cardiovascular disease European Journal of Cardiovascular Nursing. 2022;21(6):630-8.
5. Sailer M, Hense JU, Mayr SK, Mandl H. How gamification motivates: An experimental study of the effects of specific game design elements on psychological need satisfaction. Computers in Human Behavior. 2017;69:371-80.
6. Krauskopf PB, Bradshaw MJ. American Heart Association Guidelines on the Go and My Cardiac Coach. The Journal for Nurse Practitioners. 2017;13(10):e487-e9.
7. Cheng VWS, Davenport T, Johnson D, Vella K, Hickie IB. Gamification in Apps and Technologies for Improving Mental Health and Well-Being: Systematic Review. JMIR Ment Health. 2019;6(6):e13717.
8. Laing BY, Mangione CM, Tseng CH, Leng M, Vaisberg E, Mahida M, et al. Effectiveness of a smartphone application for weight loss compared with usual care in overweight primary care patients: a randomized, controlled trial. Ann Intern Med. 2014;161(10 Suppl):S5-12.
9. Björkstrand J, Schiller D, Li J, Davidson P, Rosén J, Mårtensson J, et al. The effect of mindfulness training on extinction retention. Scientific Reports. 2019;9(1):19896.
10. Fitbit step counts clarify the association between activity and chronic disease risk. Nature Medicine. 2022;28(11):2263-4.
11. Zhang Y, Pratap A, Folarin AA, Sun S, Cummins N, Matcham F, et al. Long-term participant retention and engagement patterns in an app and wearable-based multinational remote digital depression study. npj Digital Medicine. 2023;6(1):25.
12. Huberty J, Green J, Glissmann C, Larkey L, Puzia M, Lee C. Efficacy of the Mindfulness Meditation Mobile App "Calm" to Reduce Stress Among College Students: Randomized Controlled Trial. JMIR Mhealth Uhealth. 2019;7(6):e14273.
13. Sepah SC, Jiang L, Ellis RJ, McDermott K, Peters AL. Engagement and outcomes in a digital Diabetes Prevention Program: 3-year update. BMJ Open Diabetes Res Care. 2017;5(1):e000422.
14. Crane D, Ubhi HK, Brown J, West R. Relative effectiveness of a full versus reduced version of the 'Smoke Free' mobile application for smoking cessation: an exploratory randomised controlled trial. F1000Research. 2018;7:1524.
15. Stine JG, Rivas G, Hummer B, Duarte-Rojo A, May CN, Geyer N, et al. Mobile health lifestyle intervention program leads to clinically significant loss of body weight in patients with NASH. Hepatology Communications. 2023;7(4).
16. Ehrmann D, Eichinger V, Vesper I, Kober J, Kraus M, Schäfer V, et al. Health care effects and medical benefits of a smartphone-based diabetes self-management application: study protocol for a randomized controlled trial. Trials. 2022;23(1):282.
17. Perez MV, Mahaffey KW, Hedlin H, Rumsfeld JS, Garcia A, Ferris T, et al. Large-Scale Assessment of a Smartwatch to Identify Atrial Fibrillation. New England Journal of Medicine. 2019;381(20):1909-17.
18. Johnson D, Deterding S, Kuhn KA, Staneva A, Stoyanov S, Hides L. Gamification for health and wellbeing: A systematic review of the literature. Internet Interv. 2016;6:89-106.
19. Stoyanov SR, Hides L, Kavanagh DJ, Zelenko O, Tjondronegoro D, Mani M. Mobile App Rating Scale: A New Tool for Assessing the Quality of Health Mobile Apps. JMIR mHealth uHealth. 2015;3(1):e27.
20. Hatem S, Long JC, Best S, Fehlberg Z, Nic Giolla Easpaig B, Braithwaite J. Mobile Apps for People With Rare Diseases: Review and Quality Assessment Using Mobile App Rating Scale. J Med Internet Res. 2022;24(7):e36691.
21. Agnew JMR, Nugent C, Hanratty CE, Martin E, Kerr DP, McVeigh JG. Rating the Quality of Smartphone Apps Related to Shoulder Pain: Systematic Search and Evaluation Using the Mobile App Rating Scale. JMIR Form Res. 2022;6(5):e34339.
22. Roberts AE, Davenport TA, Wong T, Moon H-W, Hickie IB, LaMonica HM. Evaluating the quality and safety of health-related apps and e-tools: Adapting the Mobile App Rating Scale and developing a quality assurance protocol. Internet Interventions. 2021;24:100379.
23. Terhorst Y, Philippi P, Sander LB, Schultchen D, Paganini S, Bardus M, et al. Validation of the Mobile Application Rating Scale (MARS). PLoS One. 2020;15(11):e0241480.
24. Davalbhakta S, Advani S, Kumar S, Agarwal V, Bhoyar S, Fedirko E, et al. A Systematic Review of Smartphone Applications Available for Corona Virus Disease 2019 (COVID19) and the Assessment of their Quality Using the Mobile Application Rating Scale (MARS). Journal of Medical Systems. 2020;44(9):164.
25. Domnich A, Arata L, Amicizia D, Signori A, Patrick B, Stoyanov S, et al. Development and validation of the Italian version of the Mobile Application Rating Scale and its generalisability to apps targeting primary prevention. BMC Medical Informatics and Decision Making. 2016;16(1):83.
26. Bennett GG, Steinberg D, Askew S, Levine E, Foley P, Batch BC, et al. Effectiveness of an App and Provider Counseling for Obesity Treatment in Primary Care. American Journal of Preventive Medicine. 2018;55(6):777-86.

27. Dorsch MP, Cornellier ML, Poggi AD, Bilgen F, Chen P, Wu C, et al. Effects of a Novel Contextual Just-In-Time Mobile App Intervention (LowSalt4Life) on Sodium Intake in Adults With Hypertension: Pilot Randomized Controlled Trial. JMIR Mhealth Uhealth. 2020;8(8):e16696.
28. Duncan MJ, Fenton S, Brown WJ, Collins CE, Glozier N, Kolt GS, et al. Efficacy of a Multi-component m-Health Weight-loss Intervention in Overweight and Obese Adults: A Randomised Controlled Trial. International Journal of Environmental Research and Public Health [Internet]. 2020; 17(17). Available from: https://mdpi-res.com/d_attachment/ijerph/ijerph-17-06200/article_deploy/ijerph-17-06200.pdf?version=1598449426.
29. Gong K, Yan YL, Li Y, Du J, Wang J, Han Y, et al. Mobile health applications for the management of primary hypertension: A multicenter, randomized, controlled trial. Medicine (Baltimore). 2020;99(16):e19715.
30. Gonzalez-Sanchez J, Recio-Rodriguez JI, Fernandez-delRio A, Sanchez-Perez A, Magdalena-Belio JF, Gomez-Marcos MA, et al. Using a smartphone app in changing cardiovascular risk factors: A randomized controlled trial (EVIDENT II study). Int J Med Inform. 2019;125:13-21.
31. Höchsmann C, Müller O, Ambühl M, Klenk C, Königstein K, Infanger D, et al. Novel Smartphone Game Improves Physical Activity Behavior in Type 2 Diabetes. Am J Prev Med. 2019;57(1):41-50.
32. Ifejika NL, Bhadane M, Cai CC, Noser EA, Grotta JC, Savitz SI. Use of a Smartphone-Based Mobile App for Weight Management in Obese Minority Stroke Survivors: Pilot Randomized Controlled Trial With Open Blinded End Point. JMIR Mhealth Uhealth. 2020;8(4):e17816.
33. Lunde P, Bye A, Bergland A, Grimsmo J, Jarstad E, Nilsson BB. Long-term follow-up with a smartphone application improves exercise capacity post cardiac rehabilitation: A randomized controlled trial. Eur J Prev Cardiol. 2020;27(16):1782-92.
34. Bozorgi A, Hosseini H, Eftekhar H, Majdzadeh R, Yoonessi A, Ramezankhani A, et al. The effect of the mobile "blood pressure management application" on hypertension self-management enhancement: a randomized controlled trial. Trials. 2021;22(1):413.
35. Haufe S, Kerling A, Protte G, Bayerle P, Stenner HT, Rolff S, et al. Telemonitoring-supported exercise training, metabolic syndrome severity, and work ability in company employees: a randomised controlled trial. The Lancet Public Health. 2019;4(7):e343-e52.
36. Kario K, Nomura A, Kato A, Harada N, Tanigawa T, So R, et al. Digital therapeutics for essential hypertension using a smartphone application: A randomized, open-label, multicenter pilot study. J Clin Hypertens (Greenwich). 2021;23(5):923-34.
37. Manigault KR, McKinley D, Patel S, Truong C, Nguyen S, Akil A, et al. The impact of a pharmacist-designed mobile application on blood pressure control and medication adherence in patients with hypertension. JACCP: JOURNAL OF THE AMERICAN COLLEGE OF CLINICAL PHARMACY. 2020;3(7):1286-95.
38. Oh SW, Kim KK, Kim SS, Park SK, Park S. Effect of an Integrative Mobile Health Intervention in Patients With Hypertension and Diabetes: Crossover Study. JMIR Mhealth Uhealth. 2022;10(1):e27192.
39. Persell SD, Peprah YA, Lipiszko D, Lee JY, Li JJ, Ciolino JD, et al. Effect of Home Blood Pressure Monitoring via a Smartphone Hypertension Coaching Application or Tracking Application on Adults With Uncontrolled Hypertension: A Randomized Clinical Trial. JAMA Netw Open. 2020;3(3):e200255.
40. Santo K, Singleton A, Rogers K, Thiagalingam A, Chalmers J, Chow CK, et al. Medication reminder applications to improve adherence in coronary heart disease: a randomised clinical trial. Heart. 2019;105(4):323-9.
41. Tekkeşin A, Hayıroğlu M, Çinier G, Özdemir YS, İnan D, Yüksel G, et al. Lifestyle intervention using mobile technology and smart devices in patients with high cardiovascular risk: A pragmatic randomised clinical trial. Atherosclerosis. 2021;319:21-7.
42. Wong EML, Leung DYP, Tam HL, Wang Q, Yeung KW, Leung AYM. The Effect of a Lifestyle Intervention Program Using a Mobile Application for Adults with Metabolic Syndrome, versus the Effect of a Program Using a Booklet: A Pilot Randomized Controlled Trial. Clin Interv Aging. 2021;16:633-44.
43. Zha P, Qureshi R, Porter S, Chao Y-Y, Pacquiao D, Chase S, et al. Utilizing a Mobile Health Intervention to Manage Hypertension in an Underserved Community. Western Journal of Nursing Research. 2019;42(3):201-9.
44. Broers ER, Widdershoven J, Denollet J, Lodder P, Kop WJ, Wetzels M, et al. Personalized eHealth Program for Life-style Change: Results From the "Do Cardiac Health Advanced New Generated Ecosystem (Do CHANGE 2)" Randomized Controlled Trial. Psychosomatic Medicine. 2020;82(4).
45. Echeazarra L, Pereira J, Saracho R. TensioBot: a Chatbot Assistant for Self-Managed in-House Blood Pressure Checking. J Med Syst. 2021;45(4):54.
46. Gunawardena KC, Jackson R, Robinett I, Dhaniska L, Jayamanne S, Kalpani S, et al. The Influence of the Smart Glucose Manager Mobile Application on Diabetes Management. J Diabetes Sci Technol. 2019;13(1):75-81.
47. Hilmarsdóttir E, Sigurðardóttir Á K, Arnardóttir RH. A Digital Lifestyle Program in Outpatient Treatment of Type 2 Diabetes: A Randomized Controlled Study. J Diabetes Sci Technol. 2021;15(5):1134-41.
48. Li A, Del Olmo MG, Fong M, Sim K, Lymer SJ, Cunich M, et al. Effect of a smartphone application (Perx) on medication adherence and clinical outcomes: a 12-month randomised controlled trial. BMJ Open. 2021;11(8):e047041.
49. Yudi MB, Clark DJ, Tsang D, Jelinek M, Kalten K, Joshi SB, et al. SMARTphone-based, early cardiac REHABilitation in patients with acute coronary syndromes: a randomized controlled trial. Coron Artery Dis. 2021;32(5):432-40.
50. Yun YH, Kang E, Cho YM, Park SM, Kim YJ, Lee HY, et al. Efficacy of an Electronic Health Management Program for Patients With Cardiovascular Risk: Randomized Controlled Trial. J Med Internet Res. 2020;22(1):e15057.
51. Alonso-Domínguez R, García-Ortiz L, Patino-Alonso MC, Sánchez-Aguadero N, Gómez-Marcos MA, Recio-Rodríguez JI. Effectiveness of A Multifactorial Intervention in Increasing Adherence to the Mediterranean Diet among Patients with Diabetes Mellitus Type 2: A Controlled and Randomized Study (EMID Study). Nutrients [Internet]. 2019;

11(1). Available from: https://mdpi-res.com/d_attachment/nutrients/nutrients-11-00162/article_deploy/nutrients-11-00162.pdf?version=1547438981.
52. Vaz CL, Carnes N, Pousti B, Zhao H, Williams KJ. A randomized controlled trial of an innovative, user-friendly, interactive smartphone app-based lifestyle intervention for weight loss. Obes Sci Pract. 2021;7(5):555-68.
53. Logan AG, Irvine MJ, McIsaac WJ, Tisler A, Rossos PG, Easty A, et al. Effect of home blood pressure telemonitoring with self-care support on uncontrolled systolic hypertension in diabetics. Hypertension. 2012;60(1):51-7.
54. Hajar R. Risk Factors for Coronary Artery Disease: Historical Perspectives. Heart Views. 2017;18(3):109-14.
55. Nelson RH. Hyperlipidemia as a risk factor for cardiovascular disease. Primary care. 2013;40(1):195-211.
56. Cavero-Redondo I, Peleteiro B, Álvarez-Bueno C, Rodriguez-Artalejo F, Martínez-Vizcaíno V. Glycated haemoglobin A1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: a systematic review and meta-analysis. BMJ Open. 2017;7(7):e015949.
57. Tune JD, Goodwill AG, Sassoon DJ, Mather KJ. Cardiovascular consequences of metabolic syndrome. Transl Res. 2017;183:57-70.
58. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71(19):e127-e248.
59. National Institutes of Health. High Blood Cholesterol. National Cholesterol Education Program [Internet]. 2005. Available from: https://www.nhlbi.nih.gov/files/docs/public/heart/wyntk.pdf.
60. American Diabetes Association. Diagnosis and Classification of Diabetes Mellitus. Diabetes Care. 2010;33(Supplement 1):S62-S9.
61. Huang PL. A comprehensive definition for metabolic syndrome. Disease Models & Mechanisms. 2009;2(5-6):231.
62. Abu-El-Noor NI, Aljeesh YI, Bottcher B, Abu-El-Noor MK. Impact of a mobile phone app on adherence to treatment regimens among hypertensive patients: A randomised clinical trial study. European Journal of Cardiovascular Nursing. 2021;20(5):428-35.
63. Adams ZW, Sieverdes JC, Brunner-Jackson B, Mueller M, Chandler J, Diaz V, et al. Meditation smartphone application effects on prehypertensive adults' blood pressure: Dose-response feasibility trial. Health Psychol. 2018;37(9):850-60.
64. Adhikary R, Krishnakumar A, Kolwankar S, Shah A, Sanghavi S, Mattoo V. Effectiveness of digital therapeutics to improve blood pressure control among patients with hypertension and diabetes in India. Journal of the American College of Cardiology. 2020;75(11_Supplement_1):3583-.
65. Aschbrenner K, Naslund J, Gorin A, Mueser K, Bartels S. Randomized trial of a lifestyle intervention for young adults with serious mental illness in community mental health centers. Schizophrenia Bulletin. 2019;45(Supplement_2):S135-S.
66. Bender MS, Cooper BA, Park LG, Padash S, Arai S. A Feasible and Efficacious Mobile-Phone Based Lifestyle Intervention for Filipino Americans with Type 2 Diabetes: Randomized Controlled Trial. JMIR Diabetes. 2017;2(2):e30.
67. Block RC, Abdolahi A, Niemiec CP, Rigby CS, Williams GC. Effects of an evidence-based computerized virtual clinician on low-density lipoprotein and non-high-density lipoprotein cholesterol in adults without cardiovascular disease: The Interactive Cholesterol Advisory Tool. Health Informatics Journal. 2015;22(4):897-910.
68. Caro O, María I. Utilización de una aplicación móvil para el fomento de la adherencia terapéutica en la hipertensión arterial en atención primaria. Nure Investigacion. 2018;15(92):1-8.
69. Chandler J, Sox L, Kellam K, Feder L, Nemeth L, Treiber F. Impact of a Culturally Tailored mHealth Medication Regimen Self-Management Program upon Blood Pressure among Hypertensive Hispanic Adults. International Journal of Environmental Research and Public Health [Internet]. 2019; 16(7).
70. Chandler J, Sox L, Diaz V, Kellam K, Neely A, Nemeth L, et al. Impact of 12-Month Smartphone Breathing Meditation Program upon Systolic Blood Pressure among Non-Medicated Stage 1 Hypertensive Adults. International Journal of Environmental Research and Public Health [Internet]. 2020; 17(6).
71. Cho SMJ, Lee JH, Shim J-S, Yeom H, Lee SJ, Jeon YW, et al. Effect of Smartphone-Based Lifestyle Coaching App on Community-Dwelling Population With Moderate Metabolic Abnormalities: Randomized Controlled Trial. J Med Internet Res. 2020;22(10):e17435.
72. Choi MD, Standridge A, Landis-Piwowar K. Improving cardiac function and body composition through incentive-based smartphone application in sedentary overweight adults. FASEB journal. 2018;32(1).
73. Márquez Contreras E, Márquez Rivero S, Rodríguez García E, López-García-Ramos L, Carlos Pastoriza Vilas J, Baldonedo Suárez A, et al. Specific hypertension smartphone application to improve medication adherence in hypertension: a cluster-randomized trial. Current Medical Research and Opinion. 2019;35(1):167-73.
74. De Kluiver EP, Van Der Velde AE, Meindersma EP, Prins LF, Wilhelm M, Iliou MC, et al. P1927A European randomised controlled trial for m-health guided cardiac rehabilitation in the elderly; results of the EU-CaRE RCT study. European Heart Journal. 2019;40(Supplement_1):ehz748.0674.
75. Dorsch MP, Cornellier ML, Poggi AD, Bilgen F, Chen P, Wu C, et al. Abstract P3029: A Randomized Controlled Trial Evaluating a Novel Just-In-Time Contextual Mobile Application Intervention to Reduce Sodium Intake in Hypertension: The Lowsalt4life Trial. Hypertension. 2019;74(Suppl_1):AP3029-AP.
76. Du X, Jornten-Karlsson M, Xu Y, Guo J, Li J, Mei X, et al. P440Ehelp China, a randomised trial evaluating the effect of a smart phone-based patient support tool on treatment duration in patients prescribed rosuvastatin in China. European Heart Journal. 2017;38(suppl_1):ehx501.P440.

77. Eastwood J-A, Moser DK, Alshurafa N, Doering LV, Watson K, Sarrafzadeh M. Abstract 19005: Staying Connected: a CVD Risk Intervention for Young Black Women. Circulation. 2014;130(suppl_2):A19005-A.
78. Eisenhauer CM, Brito F, Kupzyk K, Yoder A, Almeida F, Beller RJ, et al. Mobile health assisted self-monitoring is acceptable for supporting weight loss in rural men: a pragmatic randomized controlled feasibility trial. BMC Public Health. 2021;21(1):1568.
79. Falkenhain K, Locke SR, Lowe DA, Reitsma NJ, Lee T, Singer J, et al. Keyto app and device versus WW app on weight loss and metabolic risk in adults with overweight or obesity: A randomized trial. Obesity. 2021;29(10):1606-14.
80. Fenton S, Burrows TL, Collins CE, Rayward AT, Murawski B, Duncan MJ. Efficacy of a Multi-Component m-Health Diet, Physical Activity, and Sleep Intervention on Dietary Intake in Adults with Overweight and Obesity: A Randomised Controlled Trial. Nutrients [Internet]. 2021; 13(7).
81. Foley P, Steinberg D, Levine E, Askew S, Batch BC, Puleo EM, et al. Track: A randomized controlled trial of a digital health obesity treatment intervention for medically vulnerable primary care patients. Contemporary Clinical Trials. 2016;48:12-20.
82. Frias J, Virdi N, Raja P, Kim Y, Savage G, Osterberg L. Effectiveness of Digital Medicines to Improve Clinical Outcomes in Patients with Uncontrolled Hypertension and Type 2 Diabetes: Prospective, Open-Label, Cluster-Randomized Pilot Clinical Trial. J Med Internet Res. 2017;19(7):e246.
83. Najafi Ghezeljeh T, Sharifian S, Nasr Isfahani M, Haghani H. Comparing the effects of education using telephone follow-up and smartphone-based social networking follow-up on self-management behaviors among patients with hypertension. Contemp Nurse. 2018;54(4-5):362-73.
84. Ghose A, Guo X, Li B, Dang Y. Empowering Patients Using Smart Mobile Health Platforms: Evidence from a Randomized Field Experiment. Forthcoming at MIS Quarterly, NYU Stern School of Business Forthcoming. 2021.
85. Gill DP, Stuckey MI, Shapiro S, Sabourin KJ, Hubbard RA, Petrella RJ. Lectures and Oral Presentations. Journal of Diabetes. 2013;5(s1):80.
86. Guo Y, Chen Y, Lane DA, Liu L, Wang Y, Lip GYH. Mobile Health Technology for Atrial Fibrillation Management Integrating Decision Support, Education, and Patient Involvement: mAF App Trial. The American Journal of Medicine. 2017;130(12):1388-96.e6.
87. Haufe S, Kahl KG, Kerling A, Protte G, Bayerle P, Stenner HT, et al. Employers With Metabolic Syndrome and Increased Depression/Anxiety Severity Profit Most From Structured Exercise Intervention for Work Ability and Quality of Life. Front Psychiatry. 2020;11:562.
88. Indraratna P, Biswas U, McVeigh J, Mamo A, Magdy J, Briggs N, et al. A randomised control trial of TeleClinical Care – a smartphone-app based model of care for heart failure and acute coronary syndromes. European Heart Journal. 2021;42(Supplement_1):ehab724.3083.
89. Ionov MV, Zhukova OV, Yudina YS, Avdonina NG, Emelyanov IV, Kurapeev DI, et al. Value-based approach to blood pressure telemonitoring and remote counseling in hypertensive patients. Blood Press. 2021;30(1):20-30.
90. Johnston N, Bodegard J, Jerström S, Åkesson J, Brorsson H, Alfredsson J, et al. Effects of interactive patient smartphone support app on drug adherence and lifestyle changes in myocardial infarction patients: A randomized study. American Heart Journal. 2016;178:85-94.
91. Kario K, Nomura A, Harada N, Okura A, Nakagawa K, Tanigawa T, et al. Efficacy of a digital therapeutics system in the management of essential hypertension: the HERB-DH1 pivotal trial. European Heart Journal. 2021;42(40):4111-22.
92. Khunti K, Griffin S, Brennan A, Dallosso H, Davies M, Eborall H, et al. Behavioural interventions to promote physical activity in a multiethnic population at high risk of diabetes: PROPELS three-arm RCT. 2021;25:77.
93. Kim JB, Lee SK, Lee SJ, Shine SE, Ahn JH, Lee JE, et al. Application for cardiac self-Improvement(ANSIM), a randomized controlled trial: 9-month clinical outcome. European Journal of Preventive Cardiology. 2019;26(Supple 1):S71-S127.
94. Kirwan M, Vandelanotte C, Fenning A, Duncan MJ. Diabetes self-management smartphone application for adults with type 1 diabetes: randomized controlled trial. J Med Internet Res. 2013;15(11):e235.
95. Krackhardt Markus F, Maier L, Jörntén-Karlsson M. TCT-549 The "Me & My Heart" (eMocial) Study: A Randomized Evaluation of a New Smartphone-Based Support Tool to Increase Therapy Adherence of ACS patients. Journal of the American College of Cardiology. 2019;74(13_Supplement):B542-B.
96. Lee J, Lee H. [The Effects of Smart Program for Patients Who Underwent Percutaneous Coronary Intervention (SP-PCI) on Disease-Related Knowledge, Health Behavior, and Quality of Life: A Non-Randomized Controlled Trial]. J Korean Acad Nurs. 2017;47(6):756-69.
97. Lee JH, Shim J-S, Yeom H, Lee SJ, Kim HC. Abstract MP69: The Weight Loss by Using the Smartphone Application for People with Metabolic Abnormalities: A Randomized Controlled Trial. Circulation. 2019;139(Suppl_1):AMP69-AMP.
98. Lee JY, Tang D, Xiao X, Liang X, Piao H, Xie M. Addition of the Electronic Educational Material to Doctor's Face-to-Face Education Has No Additive Effects on Hypertension Control: A Randomized Single Blind Study. Int J Hypertens. 2020;2020:8275945.
99. Lewey J, Murphy S, Zhang D, Putt ME, Elovitz MA, Riis V, et al. Effectiveness of a Text-Based Gamification Intervention to Improve Physical Activity Among Postpartum Individuals With Hypertensive Disorders of Pregnancy: A Randomized Clinical Trial. JAMA Cardiol. 2022;7(6):591-9.
100. Li X, Li T, Chen J, Xie Y, An X, Lv Y, et al. A WeChat-Based Self-Management Intervention for Community Middle-Aged and Elderly Adults with Hypertension in Guangzhou, China: A Cluster-Randomized Controlled Trial. Int J Environ Res Public Health. 2019;16(21).

101. Li W-Y, Chiu F-C, Zeng J-K, Li Y-W, Huang S-H, Yeh H-C, et al. Mobile Health App With Social Media to Support Self-Management for Patients With Chronic Kidney Disease: Prospective Randomized Controlled Study. J Med Internet Res. 2020;22(12):e19452.
102. Li Y, Gong Y, Zheng B, Fan F, Yi T, Zheng Y, et al. Effects on Adherence to a Mobile App-Based Self-management Digital Therapeutics Among Patients With Coronary Heart Disease: Pilot Randomized Controlled Trial. JMIR Mhealth Uhealth. 2022;10(2):e32251.
103. Lin P-H, Grambow S, Intille S, Gallis JA, Lazenka T, Bosworth H, et al. The Association Between Engagement and Weight Loss Through Personal Coaching and Cell Phone Interventions in Young Adults: Randomized Controlled Trial. JMIR Mhealth Uhealth. 2018;6(10):e10471.
104. Liu Z, Chen S, Zhang G, Lin A. Mobile Phone-Based Lifestyle Intervention for Reducing Overall Cardiovascular Disease Risk in Guangzhou, China: A Pilot Study. Int J Environ Res Public Health. 2015;12(12):15993-6004.
105. Liu Y, Chen J, Lamb KV, Wu P, Chang P, Cui Y, et al. Smartphone-Based Self-Empowerment App on Secondary Prevention of Patients with Cardiovascular Disease. Stud Health Technol Inform. 2019;264:1712-3.
106. Martin SS, Feldman DI, Blumenthal RS, Jones SR, Post WS, McKibben RA, et al. mActive: A Randomized Clinical Trial of an Automated mHealth Intervention for Physical Activity Promotion. Journal of the American Heart Association.4(11):e002239.
107. Martínez-Rodríguez A, Martínez-Olcina M, Mora J, Navarro P, Caturla N, Jones J. New App-Based Dietary and Lifestyle Intervention on Weight Loss and Cardiovascular Health. Sensors (Basel). 2022;22(3).
108. McGillicuddy JW, Taber DJ, Mueller M, Patel S, Baliga PK, Chavin KD, et al. Sustainability of improvements in medication adherence through a mobile health intervention. Prog Transplant. 2015;25(3):217-23.
109. Mendelson M, Vivodtzev I, Tamisier R, Laplaud D, Dias-Domingos S, Baguet JP, et al. CPAP treatment supported by telemedicine does not improve blood pressure in high cardiovascular risk OSA patients: a randomized, controlled trial. Sleep. 2014;37(11):1863-70.
110. Morawski K, Ghazinouri R, Krumme A, Lauffenburger J, Lee J, Kumar S, et al. Abstract 037: The Accuracy of Self-reported Blood Pressure in the Medication Adherence Improvement Support App for Engagement - Blood Pressure (MedISAFE-BP) Trial. Circulation: Cardiovascular Quality and Outcomes. 2017;10(suppl_3):A037-A.
111. Morawski K, Ghazinouri R, Krumme A, Lauffenburger JC, Lu Z, Durfee E, et al. Association of a Smartphone Application With Medication Adherence and Blood Pressure Control: The MedISAFE-BP Randomized Clinical Trial. JAMA Intern Med. 2018;178(6):802-9.
112. Muralidharan S, Ranjani H, Anjana RM, Gupta Y, Ambekar S, Koppikar V, et al. Change in cardiometabolic risk factors among Asian Indian adults recruited in a mHealth-based diabetes prevention trial. Digit Health. 2021;7:20552076211039032.
113. Murphy A, Farouque O, Clark D, Ramchand J, Yudi M. Suboptimal Secondary Prevention Post Acute Coronary Syndromes: Insights from the SMART-REHAB Trial. Heart, Lung and Circulation. 2019;28:S373-S4.
114. Murphy A, Farouque O, Clark D, Ramchand J, Yudi M. Impact of Gender on Meeting Secondary Prevention Targets and Depression Post Acute Coronary Syndromes: Insights from the SMART-REHAB Trial. Heart, Lung and Circulation. 2019;28:S367.
115. Ni Z, Wu B, Yang Q, Yan LL, Liu C, Shaw RJ. An mHealth Intervention to Improve Medication Adherence and Health Outcomes Among Patients With Coronary Heart Disease: Randomized Controlled Trial. J Med Internet Res. 2022;24(3):e27202.
116. Nicklas JM, Leiferman J, Pyle L, Soares A, Bull S, Tong S, et al. Feasibility of an mhealth postpartum lifestyle intervention for women with cardiometabolic risk pre-and mid-covid: the fit after baby pilot randomized controlled trial. Journal of General Internal Medicine. 2021;36(1):S178.
117. Norton MC, Clark C, Tschanz J, Wengreen H, Fauth EB, Hartin PJ, et al. O3-12-01: Improvements over six months in stress management, diet quality, and moderate physical activity are associated with changes in biomarkers of vascular health and inflammation: The gray matters study. Alzheimer's & Dementia. 2015;11(7S_Part_5):P246-P.
118. Oddsson S. Effects of a gamified mobile application to support a lifestyle-change program in adults: A controlled pilot. Diabetes. 2017;66(Supplement_1):A42.
119. Patel MS, Benjamin EJ, Volpp KG, Fox CS, Small DS, Massaro JM, et al. Effect of a Game-Based Intervention Designed to Enhance Social Incentives to Increase Physical Activity Among Families: The BE FIT Randomized Clinical Trial. JAMA Intern Med. 2017;177(11):1586-93.
120. Payne Riches S, Piernas C, Aveyard P, Sheppard JP, Rayner M, Albury C, et al. A Mobile Health Salt Reduction Intervention for People With Hypertension: Results of a Feasibility Randomized Controlled Trial. JMIR Mhealth Uhealth. 2021;9(10):e26233.
121. Persell SD, Peprah YA, Lipiszko D, Lee JY, Li J, Ciolino JD, et al. Abstract 13403: Home Blood Pressure Monitoring Plus a Mobile Phone-Based Hypertension Health Coaching App or a Blood Pressure Tracking App: A Randomized Controlled Clinical Trial. Circulation. 2019;140(Suppl_1):A13403-A.
122. Petrella RJ, Stuckey MI, Shapiro S, Gill DP. Mobile health, exercise and metabolic risk: a randomized controlled trial. BMC Public Health. 2014;14:1082.
123. Prendergast H, Lara B, Khosla S, Kitsiou S, Del Rios M, Durazo-Arvizu R, et al. Preliminary Data from a Randomized Controlled Trial for a Hypertension Education and Empowerment Intervention (TOUCHED) in an Urban, Academic Emergency Department: Opportunities in the era of COVID-19. Journal of the National Medical Association. 2020;112(5, Supplement):S16-S7.
124. Redfern J, Coorey G, Mulley J, Scaria A, Neubeck L, Hafiz N, et al. A digital health intervention for cardiovascular disease management in primary care (CONNECT) randomized controlled trial. npj Digital Medicine. 2020;3(1):117.

125. Riches SP, Rayner M, Piernas C, Aveyard P, Shepard J, Albury C, et al. Salt Swap: A feasibility randomised controlled trial of a behavioural intervention to reduce salt intake among people with raised blood pressure. Journal of Human Hypertension. 2020;34(1):15-6.
126. Sankaran S, Dendale P, Coninx K. Evaluating the Impact of the HeartHab App on Motivation, Physical Activity, Quality of Life, and Risk Factors of Coronary Artery Disease Patients: Multidisciplinary Crossover Study. JMIR Mhealth Uhealth. 2019;7(4):e10874.
127. Santo K, Singleton A, Rogers K, Thiagalingam A, Chalmers J, Chow C, et al. 1109Medication reminder apps to improve medication adherence in coronary heart disease patients (MedApp-CHD): a randomised clinical trial. European Heart Journal. 2018;39(suppl_1):ehy565.1109.
128. Santo K, Singleton A, Chow CK, Redfern J. Evaluating Reach, Acceptability, Utility, and Engagement with An App-Based Intervention to Improve Medication Adherence in Patients with Coronary Heart Disease in the MedApp-CHD Study: A Mixed-Methods Evaluation. Med Sci (Basel). 2019;7(6).
129. Sarfo F, Treiber F, Gebregziabher M, Adamu S, Patel S, Nichols M, et al. PINGS (Phone-Based Intervention Under Nurse Guidance After Stroke). Stroke. 2018;49(1):236-9.
130. Sarfo FS, Treiber F, Gebregziabher M, Adamu S, Nichols M, Singh A, et al. Phone-based intervention for blood pressure control among Ghanaian stroke survivors: A pilot randomized controlled trial. International Journal of Stroke. 2018;14(6):630-8.
131. Sears LE, Goldner D, Nagra PH, Huddleston B, Hirsch A, Osborn CY, et al. Abstract 9597: One Drop Digital App and Coaching Improves Lifestyle Risks, Glycemic Control and Psychological Well-Being in People With Hypertension and Type 2 Diabetes. Circulation. 2021;144(Suppl_1):A9597-A.
132. Sepulveda J, Pinto R, Roberto I, Chamblas I, Victoriano M, Casanova M, et al. Transmedia psychoeducational program to improve pharmacological adherence to antihypertensive treatment among elderly people. Journal of Hypertension. 2019;37:e224-e5.
133. Sim KA, Del-Olmo M, Li A, Taylor S, Cunich M, Caterson ID. A smartphone application for medication adherence in patients with obesity-related chronic conditions. Obesity Reviews. 2020;21(S1):86.
134. Sit JWH, Chair S-Y, Hui SSC, Choi K-C, Chan AWK, Wong EML, et al. A smartphone-based exercise adherence intervention for people with metabolic syndrome: a feasibility pilot study. The Lancet. 2016;388:S64.
135. Song Y, Ren C, Liu P, Tao L, Zhao W, Gao W. Effect of Smartphone-Based Telemonitored Exercise Rehabilitation among Patients with Coronary Heart Disease. J Cardiovasc Transl Res. 2020;13(4):659-67.
136. Sowell K, Williams-Brown C, Kim K, Henderson G. Impact of Weight Matters and Use of App-Based Technology on Changes in Eating Behavior in African Americans. Curr Dev Nutr. 2021;5(Suppl 2):183.
137. Steinberg DM, Kay MC, Svetkey LP, Askew S, Christy J, Burroughs J, et al. Feasibility of a Digital Health Intervention to Improve Diet Quality Among Women With High Blood Pressure: Randomized Controlled Feasibility Trial. JMIR Mhealth Uhealth. 2020;8(12):e17536.
138. Still CH, Margevicius S, Harwell C, Huang MC, Martin L, Dang PB, et al. A Community and Technology-Based Approach for Hypertension Self-Management (COACHMAN) to Improve Blood Pressure Control in African Americans: Results from a Pilot Study. Patient Prefer Adherence. 2020;14:2301-13.
139. Stuckey MI, Gill DP, Sabourin KJ, Shapiro S, Hubbard RA, Petrella RJ. Health Supported Exercise Intervention in Patients With Metabolic Syndrome: A Randomized Clinical Trial. Diabetes. 2013;62(Supplement_1):A629.
140. Stuckey MI, Gill DP, Shapiro S, Sabourin KJ, Petrella RJ. Abstract 17897: Does Prescriptive Exercise With Mobile Health Tracking Improve Self-efficacy and Health Status in Individuals With Metabolic Syndrome? Circulation. 2013;128(suppl_22):A17897-A.
141. Stuckey MI, Gill DP, Shapiro S, Sabourin K, Petrella RJ. Abstract 14062: Does a Prescriptive Exercise Program With Mobile Health Tracking Improve Cardio-Metabolic Risk Factors to a Greater Extent than Exercise Prescription Alone? Circulation. 2013;128(suppl_22):A14062-A.
142. Su MC, Chao AS, Chang MY, Chang YL, Chen CL, Sun JC. Effectiveness of a Nurse-Led Web-Based Health Management in Preventing Women With Gestational Diabetes From Developing Metabolic Syndrome. J Nurs Res. 2021;29(6):e176.
143. Sunil Kumar D, Prakash B, Subhash Chandra BJ, Kadkol PS, Arun V, Thomas JJ. An android smartphone-based randomized intervention improves the quality of life in patients with type 2 diabetes in Mysore, Karnataka, India. Diabetes Metab Syndr. 2020;14(5):1327-32.
144. Thatthong N, Sranacharoenpong K, Praditsorn P, Churak P, Ponprachanuvut P, Srisangwan N, et al. Innovative tool for health promotion for at-risk Thai people with hypertension. Journal of Public Health. 2020;28(4):437-43.
145. Thurston MM, Nguyen S, Troung C, McKinley D, Akil A, Manigault K, et al. Assessing the use of a novel mobile application to improve blood pressure and medication adherence in patients the hypertension. JACCP: Journal of the American College of Clinical Pharmacy. 2020;3(1):149.
146. Tian M, Ajay VS, Dunzhu D, Hameed SS, Li X, Liu Z, et al. A Cluster-Randomized, Controlled Trial of a Simplified Multifaceted Management Program for Individuals at High Cardiovascular Risk (SimCard Trial) in Rural Tibet, China, and Haryana, India. Circulation. 2015;132(9):815-24.
147. Torkabad SM, Bonabi TN, Heidari S. Effectiveness of smartphone-based medication reminder application on medication adherence of patients with essential hypertension: A clinical trial study. J Nurs Midwifery Sci. 2023;7(4):e140768.
148. Toro-Ramos T, Lee DH, Kim Y, Michaelides A, Oh TJ, Kim KM, et al. Effectiveness of a Smartphone Application for the Management of Metabolic Syndrome Components Focusing on Weight Loss: A Preliminary Study. Metab Syndr Relat Disord. 2017;15(9):465-73.

149. Treskes RW, van Winden LAM, van Keulen N, van der Velde ET, Beeres S, Atsma DE, et al. Effect of Smartphone-Enabled Health Monitoring Devices vs Regular Follow-up on Blood Pressure Control Among Patients After Myocardial Infarction: A Randomized Clinical Trial. JAMA Netw Open. 2020;3(4):e202165.
150. Van Horn L, Peaceman A, Kwasny M, Vincent E, Fought A, Josefson J, et al. Dietary Approaches to Stop Hypertension Diet and Activity to Limit Gestational Weight: Maternal Offspring Metabolics Family Intervention Trial, a Technology Enhanced Randomized Trial. Am J Prev Med. 2018;55(5):603-14.
151. Widmer RJ, Allison TG, Lennon R, Lopez-Jimenez F, Lerman LO, Lerman A. Digital health intervention during cardiac rehabilitation: A randomized controlled trial. American Heart Journal. 2017;188:65-72.
152. Wungrath J, Khumai N, Sutan P. The Effect of Nutritional Education Using Line Application in Conjunction with Tele-Counseling on Nutritional Knowledge and Behavior Among the Elderly with Chronic Diseases. International Journal of Pharmaceutical Research. 2021;13(1):5805-12.
153. Yadav S, Sethi R, Pradhan A, Vishwakarma P, Bhandari M, Gattani R, et al. 'Routine' versus 'Smart Phone Application Based – Intense' follow up of patients with acute coronary syndrome undergoing percutaneous coronary intervention: Impact on clinical outcomes and patient satisfaction. IJC Heart & Vasculature. 2021;35:100832.
154. Yan LL, Gong E, Gu W, Turner EL, Gallis JA, Zhou Y, et al. Effectiveness of a primary care-based integrated mobile health intervention for stroke management in rural China (SINEMA): A cluster-randomized controlled trial. PLOS Medicine. 2021;18(4):e1003582.
155. Yang P, Lo W, He ZL, Xiao XM. Medical nutrition treatment of women with gestational diabetes mellitus by a telemedicine system based on smartphones. J Obstet Gynaecol Res. 2018;44(7):1228-34.
156. Yudi M, Clark D, Tsang D, Jelinek M, Kalten K, Joshi S, et al. SMARTphone-based, Early Cardiac REHABilitation in Patients with Acute Coronary Syndromes [SMART-REHAB Trial]: A Randomised Controlled Trial. Heart, Lung and Circulation. 2017;26:S349.
157. Zhang X, Liao H, Shi D, Li X, Chen X, He S. Cost-effectiveness analysis of different hypertension management strategies in a community setting. Intern Emerg Med. 2020;15(2):241-50.
158. Zhai Y, Yu W. A Mobile App for Diabetes Management: Impact on Self-Efficacy Among Patients with Type 2 Diabetes at a Community Hospital. Med Sci Monit. 2020;26:e926719.

Appendix D

Supplementary material for Chapter 6

Supplementary material for Chapter 6

Multimedia Appendix 1

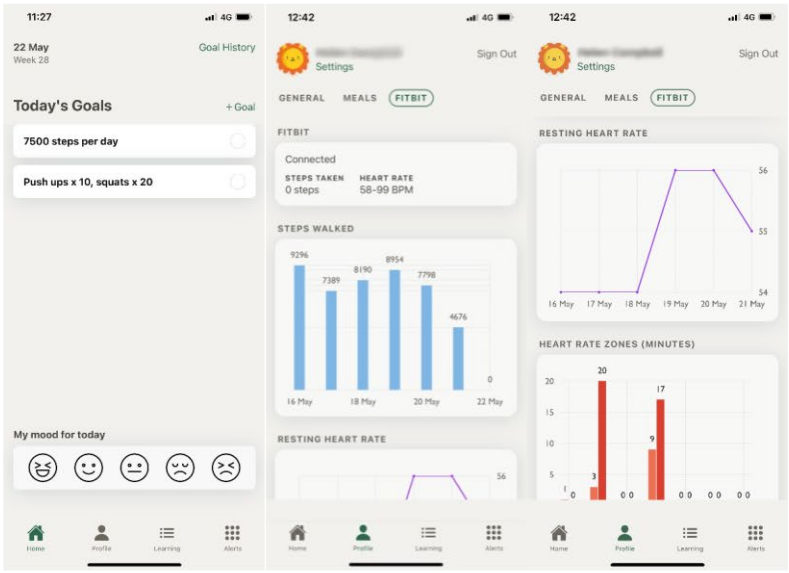
```
/* Amplify Params - DO NOT EDIT
        API_MIRTH_GRAPHQLAPIIDOUTPUT
        API_MIRTH_NOTIFICATIONTABLE_ARN
        API_MIRTH_NOTIFICATIONTABLE_NAME
        API_MIRTH_USERTABLE_ARN
        API_MIRTH_USERTABLE_NAME
        ENV
        REGION
Amplify Params - DO NOT EDIT */
const AWS = require('aws-sdk');
const { Expo } = require('expo-server-sdk');
const uuid = require('uuid');
const docClient = new AWS.DynamoDB.DocumentClient();
const expo = new Expo();
async function handler(_event) {
  const { Items } = await docClient
    .scan({
      TableName: process.env.API_MIRTH_USERTABLE_NAME,
    })
    .promise();
  const users = Items ?? [];
  const dbNotifs = [];
  const messages = [];
  const today = new Date();
  for (const user of users) {
    const { expoPushToken } = user;
    // Is valid Expo token?
    if (!expoPushToken || !Expo.isExpoPushToken(expoPushToken)) {
      continue;
    }
    const createdAtDate = new Date(user.createdAt);
    const start = new Date(createdAtDate);
    start.setMonth(createdAtDate.getMonth() + 3);
    const end = new Date(createdAtDate);
    end.setMonth(createdAtDate.getMonth() + 6);
    const isWithinInterval = today > start && today < end;
    // Some probability that user gets a message
    if (isWithinInterval && Math.random() < 0.2) {
      const message = getRandomMessage(bankMessages);
      const createdAt = new Date().toISOString();
      dbNotifs.push({
        PutRequest: {
          Item: {
            id: uuid.v4(),
            __typename: 'Notification',
            body: message,
            target: user.id,
            key: 'KEY',
            createdAt,
            updatedAt: createdAt,
          },
        },
      });
      messages.push({
        to: expoPushToken,
        priority: 'high',
        sound: 'default',
        body: message,
        data: { message },
      });
    }
  }
  if (dbNotifs.length < 1 && messages.length < 1) {
    return true;
  }
  await docClient
    .batchWrite({
      RequestItems: {
        [process.env.API_MIRTH_NOTIFICATIONTABLE_NAME]: dbNotifs,
      },
    })
    .promise();
  // TODO: remove
  // console.log(messages.map(m => ({ to: m.to, body: m.body })));
  const chunks = expo.chunkPushNotifications(messages);
  const tickets = [];
  for (const chunk of chunks) {
    try {
      const ticketChunk = await expo.sendPushNotificationsAsync(chunk);
      tickets.push(...ticketChunk);
    } catch (error) {
      console.error(error);
      console.error(error.details);
    }
  }
  const receiptIds = [];
  for (const ticket of tickets) {
    if (ticket.id) {
      receiptIds.push(ticket.id);
    }
  }
  const receiptIdChunks = expo.chunkPushNotificationReceiptIds(receiptIds);
  for (const chunk of receiptIdChunks) {
    try {
      const receipts = await expo.getPushNotificationReceiptsAsync(chunk);
      for (const receiptId in receipts) {
        let { status, message, details } = receipts[receiptId];
```

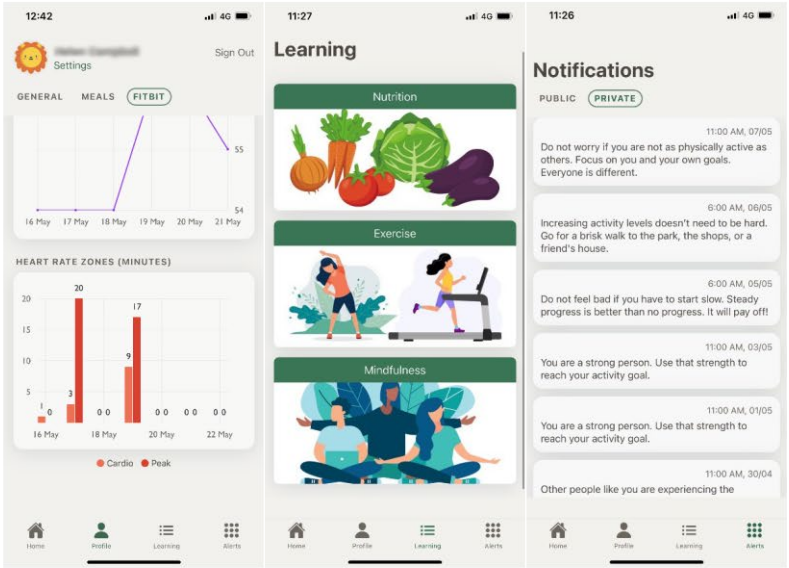
Supplementary material for Chapter 6

```
      if (status === 'ok') {
        continue;
      } else if (status === 'error') {
        console.error(`There was an error sending a notification: ${message}`);
        // https://docs.expo.io/guides/push-notifications/?redirected#errors
        if (details && details.error) {
          console.error(`The error code is ${details.error}`);
          // Remove Expo token if device can no longer receive notifications
          if (details.error === 'DeviceNotRegistered') {
            await docClient
              .update({
                TableName: process.env.API_MIRTH_USERTABLE_NAME,
                Key: { id: userId },
                UpdateExpression: 'REMOVE expoPushToken',
              })
              .promise();
          }
        }
      }
    }
  } catch (error) {
    console.error(error);
  }
}
return true;
}
exports.handler = handler;
function getRandomMessage(arr) {
  return arr[Math.floor(Math.random() * arr.length)];
}
const bankMessages = [
  'Exercise gives you endorphins. Endorphins make you happy. Be happy!',
  'Exercising can improve your mood, make you more focused and make you feel stronger mentally.',
  'Going on a long walk can help you to reduce your stress. Give it a try, see how you feel.',
  'Walking can help you to lose weight, improve your blood sugar, and protect your heart.',
  'Going for a quick walk today can make you feel more energetic.',
  'Walking can improve your mood and clear your mind.',
  'Regular walking can have long term benefits for your health. Why not walk towards feeling your best?',
  'Managing your mild body aches can be hard. Being active can help.',
  'Being more active and keeping fit sets a good example to your loved ones.',
  'Your loved ones will be proud to see the positive changes in your health over time.',
  'Do not feel bad if you have to start slow. Steady progress is better than no progress. It will pay off!',
  'Walking increases your fitness and your chances of living longer.',
  'Physical activity is a great way to feel better overall, improve your health, and lift your mood. Aim for at least 30 minutes of walking each day at a medium pace to see
the benefits.',
  'Taking part in healthy activities with others can make you feel great. The more you do, the more you will be capable of!',
  'Is something making exercise hard for you? If so, what could you do to overcome the obstacles?',
  'Haven't been active before? Don't let that hold you back. Start today and feel a sense of achievement!',
  'Have you made changes to improve your health before? How did you do it? You can do it again!',
  'You are a strong person. Use that strength to reach your activity goal.',
  'Do not feel bad if you have to start slow. Steady progress is better than no progress. It will pay off!',
  'Keep working towards your activity goals. You will get there!',
  'You can inspire others by being active yourself.',
  'Others will see the changes you are making for your health.',
  'Do not worry if you are not as physically active as others. Focus on you and your own goals. Everyone is different.',
  'Don't feel like being active? Think of those cheering you on a make them proud!',
  'Other people like you are experiencing the benefits of being active. You could too!',
  'Increasing your activity levels is good for you and those around you!',
  'When feeling down you may not feel like being active. But being active will lift your mood. Give it a go!',
  "There will be times when you do not meet your goals. That's ok, just keep moving forward. It is important not to give up.",
  'Can you find 30 minutes in your day to go for a walk? That is less time than it takes to watch one episode of a TV show.',
  'Try planning out easier ways to be more active. This could be getting off the bus a few stops early.',
  'Exercise isn't just for the gym. How could you be more active around your home, neighbourhood, or workplace?',
  'Place some comfortable shoes in a place that will prompt you to head out for a walk. Imagine the benefits it could bring!',
  'Could you pair up walking with doing errands or work? Maybe try walking while on a phone call.',
  'Try not to sit for more than 30 minutes at a time. Get up and walk around your home for a few minutes. It will benefit your health.',
  'Increasing activity levels doesn't need to be hard. Go for a brisk walk to the park, the shops, or a friend's house.',
  'Being active doesn't need to be expensive. A pair of comfortable shoes and a bottle of water is all it takes!',
  'Involve your loved ones in your activities. You can all benefit!',
  'Invite a friend or family member to go on a walk with you. Use this active time to catch up.',
  'Can a friend or family member help you to reach your goal? Identify someone who can nudge you to be more active.',
  'Why not ask your loved ones for support to be more active? Their encouragement can help you progress that little bit further',
  'Could you use walking as a way to visit new places or parks with your friends or family?',
  'Most people spend too much time sitting and not enough time moving around. Could today be a more active day for you? Give it a try.',
  'It can be difficult to find the time to exercise. What could you change to reach your activity goals?',
  'Having good support is the best way to reach your goals and manage your health. Look for people who give you support, advice, and companionship.',
];
```

Supplementary material for Chapter 6

Multimedia Appendix 2





Supplementary material for Chapter 6

Multimedia Appendix 3

MIRTH messages	BCT used	Targeting	
		Motivation	Volition
Exercise gives you endorphins. Endorphins make you happy. Be happy!	Information about health consequences	X	
Exercising can improve your mood, make you more focussed and make you feel stronger mentally.	Information about health consequences	X	
Going on a long walk can help you to reduce your stress. Give it a try, see how you feel	Information about health consequences	X	
Walking can help you to lose weight, improve your blood sugar, and protect your heart	Information about health consequences	X	
Going for a quick walk today can make you feel more energetic.	Information about health consequences	X	
Walking can improve your mood and clear your mind.	Information about health consequences	X	
Regular walking can have long term benefits for your health. Why not walk towards feeling your best?	Information about health consequences	X	
Managing your mild body aches can be hard. Being active can help	Information about health consequences	X	
Being more active and keeping fit sets a good example to your loved ones	Identify as self as a role model	X	
Your loved ones will be proud to see the positive changes in your health over time.	Social support unspecified		X
Do not feel bad if you have to start slow. Steady progress is better than no progress. It will pay off!	Information about health consequences	X	X
Walking increases your fitness and your chances of living longer	Information about health consequences	X	
Physical activity is a great way to feel better overall, improve your health, and lift your mood. Aim for at least 30 minutes of walking each day at a medium pace to see the benefits	Goal setting behaviour	X	X
Taking part in healthy activities with others can make you feel great. The more you do, the more you will be capable of!	Social support unspecified	X	X
Is something making exercise hard for you? If so, what could you do to overcome the obstacles?	Problem solving		X
Haven't been active before? Don't let that hold you back. Start today and feel a sense of achievement!	Information about emotional consequences	X	
Have you made changes to improve your health before? How did you do it? You can do it again!	Problem solving	X	
You are a strong person. Use that strength to reach your activity goal.	Information about emotional consequences		X
Do not feel bad if you have to start slow. Steady progress is better than no progress. It will pay off!	Information about health consequences	X	
Keep working towards your activity goals. You will get there!	Prompts/Cues		X
You can inspire others by being active yourself	Identify as self as a role model	X	
Others will see the changes you are making for your health	Information about others' approval		X
Do not worry if you are not as physically active as others. Focus on you and your own goals. Everyone is different			X
Don't feel like being active? Think of those cheering you on a make them proud!	Social support unspecified		X
Other people like you are experiencing the benefits of being active. You could too!	Information about others' approval	X	
Increasing your activity levels is good for you and those around you!	Information about health consequences	X	
When feeling down you may not feel like being active. But being active will lift your mood. Give it a go!	Prompts/Cues		X
There will be times when you do not meet your goals. That's ok, just keep moving forward. It is important not to give up.	Prompts/Cues		X
Can you find 30 minutes in your day to go for a walk? That is less time than it takes to watch one episode of a TV show.	Goal setting behaviour		X
Try planning out easier ways to be more active. This could be getting off the bus a few stops early.	Goal setting behaviour	X	
Exercise isnt just for the gym. How could you be more active around your home, neighbourhood, or workplace?	Prompts/Cues	X	
Place some comfortable shoes in a place that will prompt you to head out for a walk. Imagine the benefits it could bring!	Adding objects to the environment	X	X
Could you pair up walking with doing errands or work? Maybe try walking while on a phone call..	Problem solving	X	X
Try not to sit for more than 30 minutes at a time. Get up and walk around your home for a few minutes. It will benefit your health.	Goal setting behaviour		X
Increasing activity levels doesn't need to be hard. Go for a brisk walk to the park, the shops, or a friend's house.	Prompts/Cues	X	
Being active doesn't need to be expensive. A pair of comfortable shoes and a bottle of water is all it takes!	Problem solving	X	
Involve your loved ones in your activities. You can all benefit!	Social support unspecified	X	X
Invite a friend or family member to go on a walk with you. Use this active time to catch up..	Social support unspecified	X	X
Can a friend or family member help you to reach your goal? Identify someone who can nudge you to be more active.	Social support unspecified	X	
Why not ask your loved ones for support to be more active? Their encouragement can help you progress that little bit further	Social support unspecified	X	
Could you use walking as a way to visit new places or parks with your friends or family?	Social support unspecified	X	
Most people spend too much time sitting and not enough time moving around. Could today be a more active day for you? Give it a try.	Prompts/Cues	X	
It can be difficult to find the time to exercise. What could you change to reach your activity goals?	Problem solving		X
Having good support is the best way to reach your goals and manage your health. Look for people who give you support, advice, and companionship.	Social support unspecified	X	

Multimedia Appendix 4

Table 1. Sample size calculations (Liao et al. 2016)[1] from the R-shiny app.[2]

Duration of study:	90 days
Number of Decision Time Points per Day:	1
Constant Randomization Probability:	0.5
Expected Availability:	Constant
Average of Expected Availability:	0.8
Proximal Treatment Effect:	Quadratic
Average of Proximal Treatment Effect:	0.1
Day of Maximal Proximal Treatment Effect:	45
Initial value of Proximal Treatment Effect:	0.02
Desired Power:	0.8
Significance Level:	0.05
Required sample size:	58

References

1. Liao P, Klasnja P, Tewari A, Murphy SA. Sample size calculations for micro-randomized trials in mHealth. Stat Med. 2016;35(12):1944-71.
2. Seewald NJ, Sun J, Liao P. MRT-SS calculator: An R Shiny application for sample size calculation in micro-randomized trials 2016 [Available from: https://pengliao.shinyapps.io/mrt-calculator/.

Appendix E
Supplementary material for Chapter 7

Supplementary Table of Contents for Chapter 7

Supplementary Table 7.1 Laboratory studies (biochemistry and haematology)

Test	Unit	Baseline	Month 6
Glucometer Glucose Level	mmol/L	5.30	4.90
White Cell Count	$\times 10^9$/L	4.20	5.60
Haemoglobin Concentration	g/L	133.00	136.00
Platelet Count	$\times 10^9$/L	183.00	189.00
Packed Cell Volume	L/L	0.41	0.41
Mean Corpuscular Volume	fL	93.00	92.00
Red Cell Count	$\times 10^{12}$/L	4.42	4.45
Mean Corpuscular Haemoglobin	pg	30.20	30.50
Gamma GT (Liver Function Test)	U/L	21.00	36.00
ALT (Liver Function Test)	U/L	34.00	60.00
AST (Liver Function Test)	U/L	29.00	41.00
Urate Level	mmol/L	0.24	0.26
Total Cholesterol	mmol/L	3.50	3.40
Triglycerides	mmol/L	1.10	0.60
HDL Cholesterol	mmol/L	1.56	1.94
LDL Cholesterol	mmol/L	1.40	1.20
Non-HDL Cholesterol	mmol/L	1.90	1.50
Total to HDL Cholesterol Ratio	-	2.20	1.80

Supplementary Table 7.2 Dietary assessment

Category	Unit	Baseline	Month 6
Total Consumption	grams	1296.53	1503.90
Protein	grams	66.72	70.06
Total Fats	grams	71.54	56.84
Saturated Fats	grams	29.15	24.17
Trans Fatty Acids	grams	1.03	0.88
Polyunsaturated Fats	grams	7.18	7.50
Monounsaturated Fats	grams	17.95	17.45
Available Carbohydrates	grams	84.84	87.75
Sugars	grams	29.23	31.01
Added Sugars	grams	7.71	2.83
Free Sugars	grams	7.71	2.83
Starch	grams	54.98	55.85
Water Consumption	grams	1413.66	1184.85
Alcohol Intake	grams	6.74	0.054
Dietary Fibre	grams	18.08	7.85
Ash Content	grams	8.88	10.65
Cholesterol Intake	mg	390.04	316.22

Supplementary Table 7.3 Mineral intake

Mineral & macronutrients	Unit	Baseline	Month 6
Sodium	mg	1415.24	1605.20
Potassium	mg	1799.71	2367.65
Magnesium	mg	232.74	204.73
Calcium	mg	300.96	699.38
Phosphorus	mg	823.94	1044.17
Iron	mg	7.02	4.63
Zinc	mg	7.89	5.07
Selenium	µg	59.79	74.05
Iodine	µg	109.75	115.95
Protein Energy Distribution	%	21.02	24.66
Fat Energy Distribution	%	49.05	43.54
- Saturated Fats	%	19.98	18.51
- Trans Fats	%	0.70	0.67
- Monounsaturated Fats	%	33.08	35.52
- Polyunsaturated Fats	%	13.23	15.27
Carbohydrate Energy Distribution	%	25.98	29.93
Alcohol Energy Distribution	%	3.62	0.032
Dietary Fibre Energy Distribution	%	2.68	1.30
Very Long-Chain n-3 Fatty Acids	grams	0.55	2.29
Linoleic Acid	grams	5.077	4.02
Alpha-Linolenic Acid	grams	5.31	0.51
Eicosapentaenoic Acid (EPA)	grams	0.16	0.81
Docosapentaenoic Acid (DPA)	grams	0.11	0.38
Docosahexaenoic Acid (DHA)	grams	0.28	1.10
Tryptophan	grams	0.63	0.73

Supplementary Table 7.4 Vitamin intake

Vitamin	Unit	Baseline	Month 6
Thiamine	mg	0.90	0.43
Riboflavin	mg	0.82	1.10
Niacin	mg	13.11	15.16
Niacin Equivalents	mg	24.78	27.77
Vitamin C	mg	21.85	47.34
Vitamin E	mg	10.20	8.57
- Tocopherol Alpha	mg	8.27	7.55
Vitamin B6	mg	0.71	1.04
Vitamin B12	µg	2.99	5.74
Total Folate	µg	285.89	258.46
- Folate Total DFE	µg	362.49	286.15
- Folic Acid	µg	114.76	41.25
- Folate from Food	µg	171.12	217.21
Total Vitamin A Equivalents	µg	601.37	289.94
- Retinol	µg	128.97	97.14
- Beta-Carotene Equivalents	µg	2837.31	1155.99
- Beta-Carotene from Food	µg	1474.90	960.78

Supplementary Table 7.5 Food groups and energy

Food Group	Intake		Details
	Baseline	**Month 6**	
Grain Consumption	3.0 servings	2.3 servings	Whole grain ratio: 9.60% at baseline and 9.94% at month 6.
Fruits	0.13 servings	0.31 servings	All from citrus, melons, and berries
Vegetables	1.9 servings	1.8 servings	Starchy vegetables: 3.91% at baseline and 14.43% of total at month 6.
Protein Foods	2.7 servings	1.8 servings	Eggs, high and low omega-3 seafood
Dairy	0.35 servings	1.8 servings	Milk and cheese
Oil and Fat Consumption	9.3 teaspoons	5.9 teaspoons	Oil equivalents
	6.5 teaspoons	5.6 teaspoons	Solid fat equivalents
Added Sugars	1.8 teaspoons	0.8 teaspoons	123.35 kJ at baseline and 52.74 kJ at month 6.
Caffeine Intake	207.70 mg	277.61 mg	-

Textbox 1 Data dictionary

Time 1 = 6 am

Time 2 = 11 am

Time 3 = 3 pm

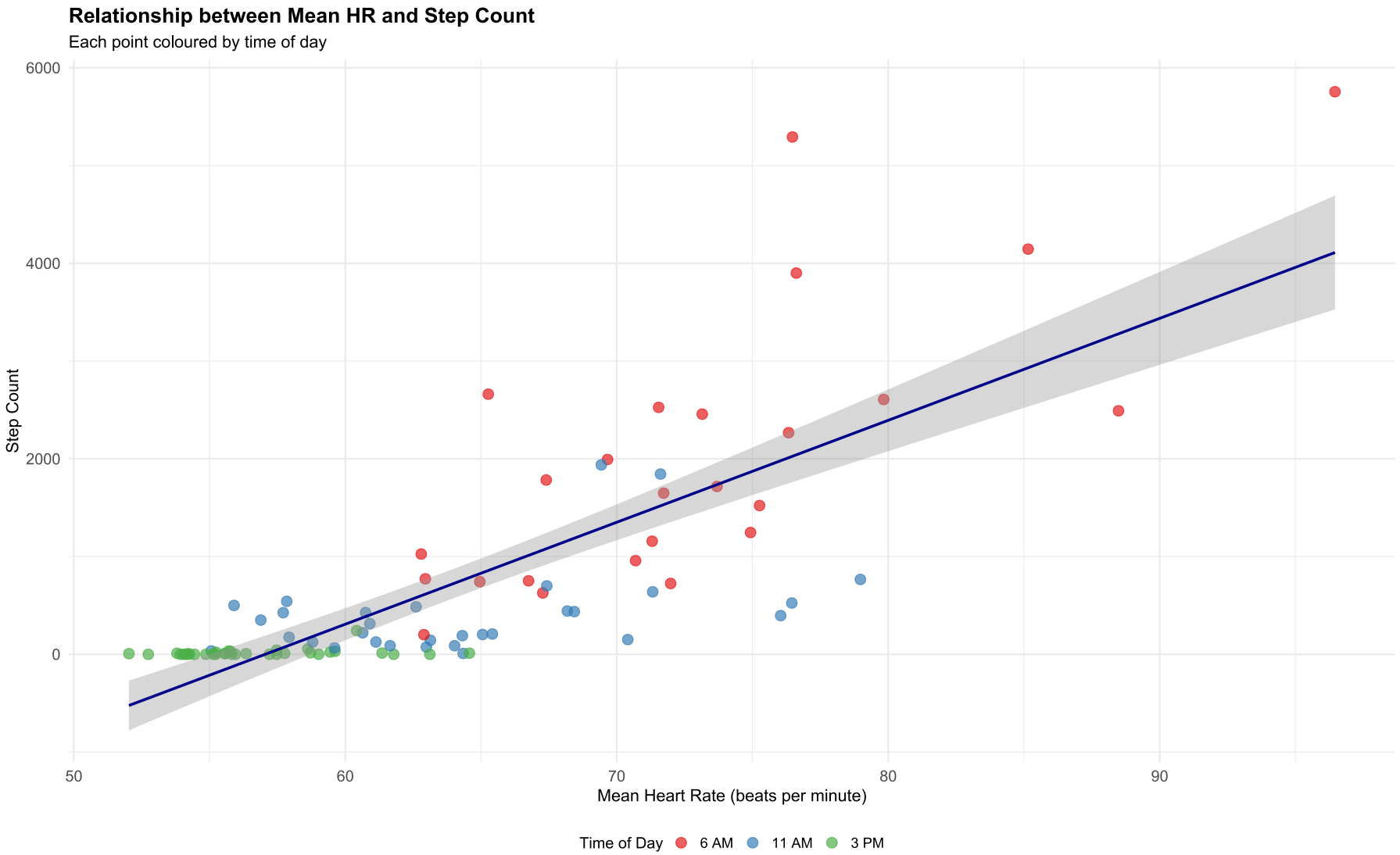
Message 1 = intervention received

Message 0 = intervention NOT received

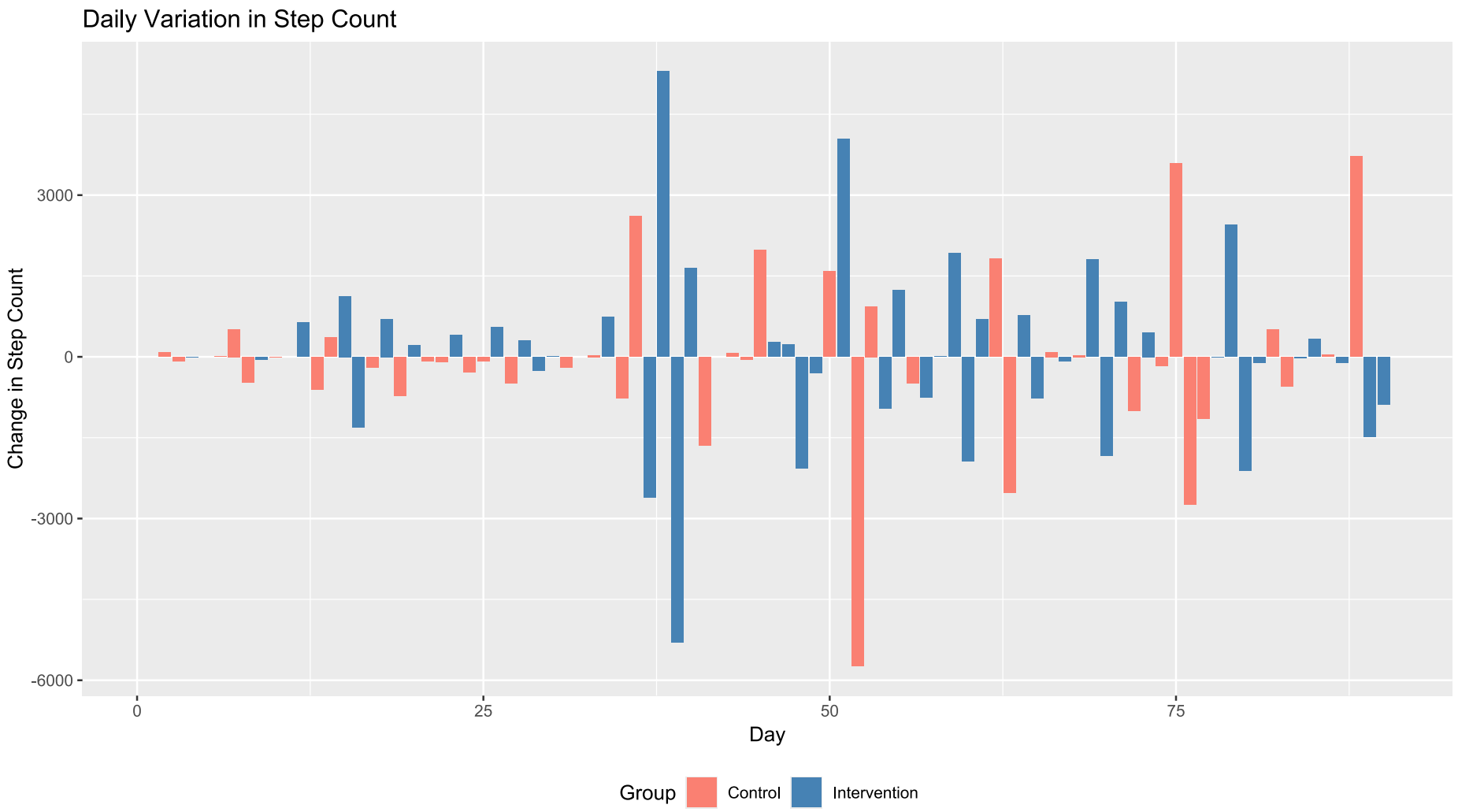
Step count = number of steps taken in the 180 minutes following the intervention.

Mean heart rate = average heart rate (beats per minute) in the 180 minutes following the intervention.

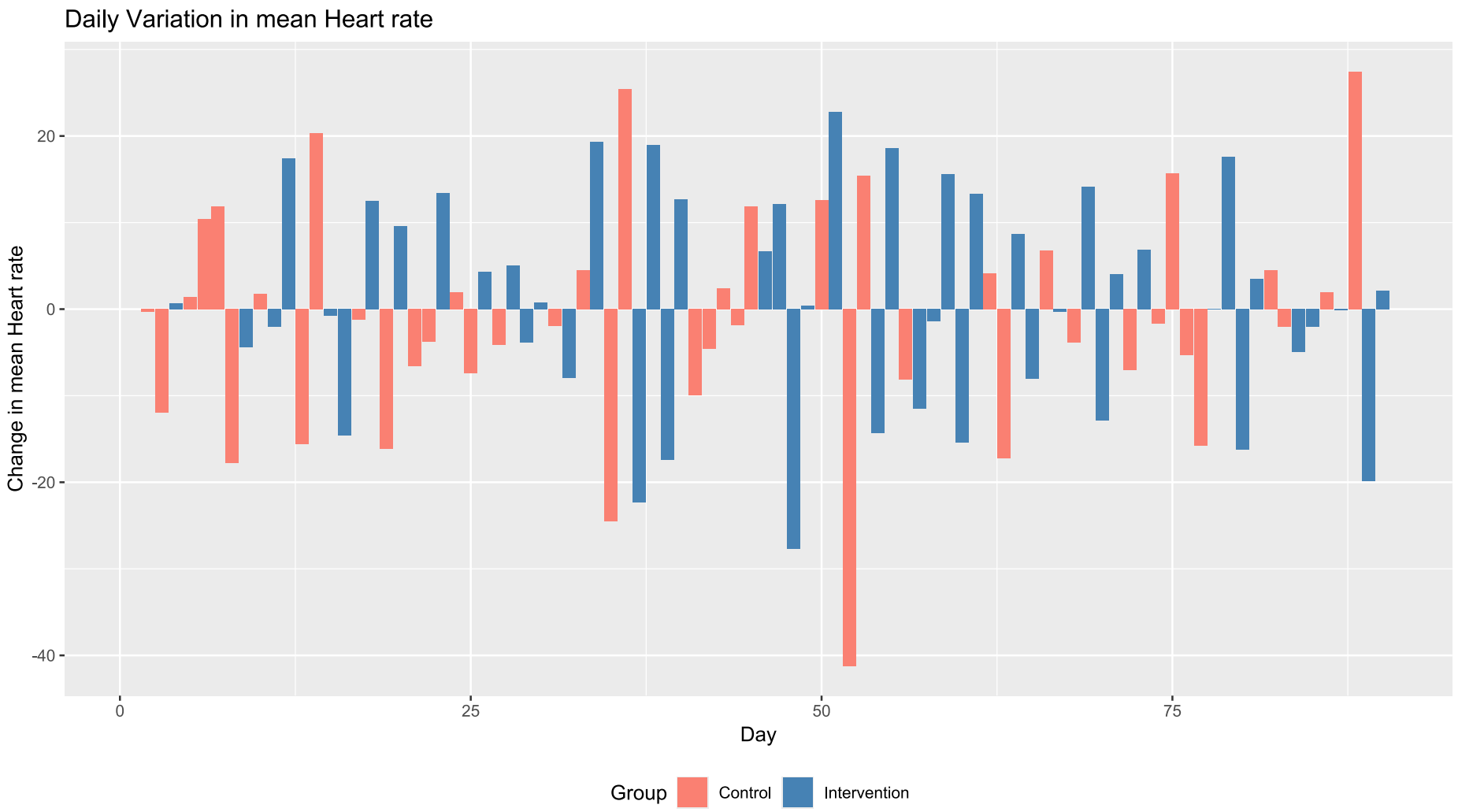
Sex 1 = female



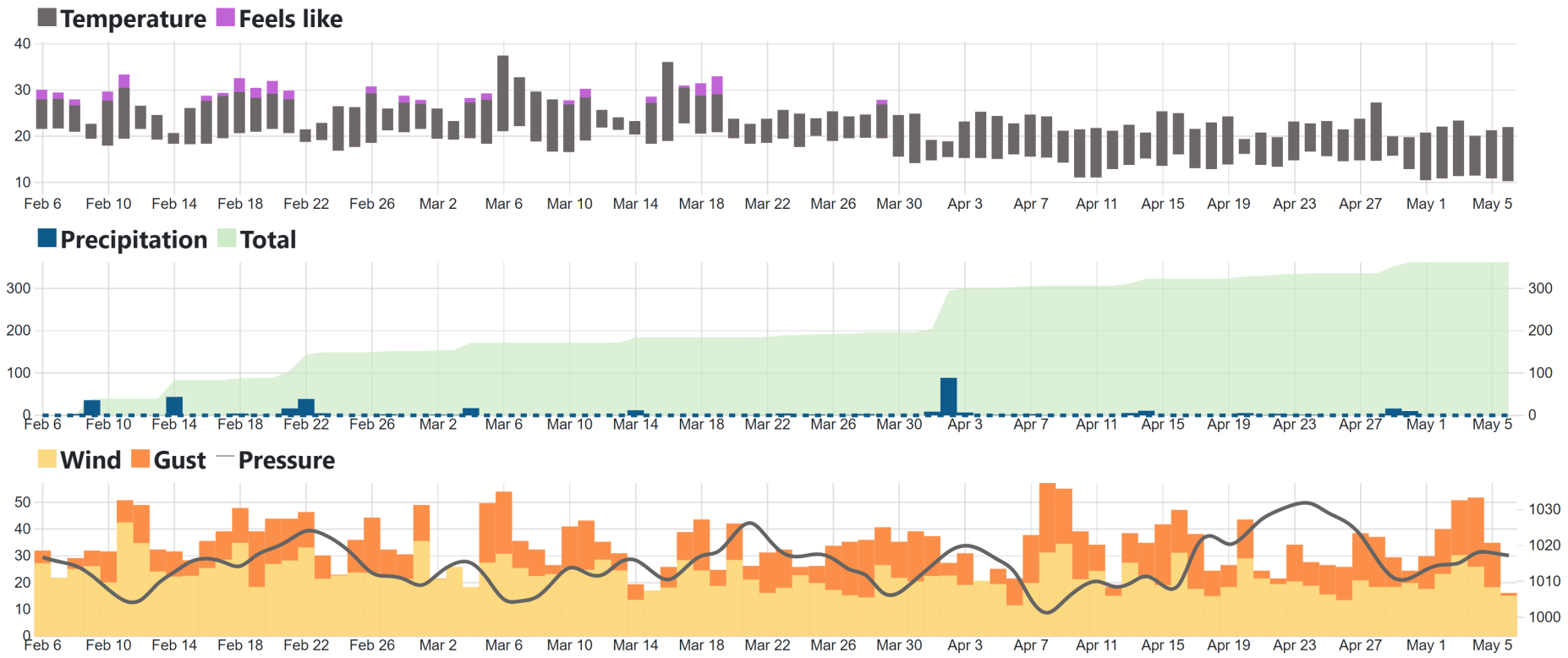
Supplementary Figure 7.1 Relationship between mean heart rate and step count.



Supplementary Figure 7.2 Change in step count over the study period of 90 days.



Supplementary Figure 7.3 Change in mean heart rate over the study period of 90 days.



Supplementary Figure 7.4 Daily weather conditions during the study period. Data from Weather Query Builder by Visual Crossing Corporation.[426]

Appendix F
PICF for LIVEPLUS

Central Clinical School
Faculty of Medicine and Health

Participant Information Sheet/Consent Form

Charles Perkins Centre, University of Sydney

Title	A randomised controlled trial to evaluate an intensive lifestyle program for reversal of coronary heart disease
Short Title	Lifestyle VulnErable PLaqUe Study (LIVEPLUS)
Protocol Number	7.0
Project Sponsor	The University of Sydney
Principal Investigator	Professor Luigi Fontana
Associate Investigator(s)	Professors Ian Wilcox, Martin Ugander, Peter Cistulli, Ian Caterson, Michael Skilton, Jacob George; A/Prof Serigne Lo, Samantha Hocking, Laura Piccio, Jinman Kim; Drs Imre Hunyor, Kirby Wong, Michele McGrady, Jessica Yang, Na Liu, Sophie Cassidy, Cynthia Kroeger, Sayan Mitra, Robin Hairong Huang, Rosie Ribeiro, Rebecca Kozor, Lynn Khor, Tian Wang, Andrius Masedunskas, Leah Avery, Angelo Sabag, Jing Xu, David Hutchinson, Isabella de Ciutiis, Juan Joseph
Location	Royal Prince Alfred Hospital and Charles Perkins Centre

Part 1 What does my participation involve?

Introduction

You are invited to take part in this research project. This is because you have a diagnosis of Coronary Heart Disease (CHD). The research project is testing a new lifestyle treatment for CHD. This new treatment is called 'Intense Lifestyle Program' (ILP).

Professor Fontana, the lead investigator, has previously shown that following a healthy lifestyle can improve multiple cardiometabolic risk factors. However, we do not know yet, if this translates in functional and structural improvements of the heart in individuals with CHD. This study is designed to determine the effects of a comprehensive ILP on physiology, metabolism, body composition, and progression of CHD by state-of-the-art imaging techniques.

The study is being funded by a grant from the Australian Youth and Health Foundation.

What does participation in this research involve?

If you agree to participate in this study, you will be asked to sign the Participant Consent Form. You will then be requested to visit our lab for clinical testing, as well as follow a lifestyle programme for 12 months.
At the beginning, you will be required to complete a baseline testing period prior to study randomization. After the completion of the baseline period, you will be randomly assigned to one of two groups for the next 12 months. By "random", we mean that neither you nor any of the study staff

members can select the group you will be in. Using a procedure, like flipping a coin, a computer program assigns you to one of the groups. You will keep this group assignment for the remainder of the study.

1-ILP and optimal medical therapy (OMT) group: If you are assigned to this group you will be asked to eat a pesco-vegetarian diet, with fasting on 2 days of the week. To help with this you will be provided with fresh ingredients and recipes for the first month after your assignment. During the remaining 11 months in the study, you will make your own food selections and prepare your own meals at home but will receive either online or face-to-face appointments with your dietician every 2 weeks for the first 3 months and monthly thereafter. You will also be given a Fitbit physical activity tracker, exercise advice from an exercise physiologist, and mindfulness/yoga training. You will be asked to download and use a phone app which will help us track your progress. Once you have completed the 12 months you won't have access to the ILP appointments and support. You have one in two chances to be assigned to this group

2-Group two: Group two will be the 'OMT' group. If you are assigned to this group you will be offered an online appointment or face-to-face consultation with a dietician at 0,3,6,9, months to guide you through a healthy diet according to the American Heart Association guidelines, but no food will be provided. You will also be given a Fitbit physical activity monitor to track your physical activity and sleep patterns. At the end of the 12 months you will also be offered a mindfulness/yoga programme. You have one in two chances to be assigned to this group.

Whatever group you are in, you should agree to avoid taking any new non-prescription medications, vitamins or nutritional supplements during the study without informing the study physician and agree to inform the study personnel of any changes in any medications prescribed by a personal physician.

Pre-screening video call

Before the baseline testing period, the research team will organise a video call to explain details of the study which will also be an opportunity for you to ask any questions and talk through any uncertainties you may have. This is a good chance to meet the research team and work out if this study is right for you. If you are interested in taking part, the research team will organise your first clinic visit. This video call will be recorded.

Clinical testing

As a participant in this study, you will be requested to undergo a combination of imaging and clinical tests. These will be predominantly conducted at our institute which is located at the Charles Perkins Centre Royal Prince Alfred clinic (CPC-RPA clinic), University of Sydney. In most cases you will be asked not to eat or drink anything except water from 10 pm the night before each visit.

1- Baseline visits:

Below are the number examinations which we will carry out during your baseline visits. We will most likely spread these assessments over 2 days, but we can fit around your schedule and be flexible with the times and days.

- **Consent (30 minutes):** Before consent is taken, you will have an opportunity to ask any questions and talk through any uncertainties you may have. If you are happy to proceed with the study, you will be asked to sign a consent form on a computer saying that you would like to take part in the research study.

- **Physical examination and medical history (30 minutes):** We will ask you questions about your medical and family history before undertaking a full body examination which will include blood pressure (BP), resting electrocardiogram (ECG), height, weight, waist and hip circumference, and vital signs (oral temperature, respiratory rate, and pulse rate)

- **Oral Glucose Tolerance Test (OGTT) (2 hours):** A cannula will be placed in your arm and a blood sample will be collected. You will then be asked to drink a sugary drink and then blood samples will be collected at regular intervals for 2 hours after you ingest the sugary drink. During this test, we will ask you to complete questionnaires around quality of life, mental health, and physical activity. We will also give you your Fitbit physical activity monitor and explain how to use it.

- **Research Food Diary assessment (10 minutes):** We will ask you to download an app on your phone and explain how to use the app. Over the following week you will be required to enter all the foods you eat and the amount into this phone app for 4 days.

- **Sleep monitor assessment (30 minutes):** You will be given a home sleep device for overnight use which reports apnoeas (suspension of breathing), snoring, blood oxygen saturation and breathing patterns. We will ask you to wear the device during the upcoming night and be required to complete questionnaires on sleep. The sleep device (Nox-T3+ device by NoxMedical (Iceland)) is used clinically throughout Australia. We will demonstrate how to use the device during your clinic visit.

- **Urine and Stool:** You will be provided with urine and stool collection kits that you will be asked to collect at home to bring with you on your next visit.

Dual energy X-ray absorptiometry (DXA) scanning (45 minutes): This test measures bone density. You will be requested to lie without moving on a bed for a few minutes while an X-ray emitting arm sweeps over your whole body and then over your lumbar spine and hip region. The dose of radiation used is very low (please see risks section below).

Vascular and cardiac measures (1.5 hours): You will be asked to lie down supine (face up) on a bed while we perform the following measures.

- **Carotid intima-media thickness (cIMT) (30 minutes):** We will use ultrasound to image the main blood vessels in your neck (the carotid arteries and jugular veins).
- **Flow-mediated dilatation (FMD) (30 minutes):** We will use ultrasound to visualise blood vessels in your arm, before and after inflation of a blood pressure cuff to 240 mmHg (quite tight) for 5 minutes. This may cause some discomfort, but the test has no known side effects.
- **Autonomic function (30 minutes):** Continuous blood pressure and ECG will be recorded for 10 minutes. Along with the usual arm blood pressure cuff and ECG leads, you will also be attached to a finger cuff which maintains pressure on the finger.
- **Pulse wave velocity (30 minutes):** This measures the velocity of blood moving between two sites. A probe will be used to detect pulse wave velocity around your neck and groin area.

6-minute walk test (10 minutes): You will be asked to walk around 2 cones which are spaced around 30 meters apart, in a 6-minute time window. This will give the researchers an idea of your current fitness levels.

2- Baseline MRI visit (around 2 hours)

Magnetic resonance imaging (MRI): MRI will be performed at North Shore Radiology and Nuclear Medicine (St Leonards, NSW, 2065). The examination will take approximately 1.5 hours. Using MRI we will measure blood flow in the heart and the amount of fat in your liver. You will be asked not to consume any foods or drinks containing caffeine for 24 hours prior to the scan. When you arrive, you will be asked to complete a MRI safety form. If you are safe to enter a MRI machine you can proceed with the study. You will then get changed into a hospital gown and remove all foreign bodies (eg jewelry) from your body. A cannula will be inserted into your forearm which allows the administration of contrast dye (gadolinium) and a medication (adenosine) that increases your heart rate and blood flow to your heart.

The MRI scan involves lying on a table, which moves you head first into a cylindrical magnet, and being connected to a heart monitor for the duration of the scan. Firstly, you will be asked to perform breath holds on expiration for regular short periods (6-10 seconds at a time) whilst the first set of pictures are taken. Then you will be requested to exercise on a cycling machine while lying down on the MRI bed for a duration of approximately 8-12 minutes. Subsequently, the adenosine medication and gadolinium will be infused into the cannula in your forearm for 4 minutes. You will then be requested to immerse your hands or feet in ice water for approximately 4 minutes. Finally, we will then spray a medication underneath your tongue (glyceryl trinitrate) that expands your blood vessels. During all these maneuverers MRI pictures will be taken of your heart. At all times during the scan, an experienced radiographer and study doctor will watch you. Once the MRI scan is completed the cannula will be removed. The MRI medications that you've been given do not affect you after the scan and you can do normal things including driving, exercise, and drinking tea or coffee after the MRI.

For detailed risks of the MRI scan please refer to the section below on "what are the known risks of participating in the study".

3- 1-month visit

- **Urine and Faeces sample:** You will be asked to return a urine and faeces sample, kits for which will have been sent to your home address the week before.
- **Fasting blood sample (30 minutes):** A trained investigator will collect 60-100 mL of blood from a cannula in a vein in your arm.
- **Physical examination (30 minutes):** Including blood pressure, weight, waist and hip circumference.
- **Vascular and cardiac measures (2 hours):** Exactly as described in Baseline CV testing visit.
- **Food diary assessment:** Exactly the same as described in the Screening visit.

4- 6-month visit

Exactly the same as the 1 month.

5- 12-months visit

This will include the same assessments as the baseline visit. Again, we can be flexible about how many days we perform these measurements over.

6- End-study CTCA visit (around 1 hour)

- **CT coronary angiogram:** This scan will be performed in the same way as the one prior to your recruitment into the study. It will occur on the same scanner at Royal Prince Alfred Hospital. You may require an oral beta blocker medication to temporarily slow the heart rate. A tablet of glyceryl trinitrate will be administered under the tongue to help dilate the coronary arteries. It may cause a headache which resolves within a few minutes. Intravenous contrast agent will be given via a cannula in a vein in your arm. There are the (low) risks of an allergic reaction to the contrast agent, with experienced nursing, medical and radiography staff present at all times. The scan itself takes around 10 minutes.

7- End-study MRI visit (around 2 hours)
Exactly the same as Baseline MRI visit.

8- Follow-up visit (around 3 hours)
This will be similar to the Baseline CV testing visit with the following procedures; DXA scanning, vascular and cardiac measures, and 60-minute walk test.

Do I have to take part in the study?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage. If you do decide to take part, you will be given this Participant Information and Consent Form to sign electronically and you will be sent a copy.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with the University of Sydney.

What are the known risks of participating in this study?

All medical procedures involve some risk of injury. In addition, there may be risks associated with this study that are presently unknown and unforeseeable. In spite of all precautions, you might develop medical complications from participating in this study. The known risks of this study are:

Blood sampling

This involves some discomfort at the site at which the cannula is inserted and from which blood is taken, and there is a risk of some minor bruising at the site, which may last from one to two days. Fainting and local infection can also occur when blood is taken, although these are rare.

CT and DEXA exposure to radiation

This research study involves exposure to a small amount of radiation. As part of everyday living, everyone is exposed to natural occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this study is about 3.8 mSv. The dose from this study is comparable to that received from many diagnostic medical X-rays and nuclear medicine procedures. At this dose level, no harmful effects of radiation have been demonstrated as any effect is too small to measure. The risk is believed to be low and theoretically is approximately equivalent to 1.7 years of background radiation.

MRI scans

The potential risks of the MRI examination involves the following.

General:

- Claustrophobia (uncommon – occurs in 10-15 people in every 100)
- Difficulty following breathing instructions (uncommon)
- Bruising and discomfort associated with cannulation (uncommon)
- Fatigue from exercising on the supine bike
- Discomfort from the ice water

During administration of Adenosine:

Most people feel flushed, short of breath, chest tightness and/or their heart racing. This means the drug is working. When the medication is stopped, any symptoms wear off very quickly over the next 10 seconds to 1 minute.

Severe side effects of Adenosine are rare but include:

Occurring in 1 in 1500 people:

- The heart goes very slow or stops (Asystole). This needs drugs or a temporary pacing wire to treat.
- A fast heart beat (Ventricular Tachycardia). This may need an electric shock to return to the normal heart beat.
- Ongoing severe chest pain. This requires drugs to treat.
- Heart attack.
- Severe shortness of breath or asthma attack. This requires drugs to treat.

Occurring in 1 in 10,000 people:

- Death

During administration of Glyceryl Trinitrate:

Flushing sensation (warmth, sensation), a drop in blood pressure leading to light headedness (uncommon), very mild short lived headache (common), mild to moderate headache that usually settles with paracetamol (uncommon), palpitations (heart racing).

The possible adverse effects or risks related to the contrast injection (gadolinium):

- nausea (uncommon and short lived)
- allergic reaction/anaphylaxis (very rare but serious)
- Nephrogenic systemic fibrosis – a condition of fibrosis or thickening of the skin and internal organs (very rare but permanent – occurs in those with severe kidney failure only)
- People who should not receive gadolinium in this study include –
  a) Those who have severe kidney failure
  b) Those who have hepatorenal syndrome (a combination of kidney failure and advanced chronic liver disease)
  c) Those who have recently had a liver transplant

The medications (adenosine and glyceryl trinitrate) are used in routine health care and generally well tolerated. While we do not anticipate a high likelihood of the above risks occurring, we will have the reversal agents for these medications ready at hand (aminophylline 125mg intravenously for adenosine; intravenous fluids for low blood pressure from glyceryl trinitrate). The effects of both medications are short lived, so the effects are rapidly self-limiting (adenosine <10 seconds, glyceryl trinitrate 1-3

minutes). A fully equipped resuscitation trolley with defibrillator will also be readily accessible during imaging.

COVID-19

COVID-19 is an ongoing public health concern and is taken very seriously, by regulation, at all study sites. Your risk of contracting COVID-19 as a result of participating in this study are low. Various regulations are in place to keep this risk low. Prior to each visit, you will be pre-screened for COVID symptoms via phone and encouraged to reschedule your visit if experiencing symptoms. Self-isolation and COVID testing will be recommended. Further, participants and staff will be pre-screened using a Building Access Pass system for COVID symptoms to enhance contact tracing and screening. This process consists of scanning a QR code with you mobile device and entering first and last names and email and phone number to receive a "green check." You will then undergo a temperature screening, be questioned about symptoms and visits to hotspots, and be given a mask to wear. Those in the waiting room will be socially distanced by at least 1.5 meters. Social distancing will continue in treatment rooms and study staff will be wearing appropriate personal protective equipment. Treatment rooms will be clean between each visit.

Costs

You will not be paid for participation in this clinical trial. Those assigned to the intense lifestyle programme will receive 1-months' worth of food at no cost, and no matter which group you are in, you will receive a Fitbit device to keep as long as you complete the 12 months. If you dropout before the end you will be required to return the Fitbit device.

Am I eligible?

You must have had a recent CT scan and be referred from your cardiologist. You must be able to use a smartphone and be willing to undergo the 12 months of clinical testing.

Can I withdraw from the study?

Participation in this study is completely voluntary. You do not have to take part in it. If you do take part, you can withdraw at any time without having to give a reason. Whatever your decision, please be assured that it will not affect your medical treatment or your relationship with the staff who are caring for you. However, please note that information or samples collected from yout prior to withdrawal from the study cannot be withdrawn.

What will happen to the samples collected from me?

Blood

Some of your blood will be immediately analysed in the medical clinics for fasting concentrations of serum glucose, insulin, triglycerides, cholesterol, HbA1c, liver enzymes, C-reactive protein and other biochemical tests. We will also measure how glucose and insulin responds to ingesting a standard 75-g of glucose. Together with waist circumference and blood pressure measurements, these analyses will be used to assess your metabolic health. We also ask you to consider giving your permission for storage of a sample of your blood at the Charles Perkins Centre (University of Sydney, Camperdown Campus) for future research. Some of this stored blood sample will be used to examine your genes (DNA) and others biochemical markers that might become available in future. Genes are made of DNA – the chemical structure carrying your genetic information that determines many human characteristics such as the colour of your eyes or hair. Researchers study genes in order to understand why some people have a certain condition such as CHD and why some people do not. Understanding a person's genes also may

be able to explain why some people respond to a treatment, while others do not, or why some people experience a side effect or why their disease progresses more rapidly than others.

Urine and stool

We will ask you to consider giving your permission for storage of your urine and stool samples at the Charles Perkins Centre (University of Sydney, Camperdown Campus) for future research.

Long-term storage

Your blood, urine and stool samples will be stored at the Charles Perkins Centre for 15 years or longer, for as long as they are viable for biological analyses. The reason for this is that in the future, new hormones, metabolites, proteins, genes or other factors are likely to be discovered that could provide useful biomedical insights if investigated in the samples collected in this study.

Will anyone else know the results?

In the event that your results suggest a medical condition that may require treatment, your results may be reported to your general practitioner. Otherwise, all the information collected from you for the study will be treated confidentially, and only the investigators named above will have access to it. The study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

Will the study benefit me?

We cannot promise any benefits to you for your participation in the study. However, possible benefits include gaining information about your current health; receiving dietary, exercise training and mindfulness advice at no charge. You may lose weight if enrolled in the "ILP+OMT" group of the study. Weight loss has secondary benefits for you and society; such as loss of body fat, decreased risk of diabetes, lowering blood pressure, lowering of blood cholesterol and improvements in cardiometabolic health. Moreover, this treatment program is designed to help you live a healthier lifestyle and therefore reduce your cardiovascular risk. If you are assigned to the Intense Lifestyle Group, you will be provided with meals free of charge for the first month. If you are assigned to the OMT group, you will be provided with a flexible and balanced menu planner that is tailored to your individual circumstances and preferences. All participants will be given educational materials outlining the principles of healthy eating, as well as a physical activity monitor to track your daily activity and sleep. Throughout the study you will complete a number of test procedures to assess your health, at no cost. These procedures are expensive and unavailable to the general public. At the end of the study you will be provided with a detailed report of your health profile changes over the course of the study. In addition to these direct benefits, we expect that your participation in this project will help other people who are attempting to manage their cardiovascular risk, by furthering knowledge of healthy lifestyle behaviours.

What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, the research team will tell you about it and discuss with you whether you want to continue in the research project. If you decide to withdraw, the research team will make arrangements for your regular health care to continue. If you decide to continue in the research project you will be asked to sign an updated consent form. Also, on receiving new information, the research team might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

Can I have other treatments during this research project?

If you are participating in this research project, you might not be able to participate in other research studies. It is important to tell the research team about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell the research team about any changes in any medications during your participation in this research project.

What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing. If you do withdraw your consent during the research project, the research team will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project. Data collected by third party companies such as Fitbit and Marley Spoon is out of our control and subject to their privacy laws.

What if I require further information about the study or my involvement in it?

When you have read this information, one of the members of the research team will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to email the team at liveplus.study@sydney.edu.au or telephone on +61 2 91176673.

What if I have a complaint or any concerns?

This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number X20-0229.

Part 2 How is the research project being conducted?

Where will my data be stored and will it be kept confidential?

By signing the consent form you consent to the research team using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. This identifiable data includes your name, DOB, and address, which will be encrypted on the RPA hospital computer servers which provides a high level of security. You will be assigned a unique study ID number to replace your name or address on any data forms. Any non-identifiable clinical data which we collect from you will be stored on secure computer servers within the University of Sydney which can only be accessed by members of the research team. We will keep your data for at least 15 years. Study results may be presented at a conference or in a scientific publication, but individual participants will not be identifiable in such a presentation.

Information about you may be obtained from your health records held at this and other health services for the purpose of this research. By signing the consent form you agree to the study team accessing health records if they are relevant to your participation in this research project. Your health records and any information obtained during the research project are subject to inspection (for the purpose of verifying the procedures and the data) by the relevant authorities and authorised representatives of the the University of Sydney or as required by law. By signing the Consent Form, you authorise release of, or access to, this confidential information to the relevant study personnel and regulatory authorities as

noted above. Information about your participation in this research project may be recorded in your health records.

The LIVPLUS phone app will backup your data within your smartphone as well as in an online cloud server which is based in Sydney and subject to Australian laws.
The App does not provide the functionality to delete the data stored in the cloud server, even upon deletion of the App, the data will remain. However, you may formally make a request (via email or phone call) to delete your data in the cloud server. Access to any LIVEPLUS app data will be limited to the research study team.

Can I access my data?

In accordance with relevant Australian and NSW privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact the study team member named at the end of this document if you would like to access your information.

What will Fitbit, Research food diary, Marley Spoon, and the LIVEPLUS app do with my data?

The below third party companies are involved in this study. The research team will be diligent as to maintain your privacy and security with the data we collect, however any data shared with a third party company is out of our control once they have the data. We won't share any clinical data collected during the trial with these companies. A summary of the data collected by these companies can be seen in the table below.

Third party	What data will you share with them	Where is your data stored?	Will the research team access this data?	Interests (commercial, business other)
Fitbit	Personal details (name, email, password, date of birth, gender, height, weight, phone number. Data collected from your device e.g. step count and heart rate If you have an Android device location permission must be turned on.	Cloud server based in the US.	Yes, the research team will be able to view your Fitbit data.	None.
Marley Spoon	Personal details (name, address, email, phone number)	The data they collect from you may be transferred to and stored at a destination outside Australia.	Yes, the research team will be able to view the meals you purchase	None.

			over the 4 weeks.	
Research Food Diary (Xyris software)	Xyris will only access *Research Food Diary* users' data for troubleshooting and bug fixing purposes; they access this data only with express permission from you.	Amazon Web Service stored in the Sydney, Australia data centre. However, in case of disaster recovery purposes the data is replicated in other data centres, possibly overseas.	Yes, you will be required to share your food diary to the research team.	None.
LIVEPLUS app	Your usage of the app will be collected and data which is entered into the app yourself (no clinical data will be included).	Amazon Web Service stored in the Sydney, Australia data centre.	Yes, the research team will be able to monitor your progress on the app.	One of the investigators, Robin Huang, will be using participant interaction with the app for the purpose of his PhD project. Mr Huang is also Founder of Vulsen Pty Ltd, the company developing the Liveplus App to be used in this study. The University of Sydney has put in place a plan to manage any potential conflicts of interests that might arise from his involvement in the study.

For more detail on each company's private policy see the links below:
1-Fitbit: https://www.fitbit.com/au/legal/privacy-policy
2-Marley Spoon: https://marleyspoon.com.au/privacy.
3-Research Food diary: https://support.easydietdiary.com/hc/en-us/articles/202429019-Privacy-Policy

To contact each company use the following:
1-Fitbit: data-protection-office@fitbit.com.
2-Marley Spoon: contact@marleyspoon.com.au
3-Research Food diary: info@xyris.com.au
4-LIVEPLUS app: rhuang2295@gmail.com

Who is organising and funding the research?

The Australian Youth and Health foundation are funding this study and the University of Sydney is organising the study.

Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the Sydney Local Health District (SLHD) HREC.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies

What if I require further information about the study or my involvement in it?

When you have read this information, one of the members of the research team will discuss it with you further and answer any questions you may have. If you would like to know more at any stage, please feel free to contact the team on liveplus.study@sydney.edu.au

Compensation for injuries or complications

If you suffer any injuries or complications as a result of this study, you should contact the study doctor as soon as possible, who will assist you in arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

What if I have a complaint or any concerns?

This study has been approved by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District. Any person with concerns or complaints about the conduct of this study should contact the Executive Officer on 02 9515 6766 and quote protocol number X20-0229.

The conduct of this study at the [name of hospital] has been authorised by the [name of Local Health District]. Any person with concerns or complaints about the conduct of this study may also contact the Research Governance Officer [or other officer] on [telephone number] and quote protocol number [insert local protocol number].

Consent Form

Title	A randomised controlled trial to evaluate intensive lifestyle program for reversal of coronary heart disease
Short Title	LIfestyle VulnErable PLaqUe Study (LIVEPLUS)
Protocol Number	7.0
Project Sponsor	The University of Sydney
Coordinating Principal Investigator/ Principal Investigator	Professor Luigi Fontana
Location	Royal Prince Alfred Hospital and Charles Perkins Centre

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I understand that my participation in this study will allow the researchers to have access to my medical record, and I agree to this.

I consent to the storage and use of blood and tissue samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research

I give permission for my GP to be contacted about any incidental findings.

I understand that by participating in this trial, I will be sharing my data with third party companies.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Witness* to Participant's Signature (please print) _____

Signature _____ Date _____

Declaration by Senior Researcher

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Senior Researcher[1] (please print)	_____
Signature _____	Date _____

Note: All parties signing the consent section must date their own signature

Appendix G
Clinical Trial Research Agreement

DocuSign Envelope ID: 8474986B-BA24-47BE-96B0-BAD5527BC396

X20-0229.

THE UNIVERSITY OF SYDNEY

Clinical Trial Research Agreement

Collaborative or Cooperative Research Group (CRG) Studies – Standard Form

The body of this Agreement (that is from the following page to the execution clauses) is intended to be identical to the standard form a copy of which is located at http://medicinesaustralia.com.au/issues-information/clinical-trials/clinical-trials-research-agreements. Any textual change to the body of this Agreement is to be ignored, and reference instead had to the standard form, as amended by Schedule 4 by way of Special Conditions.

Details of the parties

Name of Institution:	**Sydney Local Health District**
Address:	Level 11, KGV Building, Missenden Road, Camperdown NSW 2050
ABN:	17 520 269 052
Contact for Notices:	Professor Luigi Fontana
Fax for Notices:	
Phone Number:	+61 2 8627 7499

Name of CRG:	**The University of Sydney**, a body corporate under *The University of Sydney Act 1989*
Address:	Level 3, F23 Administration Building, Camperdown NSW 2006
ABN:	15 211 513 464
Contact for Notices:	Contracts Manager - Clinical Trials
Fax for Notices:	+61 2 8267 8145
Phone Number:	+61 2 8627 9559

Study Name:	A randomised controlled trial to evaluate an intensive lifestyle program for reversal of coronary heart disease
Protocol Number:	X20-0229 & 2020/ETH01273
Date of Agreement:	**Date of the last party to sign the Agreement**

This agreement is made between the CRG and Institution

Purpose of the Agreement

According to this Agreement:

A. The CRG is an academic and/or non-commercial collaborative research group responsible for sponsoring, initiating, managing, developing and coordinating the Study.

B. The Institution, through the Principal Investigator, is responsible for the conduct of the Study at the Study Site(s).

C. The Study will be conducted on the terms and conditions set out below.

D. The parties acknowledge that they are not for profit organisations and the Study will be conducted in the spirit of cooperation and collaboration.

OPERATIVE PROVISIONS

1. **INTERPRETATION**

1.1 In this Agreement:

Adverse Event has the meaning given in the TGA document "Access to Unapproved Therapeutic Goods – Clinical Trials in Australia" (October 2004) or replacement.

Affiliate means any company which (directly or indirectly) controls, is controlled by or is under common control with the CRG.

Agreement means this Agreement, including all the Schedules.

Background Intellectual Property (**Background IP**) of a party means information, techniques, know-how, software and materials (regardless of the form or medium in which they are disclosed or stored) that are provided by or on behalf of that party to the other for use in the Study (whether before or after the date of this Agreement) or used by that other party in conducting the Study, and all Intellectual Property in them, but excludes the Study Materials

Biological Samples means any physical samples obtained from Study Participants in accordance with the Protocol for the purposes of the Study.

Case Report Form means a printed, optical or electronic document or database designed to record all of the information, which is required by the Protocol to be reported to the CRG on each Study Participant.

Confidential Information means:

(1) in respect of the CRG:

(a) all information collected in the course of, resulting from, or arising directly out of the conduct of the Study, whether at the Study Site or elsewhere;

(b) the Protocol, the Investigator's Brochure, information related to the Protocol, Study Materials and Investigational Product;

(c) know-how, trade secrets, ideas, concepts, technical and operational information, scientific or technical processes or techniques owned by the CRG or its Affiliates;

(d) know-how, methodology, trade secrets, processes, sequences, structure and organisation of the Study; and

(e) information concerning the business affairs of the CRG or its Affiliates;

(2) in respect of the Institution, information in relation to the Institution's business, operations or strategies, intellectual or other property or actual or prospective suppliers or competitors;

but Confidential Information does not include Personal Information.

CRG means the collaborative or cooperative research group so described on the first page of this Agreement.

Equipment means the equipment supplied to the Institution by or on behalf of the CRG for the purposes of the Study, including that specified in **Schedule 1**.

Essential Documents means documents which individually and collectively permit evaluation of the conduct of the Study and the quality of the data produced.

GCP Guideline means the Committee for Proprietary Medicinal Products (CPMP)/International Conference on Harmonisation (ICH) Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) as adopted with annotation by the TGA, or its replacement.

GST means the Goods and Services Tax payable under a GST Law.

GST Law means the same as in *A New Tax System (Goods and Services Tax) Act 1999 (Cth)* as amended from time to time, and any regulations made pursuant to that Act.

Institution means the body so described on the first page of this Agreement.

Intellectual Property means all present and future industrial and intellectual property rights, including without limitation:

(1) inventions, patents, copyright, trade business, company or domain names, rights in relation to circuit layouts, plant breeders rights, registered designs, registered and unregistered trade marks, know how, trade secrets and the right to have confidential information kept confidential, and any and all other rights to intellectual property which may subsist anywhere in the world; and

(2) any application for or right to apply for registration of any of those rights.

Investigational Product is the medicine(s), trial interventions or device(s) being trialled or tested in the Study as set out in **Schedule 1**, and includes where relevant any placebo.

Investigator's Brochure is a compilation of the clinical and non-clinical data on the Investigational Product(s) which are relevant to the study of the Investigational Product in humans.

Multi-centre Study is a Study conducted by several investigators according to a single protocol at more than one study site.

NHMRC means the National Health and Medical Research Council of the Commonwealth of Australia.

Personal Information has the same meaning as in the *Privacy Act 1988 (Cth)*.

Personnel means employees, agents and/or authorised representatives, and includes in the case of the Institution, the Principal Investigator.

Principal Investigator is the person responsible for the conduct of the Study at the Study Site as described in **Schedule 1**.

Protocol means the document identified in **Schedule 3** which describes the objective(s), design, methodology, statistical considerations and organisation of the Study, and subject to **clause 2.3**, as amended from time to time, as agreed by the parties, and most recently approved by the Reviewing HREC.

Publish means to publish by way of a paper, article, manuscript, report, poster, internet posting, presentation, slides, abstract, outline, video, instruction material or other disclosure of the Study Materials, in printed, electronic, oral or other form. **Publication** has a corresponding meaning.

Regulatory Authority means any body which has jurisdiction over the conduct of the Study at the Study Site and includes the TGA, and any overseas regulatory authorities who may audit or require to be audited, any part of the Study or Study Materials.

Relevant Privacy Laws means the *Privacy Act 1988 (Cth)* and any other legislation, code or guideline which applies in the jurisdiction in which the Study Site is located and which relates to the protection of Personal Information.

Reviewing HREC means the Human Research Ethics Committee reviewing the Study on behalf of the Institution as described in **Schedule 1**.

Serious Adverse Event has the meaning given in the TGA document "Access to Unapproved Therapeutic Goods – Clinical Trials in Australia" (October 2004) or its replacement.

Software means the software supplied to the Institution by or on behalf of the CRG for the purposes of the Study, including that specified in **Schedule 1**.

Study means the investigation to be conducted in accordance with the Protocol.

Study Completion means:

(1) the final study database for the Study has been locked; or

(2) all study follow-up requirements have been met, and a copy of the letter from Reviewing HREC acknowledging receipt of the final report and/or closure letter from the Principal Investigator has been received by the CRG; or

(3) as otherwise determined by the CRG and notified to the Institution in writing

Study Materials means all the materials and information created for the Study or required to be submitted to the CRG including all data, results, Biological Samples, Case Report Forms (or their equivalent) in whatever form held, conclusions, discoveries, inventions, know-how and the like, whether patentable or not relating to the Study which are discovered or developed as a result of the Study, but excluding the Institution's ordinary patient records.

Study Participant means a person recruited to participate in the Study.

Study Site means the location(s) under the control of the Institution where the Study is actually conducted as set out in **Schedule 1**.

TGA means the Therapeutic Goods Administration of the Commonwealth of Australia or any successor body.

1.2 Except where the context otherwise requires:

(1) clause headings are for convenient reference only and are not intended to affect the interpretation of this Agreement;

(2) where any word or phrase has a defined meaning, any other form of that word or phrase has a corresponding meaning;

(3) any reference to a person or body includes a partnership and a body corporate or body politic;

(4) words in the singular include the plural and vice versa;

(5) all the provisions in any schedule to this Agreement are incorporated in, and form part of, this Agreement and bind the parties;

(6) a reference to a replacement of a document or standard, means any document or ruling which amends, updates, replaces or supersedes that document or standard;

(7) if a period of time is specified and dates from a given day or the day of an act or event, it is to be calculated inclusive of that day;

(8) a reference to a monetary amount means that amount in Australian currency unless specified otherwise in **Schedule 2**; and

(9) references to a party include its Personnel.

2. THE STUDY

2.1 The parties must comply with, and conduct the Study in accordance with the Protocol and any conditions of the Reviewing HREC. In addition the parties must comply with the following, as applicable:

(1) any requirements of relevant Commonwealth or State or Territory laws or of Regulatory Authorities;

(2) the requirements of the TGA in Access to Unapproved Therapeutic Goods – Clinical Trials in Australia (October 2004) or its replacement and any other TGA publication or guideline that relates to clinical trials, or other such regulations or guidances governing the conduct of clinical research in the jurisdiction of the Study;

(3) the GCP Guideline;

(4) the principles that have their origins in the Declaration of Helsinki adopted by the World Medical Association in October 1996 (as accepted by the Australian Government);

(5) the NHMRC National Statement on Ethical Conduct in Human Research (2007) or replacement, and any other relevant NHMRC publication or guideline that relates or may relate to clinical trial;

(6) any Study specific and standard operating procedures provided by the CRG prior to the commencement of the Study; and

(7) any reasonable direction given by the CRG in order to ensure the safe conduct of the Study and compliance with applicable regulatory requirements.

2.2 If any issue relating to the safety of Study Participants arises which requires a deviation from the Protocol, the Institution through the Principal Investigator may immediately make such a deviation without breaching any obligations under this Agreement. If there is a need for such a deviation the Institution must notify the CRG and the Reviewing HREC of the facts and circumstance causing the deviation as soon as is reasonably practical, but in any event no later than 5 working days after the change is implemented.

2.3 From time to time, the CRG may modify the Protocol by written notice to the Institution and Principal Investigator. Except where the modification is necessary to eliminate an immediate hazard to Study Participants, or involves only logistical or administrative aspects of the trial, any modification may not be implemented before approval by the Reviewing HREC. If the parties determine that a modification will affect the cost of the Study, the parties shall amend **Schedule 2** as agreed between them.

3. PRINCIPAL INVESTIGATOR

3.1 Role of Principal Investigator

The Institution has authorised the Principal Investigator as the person responsible on a day to day basis for the conduct of the Study at the Study Site. The Principal Investigator does not have authority on behalf of the Institution to amend this Agreement or the Protocol.

3.2 Liability for Principal Investigator

For the purpose of this Agreement only, and as between the CRG and the Institution only, the Institution agrees to be responsible for the acts and omissions of the Principal Investigator in relation to the conduct of the Study, to the extent that such responsibility would attach to the Institution in accordance with its obligations under this Agreement or under the common law on the basis that the Principal Investigator is acting as an employee of the Institution. Nothing in this clause or Agreement affects any pre-existing contractual or other arrangement which may be in place between the Institution and the Principal Investigator.

3.3 Obligations and responsibilities

The Institution is responsible for ensuring that the Principal Investigator:

(1) thoroughly familiarises themselves with the appropriate use of the Investigational Product(s), as described in the Protocol, Investigator's Brochure, information relating to the Investigational Product and any other information sources provided by the CRG;

(2) ensures written approval has been obtained to conduct the Study from the Reviewing HREC and the Institution prior to Study initiation. Written documentation of approval by the Reviewing HREC and the Institution must be provided to the CRG;

(3) conducts the Study according to the Protocol without changes, except as provided in **clause 2.2** or **2.3**, or as agreed to in writing by the CRG and the Institution and approved in accordance with **clause 3.3(4)**;

(4) ensures that any amendments to the Protocol are approved by the Reviewing HREC and CRG prior to implementation of the amendment;

(5) as soon as is practical advises the CRG if the Responsible HREC alters its approval of the Study;

(6) obtains prior written approval from the CRG and the Responsible HREC of any proposed advertisements to be used for the purpose of Study Participant recruitment in the Study;

(7) provides the CRG with evidence of the Principal Investigator's qualifications through a current curriculum vitae and/or other relevant documentation and a list of appropriately qualified persons to whom they have delegated significant Study-related duties, if required;

(8) uses their best endeavours to recruit the target number of Study Participants, within the recruitment period, specified in **Schedule 1**, provided that if the overall target number of Study Participants for the Study is reached, the CRG may direct the Institution to cease recruitment;

(9) is available when a clinical research representative of the CRG visits the Study Site, as mutually agreed prior to the visit, and is contactable by telephone or electronic mail as frequently as is reasonably required;

(10) notifies the CRG, the Institution and the Reviewing HREC of any Adverse Events (including Serious Adverse Events) that occur during the course of the Study in accordance with the Protocol, and relevant ethical and regulatory guidelines, and in the case of the Institution and the Reviewing HREC with their policies and procedures;

(11) completes Case Report Forms within the agreed time period. The Principal Investigator will ensure that Study Participants' identifying information are removed from all records being transferred to the CRG;

(12) provides regular written progress reports to the CRG in relation to the Study as required by the Protocol;

(13) completes and returns to the CRG as required any Study related materials within a reasonable time period;

(14) is not subject to any obligations, either contractually or in any other way, which would unreasonably interfere with or prohibit the performance of work related to this Study; and

(15) ensures that informed consent to participate in the Study is obtained from each Study Participant prior to their enrolment in the Study and documented using an information and consent document which has been reviewed and approved by the CRG, the Institution and the Reviewing HREC.

4. INSTITUTION OBLIGATIONS AND RESPONSIBILITIES

4.1 If the Principal Investigator leaves the Institution or otherwise ceases to be available then:

(1) the institution must notify the CRG as soon as is practical;

(2) the Institution must consult with the CRG and use reasonable endeavours to nominate as soon as practicable a replacement reasonably acceptable to both parties; and

(3) if a replacement cannot be found who is acceptable to both parties, the CRG may require recruitment into the Study by the Institution to cease, and the CRG may terminate this Agreement in accordance with **clause 14.4**.

4.2 If the Principal Investigator fails to carry out those obligations specified in **clauses 3.3(2), (3), (4), (8), (10), (11), (13),** or **(15)**, then the Institution must itself perform those obligations and rectify and make good any breach. The Institution will ensure that any Personnel who assist in the conduct of the Study are informed of and agree to abide by all terms of this Agreement relevant to the activities they perform.

4.3 The Institution warrants that to the best of its knowledge, it, its affiliates and any other person involved in the conduct of the Study, including the Principal Investigator, are properly registered with appropriate professional registration bodies and have not been disqualified from practice or disbarred or banned from conducting

clinical trials by any Regulatory Authority for debarment. Furthermore, the Institution shall notify the CRG as soon as practical after it becomes aware of any such disqualification, disbarment or ban.

4.4 The Institution will not engage in any conduct on the CRG's behalf which is in violation of, or potentially in violation of, any applicable local or foreign laws or regulations.

4.5 The Institution warrants, represents and undertakes to the CRG that it has not offered, promised or paid, either directly or indirectly, any Benefit to a government official (including, but not limited to, a healthcare professional employed by a government-owned healthcare facility) to induce such government official to act in any way in connection with his or her official duties with respect to services performed under this Agreement or to otherwise obtain an improper advantage for the Institution or the CRG (**Improper Payment**), and has not received an Improper Payment, and will not offer, promise, pay, authorise or receive any Improper Payment in the future. For the purposes of the foregoing, Benefit includes but is not limited to money, financial or other advantage, travel expenses, entertainment, business or investment opportunities, charitable donations or any other thing of value.

4.6 The Institution must have adequate security measures to ensure the safety and integrity of the Investigational Product(s), Essential Documents and Study records and reports, Equipment and any Study related materials held or located at the Study Site.

4.7 Subject to **clause 9**, the Institution will allow regular monitoring and scheduled audit visits in accordance with the GCP Guideline and as required by Regulatory Authorities or as specified in the Protocol and permit access to the Essential Documents (including original records), Study records, reports, other Study related materials and its Personnel as soon as is reasonably possible upon request by the CRG, Regulatory Authority, Reviewing HREC or any third party designated by the CRG. Any such access is to take place at times mutually agreed during business hours and subject to such reasonable conditions relating to occupational health and safety, security, and confidentiality as the Institution may require.

4.8 The Institution will make available adequate facilities, equipment and any other resource of the Institution reasonably required to safely follow the Protocol, provided that any amendments to the Protocol which take place after the execution of this Agreement and requiring any additional use of facilities, equipment, staff or resources, have been approved in writing by the Institution and the Reviewing HREC.

4.9 The Institution will have an adequate number of appropriately qualified Personnel for the foreseen duration of the Study and ensure that such Personnel are adequately informed about the Protocol, the Investigational Product(s), and their Study related duties and functions. The Personnel appointed by the Institution to assess Study Participants will attend an investigator meeting or a pre-study/initiation meeting, where appropriate.

4.10 The Institution must retain and preserve a copy of all Study Materials, including copies of signed consent forms, Case Report Forms, Protocol, information relating to the Investigational Product, correspondence and investigator files for at least 15 years from Study Completion and must ensure that no Study related materials are destroyed before the expiration of this time period without the written approval of the CRG. The Institution agrees to notify the CRG before destroying any Study Materials.

4.11 The Institution will ensure that the Study is subject to the continuing oversight of the Reviewing HREC throughout its conduct.

4.12 If the Institution is contacted by any Regulatory Authority in connection with the conduct of the Study, the Institution shall immediately notify the CRG, unless prevented from doing so by law.

4.13 The Institution will provide the CRG with all reasonable assistance and cooperation to rectify any matter raised by a Regulatory Authority or as the result of an audit of the Institution or Study Site. This includes execution of any documents reasonably requested by the CRG in connection with the requirements of a Regulatory Authority or the CRG as a result of such an audit. Any costs resulting from such audit shall be borne equally by the parties, unless the cost has resulted solely from an act or omission of a party, in which case that party will bear the total costs.

4.14 The Institution shall obtain approval, in writing, from the CRG for any press statements or promotional statements regarding the Study or the Investigational Product(s) before the statements are released, unless the statement or disclosure is required by:

(1) law;

(2) any policy, guideline or direction of government or any government department or agency;

(3) any Regulatory Authority; or

(4) is, in the absolute discretion of the Institution, Minister for Health, Department of Health or any government official, reasonably necessary in the public interest or to protect the health and safety of any individual.

5. CRG OBLIGATIONS AND RESPONSIBILITIES

5.1 Prior to the Agreement being executed, the CRG or its designate must provide the Principal Investigator, and through the Principal Investigator the Institution and the Reviewing HREC, with all current and relevant information regarding the Investigational Product that is reasonably available to the CRG and required to justify the nature, scope and duration of the Study.

5.2 The CRG will act as sponsor of the Study for the purposes of the TGA's CTN Scheme or CTX Scheme (or any successor scheme). The CRG is responsible for preparing and submitting all documents required by the TGA to file an application for initiating and conducting the Study.

5.3 The CRG will implement and maintain quality assurance and quality control systems to ensure that the Study can be conducted and data generated, documented, recorded and reported in compliance with all of the documents referred to in **clause 2**.

5.4 The CRG will register the Study on the appropriate clinical trials registry.

5.5 The CRG will designate appropriately qualified personnel to advise on Study-related medical questions or problems.

5.6 The CRG will, as soon as it becomes aware, advise the Institution, through the Principal Investigator and TGA of the cessation elsewhere of any relevant trial, or the withdrawal of the Investigational Product from any other market for safety reasons.

5.7 The CRG will notify the Institution of any Adverse Events (including Serious Adverse Events) that occur during the course of the Study (either at the Study Site or other

study sites, including overseas sites) which may require alteration of the conduct of the Study, or which may affect the rights, interests, safety or well-being of Study Participants.

5.8 The CRG will cooperate with the Institution and/or the Responsible HREC in investigating any Adverse Event (including Serious Adverse Event) arising out of or in connection with the Study.

5.9 To assist the Institution to comply with **clause 8**, the CRG will provide the Institution with adequate information and all necessary product accountability forms.

6. PAYMENTS

6.1 In consideration of the Institution conducting the Study, the CRG will pay to the Institution as nominated in **Schedule 2** in the manner and on the basis of the amounts and at the times set out in **Schedule 2.** The amounts set out in **Schedule 2** do not include GST. At the time of payment, the CRG must pay to the Institution any amount of GST that the Institution is required to pay in addition to the amounts set out in **Schedule 2**, and in accordance with GST Law.

6.2 The CRG reserves the right to refuse to pay to the Institution payments specific to Study Participants entered into the Study who do not meet the entry criteria specified in the Protocol.

6.3 If a Study Participant discontinues their participation in the Study or if the Study is terminated as a whole, only those costs incurred up until the date of discontinuation or termination, including costs of final visit and completion of all Case Report Forms, will be paid.

6.4 Payments will be made by the CRG upon either receipt of a valid tax invoice or a "Recipient Created Tax Invoice" issued by the CRG.

6.5 The CRG and the Institution each warrant that they are registered under GST Law. Tax invoices must identify supplies for which GST is payable.

7. PROVISION OF EQUIPMENT & SOFTWARE

7.1 The CRG will facilitate the supply of the Equipment and Software by the manufacturer to the Institution and Principal Investigator at no cost to the Institution.

7.2 Unless otherwise agreed by the parties in writing, the Institution must ensure that the Equipment and Software is used only by the Principal Investigator and Personnel involved in the conduct of the Study and only for the purposes of the Study.

7.3 If proper usage of the Equipment or Software requires training, the Institution agrees that:

(1) the Principal Investigator and Institution's Personnel will make themselves available for training in using the Equipment and Software, at no cost to the Institution; and

(2) the Equipment and Software will only be used as described in written directions provided by the CRG.

7.4 The Institution must take all reasonable steps in the use and security of the Equipment to ensure that it is not lost or damaged.

7.5 Subject to **clause 7.6**, at any time after Study Completion, the Institution must comply with any request from the CRG:

(1) on behalf of the manufacturer, to return to the manufacturer the Equipment or Software and all related training materials and documentation provided by the manufacturer

(2) to return all related training materials and documentation provided by the CRG to the CRG at no cost to the Institution.

7.6 If the CRG does not request the return of the Equipment or Software or any related training materials and documentation within 60 days after the Study Completion, the Institution may return, retain as its own at no cost, or destroy the same.

7.7 The CRG will comply with any reasonable request from the Institution to assist in maintaining the Equipment or Software in good working order, and ensuring that it is in a safe condition and compliant with the requirements of the relevant licensing and safety authorities at all times.

7.8 The Institution will not copy the Software unless specifically authorised by the CRG.

8. INVESTIGATIONAL PRODUCT & PRODUCT LIABILITY

8.1 The CRG will facilitate the supply of such quantities of the Investigational Product as will be required for the purpose of the Study.

8.2 The Institution must:

(1) ensure that all Investigational Product is used strictly according to the Protocol and is not used for any other purposes, unless agreed in writing by the CRG;

(2) provide a written explanation accounting for any missing Investigational Product;

(3) not charge a Study Participant or third party payer for Investigational Product; and

(4) keep all Investigational Product under appropriate storage conditions as specified in the Protocol in a secured area accessible only to authorised Personnel, and that complete and current records are maintained for all received, dispensed and returned Investigational Product.

8.3 On termination of this Agreement, the Institution must promptly return (or destroy if requested by the CRG, and provide evidence of such destruction) to the CRG or its designate any unused Investigational Product(s).

9. CONFIDENTIALITY

9.1 Subject to **clause 9.2**, each Party must not, and must ensure their Personnel do not, use or disclose any Confidential Information of the other party, other than where and only to the extent that such use or disclosure is necessary for the performance of the Study, the exercise of its rights or the performance of its obligations under this Agreement.

9.2 The Institution may use or disclose CRG Confidential Information in any of the following circumstances:

(1) for the purposes of complying with the Institution's internal complaint procedures, accident reporting procedures, quality assurance activities, disciplinary procedures or any applicable policy in relation to patient safety, Adverse Events and/or reportable incidents;

(2) for the purposes of disclosing any material risks identified during the Study or subsequent to it, to Study Participants, Principal Investigators, medical practitioners administering treatment to Study Participants, Responsible HRECs and Regulatory Authorities;

(3) for the purposes of complying with the requirements of any Regulatory Authority;

(4) to enable the Reviewing HREC to monitor the Study;

(5) where the CRG consents in writing to the disclosure;

(6) as part of a publication issued under the provisions of **clause 12**;

(7) where release of the Confidential Information is required by law, with notice as soon as reasonably practical to the CRG, and subject to the Institution upon request providing reasonable assistance to enable the CRG to obtain a protective order or other remedy to resist disclosure or ensure confidential treatment for any required disclosure

(8) for the purposes of the Institution seeking legal advice; or

(9) disclosure to the Institution's insurer.

9.3 Where Confidential Information is disclosed in accordance with **clause 9.2(1)** or **9.2(4)**, the Confidential Information must only be used in connection with the legitimate purposes of the Institution, and only disclosed to those who have a need to know it for such purposes and are obligated to keep the information confidential.

9.4 The CRG may disclose Institution Confidential Information to its lawyers for the purposes of obtaining legal advice or to its Affiliates but only on a needs to know and confidential basis. The CRG may disclose Institution Confidential Information if required by law, with notice as soon as reasonably practical to the Institution, and subject to the CRG upon request providing reasonable assistance to enable the Institution to obtain a protective order or other remedy to resist disclosure or ensure confidential treatment for any required disclosure.

9.5 The parties are responsible for ensuring that their Personnel are aware of the obligations in respect of Confidential Information in this **clause 9**, and are bound in similar terms to keep such information confidential, but are not responsible if those Personnel deliberately and intentionally fail to observe those restrictions.

9.6 Information will not be Confidential Information and subject to the provisions of this **clause 9** where:

(1) the information has been independently received from a third party who is free to disclose it;

(2) the information is in or has entered the public domain other than as a result of a breach of this Agreement;

(3) the party already knew the information, the prior knowledge of which it can document by prior written records; or

(4) the party independently develops, discovers or arrives at the information without use, reference to, or reliance upon, the Confidential Information.

10. PRIVACY

10.1 Each party must ensure that any Personal Information of Study Participants or Personnel it obtains or holds as a result of the conduct of the Study is collected, stored, used and disclosed by it in accordance with the Relevant Privacy Laws.

10.2 Each party will promptly report to the other party any unauthorised access to, use or disclosure of Personal Information of Study Participants ("Incident") of which it becomes aware, and will work with the other party to take reasonable steps to remedy the Incident.

11. LIABILITY AND INSURANCE

11.1 Each party is liable for its acts and omissions in relation to the conduct of the Study.

11.2 Each party must maintain such insurances as are reasonably available and necessary to provide indemnity to it in relation to any liability which it may incur in conducting the Study or performing its obligations under this Agreement.

11.3 The Institution satisfies the requirements of **clause 11.2** if it is entitled to indemnity under a program or scheme of insurance or indemnity that is arranged by a State or Territory of the Commonwealth of Australia.

12. PUBLICATIONS

12.1 The Institution, its personnel and the Principal Investigator must not Publish or present any aspect of the Study without the prior written approval of the CRG such approval not to be unreasonably withheld. However, the Institution may use and present any information concerning the Study for the purposes of internal training, education, evaluation or discussion without the consent of the CRG.

12.2 The CRG acknowledges that the Institution may periodically wish to distribute information releases and announcements regarding the progress of research, including this Study. The Institution agrees that they will not release such written or oral material regarding the Study to the news media or a third party without the prior written approval of the CRG, such approval not to be unreasonably withheld.

12.3 The parties agree that publications or presentations of any of the results from the Study will take into account the co-operative nature of the conduct of the Study and the overall objective of increasing public knowledge and shall be in accordance with accepted scientific practice, academic standards and customs and in accordance with the Protocol and with any more specific publication/presentation guidelines developed during the course of the Study, including but not limited to the following:

(1) If the Study is a Multi-centre Study, the results from a single centre must not be Published before the Publication of results from all centres.

(2) Individuals making a substantial contribution to the Study will be recognised with co-authorship in the Publication of results from the Study, unless they elect not to be recognised.

13. STUDY RESULTS AND INTELLECTUAL PROPERTY

13.1 The CRG grants to the Institution and its Personnel the right to use the Background IP of the CRG and the Study Materials as required to carry out the Study and perform this Agreement. Except for this right, neither the Institution nor any of its Personnel acquires any right or interest in any Intellectual Property provided by or on behalf of the CRG

13.2 In order to carry out the Study, the Institution may use Intellectual Property which is part of the Institution's Background IP. Any such Background Intellectual Property remains the sole property of the Institution. The Institution grants to the CRG a non-

exclusive, perpetual, royalty free licence to use (including the right to sub-licence) the Institution's Background IP solely for the purpose of the commercialisation of the Study Materials.

13.3 Subject to **clause 13.2**, all Intellectual Property in the Study Materials will vest automatically upon its creation in the CRG, and the Institution presently assigns the CRG all existing and future Intellectual Property rights (including all future copyright) contained in the Study Materials. The Institution agrees to execute or procure the execution by its Personnel of any documents reasonably necessary to give effect to this assignment, at the CRG's expense.

13.4 As a general principle, any Intellectual Property specifically relating to any Investigational Product or Equipment shall be the sole property of the company owning the Investigational Product or Equipment. Nothing in this Agreement transfers any Intellectual Property rights (other than a right to use where expressly stated in this Agreement) in the Equipment and the Investigational Product to the Institution or the Principal Investigator.

13.5 The Institution must promptly disclose and communicate in writing to the CRG full particulars of any Intellectual Property that the Institution or Principal Investigator make, discover or conceive in the course of the Study that is directly related to the Study Materials.

14. TERM AND TERMINATION

14.1 This Agreement commences from the date specified on the first page of this Agreement, or if such date is not included on the date this Agreement is last signed by either the CRG or Institution. In the ordinary course of events this Agreement terminates on Study Completion.

14.2 A party may terminate this Agreement with 30 days prior written notice or such shorter time period as is reasonably required in the circumstances if the other party:

(1) is in breach of any obligations under the Agreement or the Protocol (including without just cause to meet a timeframe) and fails to remedy such breach where it is capable of remedy within 30 days of a written notice from the terminating party specifying the breach and requiring its remedy;

(2) is declared insolvent or has an administrator or receiver appointed over all or any part of its assets or ceases or threatens to cease to carry on its business; or

(3) assigns this Agreement to a person considered unsuitable to perform the Agreement as set out in **clause 20.3**.

14.3 In addition to **clause 14.2**, a party may terminate this Agreement immediately by written notice to the other party if it believes on reasonable grounds that:

(1) continuing the Study poses an unacceptable risk to the rights, interests, safety or well-being of Study Participants; and

(2) terminating this Agreement is the most appropriate way to respond to that risk.

14.4 The CRG may terminate this Agreement if the Institution breaches **clause 4.5** or if the CRG learns that the Institution is making, or has made, Improper Payments (within the meaning of **clause 4.5**) to government officials with respect to services performed on behalf of the CRG or any other company. Further, in the event of such

termination, the Institution will not be entitled to any further payment or compensation.

14.5 The CRG may terminate this Agreement immediately by giving notice if the Principal Investigator leaves the institution and an acceptable replacement cannot be found in accordance with **clause 4.1(3)**.

14.6 The CRG may terminate this Agreement with 30 days prior written notice to the Institution. In the event of such early termination, the CRG will pay the reasonable costs of the Institution relating to the Study calculated in accordance with **Schedule 2**.

14.7 In the event of termination, the Institution must promptly initiate all appropriate action to close the Study and, subject to any applicable retention requirements imposed by law, return to the CRG (or destroy if requested by the CRG, and provide evidence of such destruction) any completed Case Report Forms and other materials received from the CRG before Study Completion.

14.8 In the event of termination the CRG must take all appropriate action to close out the Study Site in a timely manner.

14.9 In the event of early termination, the CRG will cooperate with the Institution to ensure that Study Participants who may be affected by termination receive adequate medical care. This may include facilitating the provision of Investigational Product in certain circumstances at no cost to the Institution.

14.10 The following provisions survive termination of this Agreement, **clauses 1.1, 1.2, 4.7, 4.10, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19** and **20.**

15. DISPUTES

15.1 No party may commence legal proceedings against another in respect of a dispute arising in relation to this Agreement (except for urgent interlocutory relief) unless the parties have complied with this clause and that party has first notified the other party in writing of the dispute and has used all reasonable endeavours to resolve the dispute with the other party within 28 days of the giving of that notice ("**Initial Period**").

15.2 If the dispute is not resolved within the Initial Period, then the dispute shall be referred within a further 28 days to the Australian Disputes Centre for mediation or any other agreed venue which conducts mediation. The parties will by agreement appoint a mediator to mediate the dispute in this forum. If the parties cannot agree to a mediator within 14 days of the end of the Initial Period, then the mediator will be nominated by the then current President of the Law Society of the State or Territory in which the Institution is located. Any documents produced for the mediation are to be kept confidential and cannot be used except for the purpose of settling the dispute.

15.3 Each party must bear its own costs of resolving a dispute under this clause, and unless the parties otherwise agree, the parties to the dispute must bear equally the costs of the mediator.

15.4 In the event that the dispute is not settled at mediation within 28 days (or such other period as the parties agree in writing) after the appointment of the mediator, then the parties are free to pursue any other procedures available at law for the resolution of the dispute.

16. APPLICABLE LAW

This Agreement will be governed by, and construed in accordance with, the law for the time being in force in the State or Territory in which the Institution is located and the parties submit to the jurisdiction of that State or Territory and courts entitled to hear appeals from those courts.

17. NOTICES

17.1 A notice, consent, approval or other communication (each a **notice**) under this Agreement must be:

(1) delivered to the party's address; or

(2) sent by pre-paid mail to the party's address; or

(3) transmitted by facsimile to the party's address.

17.2 A notice given by a party in accordance with this clause is treated as having been given and received:

(1) if delivered to a person's address, on the day of delivery if a business day, otherwise on the next business day; or

(2) if sent by pre-paid mail, on the third business day after posting; or

(3) if transmitted by facsimile to a person's address and a correct and complete transmission report is received, on the day of transmission if a business day, otherwise on the next business day.

17.3 The addresses of the parties for the purposes of giving any notice are set out on the front page of this Agreement.

18. WAIVER

18.1 No right under this Agreement is waived or deemed to be waived except by notice in writing signed by the party waiving the right. A waiver by any party in respect of any breach of a condition or provision of this Agreement will not be deemed to be a waiver in respect of any other breach.

18.2 Failure or delay by any party to enforce any provision of this Agreement will not be deemed to be a waiver by that party of any right in respect of any other such breach.

19. VARIATIONS

No variations of this Agreement are legally binding on any party unless evidenced in writing signed by all parties.

20. ASSIGNMENT

20.1 Subject to **clause 20.2**, a party (the **Assigning Party**) may assign its rights or novate its rights and obligations under this Agreement after obtaining the prior written consent of the other party (the **Other Party**).

20.2 The Assigning Party's request for the Other Party's consent to an assignment or novation of this Agreement must include:

(1) the name and the address of the proposed assignee or novatee;

(2) a copy of the proposed deed of assignment or novation; and

(3) such other information as the Other Party reasonably requires.

20.3 Provided the proposed novatee is an Australian entity, the Other Party must give its consent promptly if:

(1) the Assigning Party provides evidence that ought reasonably satisfy the Other Party that the proposed novatee is financially secure and has the ability to carry out the Assigning Party's obligations under this Agreement;

(2) the proposed novatee signs a deed or agreement in which it covenants with the Other Party and the Assigning Party to perform the obligations of the Assigning Party under this Agreement;

(3) the Assigning Party is not in breach of this Agreement; and

(4) the Assigning Party pays the Other Party's reasonable costs of giving its consent.

20.4 The Assigning Party remains liable for its obligations under this Agreement even if it assigns its rights pursuant to **clause 20.1**.

21. ENTIRE AGREEMENT

This Agreement together with its schedules constitutes the entire agreement between the parties in relation to the Study and supersedes all prior representations, agreements, statements and understandings, whether verbal or in writing in relation to the Study.

22. FURTHER DOCUMENTS

Each party will do anything (including executing any document), and will ensure that its Personnel do anything (including executing any document), that the other party may reasonably require to give full effect to this Agreement.

23. SEVERANCE

If any part of this Agreement is prohibited, void, voidable, illegal or unenforceable, then that part is severed from this Agreement but without affecting the continued operation of this Agreement.

24. RELATIONSHIP OF THE PARTIES

Nothing in this Agreement creates a relationship of employer and employee, principal and agent, joint venture or partnership between the parties and no party will hold itself out as an agent for another.

25. FORCE MAJEURE

If any party is delayed or prevented from the performance of any act required under this Agreement by reason of any act of God, act of nature, including any epidemic or outbreak of pandemic disease, fire, act of government or state, war, civil commotion, insurrection, embargo, prevention from or hindrance in obtaining raw material,

energy or other supplies, labour disputes of whatever nature or whatever reason beyond the control of the party (a Force Majeure Event), the affected party shall promptly notify the other party in writing, giving details of the Force Majeure Event, the acts affected by the Force Majeure Event and the extent to which they are affected, and performance of such acts shall be excused for the period of such event provided that if such interference lasts for any period in excess of 30 days either party may, by written notice to the other, terminate this Agreement.

26. COUNTERPARTS

This Agreement may be executed in any number of counterparts. All counterparts taken together are deemed to constitute one and the same Agreement.

27. CONFLICT

In the event of any inconsistency between this Agreement and the Protocol, this Agreement prevails.

In witness hereof, the parties have caused this Agreement to be executed as of the Agreement Date below.

Signed on behalf of the **CRG**

DocuSigned by:

Signed: [redacted]

Name: Laurent Rivory

Position: Pro-Vice-Chancellor (Research)

Date: 12/5/2021

Signed on behalf of the **INSTITUTION**

Signed: Dr Teresa Anderson

Name: [redacted] ecutive

Position: Health District

Date: 9.6.21

The Principal Investigator acknowledges this Agreement and understands the obligations it imposes.

Acknowledged by the **PRINCIPAL INVESTIGATOR**

Signed: [redacted]

Name: Luigi Fontana

Position: Leonard P Ullmann Chair in Translational Metabolic Health

Date: 03 /05 / 2021

DocuSign Envelope ID: 8474986B-BA24-47BE-96B0-BAD5527BC396

Schedule 1: Key Information

(to be inserted by CRG)

Study Name:	A randomised controlled trial to evaluate an intensive lifestyle program for reversal of coronary heart disease (Lifestyle VulnErable PLaqUe Study (LIVEPLUS))
Study Site/s:	CPC-RPA Clinic
Protocol Number:	4.0
Target number of Study Participants:	Minimum: **120**
	Maximum: **150**
Recruitment Period:	Start: 01 / 03 / **2021**
	End: 01 / 05 / **2024**
Principal Investigator Name:	Professor Luigi Fontana
Address:	Charles Perkins Centre
	Faculty of Medicine and Health
	State: NSW P/code: 2050
Reviewing HREC:	Sydney Local Health District Ethics Review Committee (RPAH Zone)
Equipment provided by the CRG:	Nil
At end of Study, Equipment is to be: (refer to clauses 7.5 & 7.6)	❑ Returned to manufacturer; ❑ Returned to CRG; ❑ Retained by Institution; ❑ Destroyed by Institution
Software provided by the CRG	Nil
Investigational Product:	Nil

DocuSign Envelope ID: 8474986B-BA24-47BE-96B0-BAD5527BC396

Schedule 2: Payments

1-NSW HEALTH PATHOLOGY

Per patient cost:
NSW health pathology will undertake analysis on blood samples.
Cost per patient=$56.70 (see breakdown below*)

*breakdown of full pathology costs:

Qty	Description	Unit price (AUD)
1	FBC	10.20
1	EUC, LFT, UA, LDL, Triglycerides, Total Cholesterol, Fasting Glucose	10.65
1	HDL, non-HDL Cholesterol	6.70
1	HbA1c	10.10
1	Oral Glucose Tolerance Test (OGTT) at 0,30,60,120 min (including Glucose & Insulin measures)	11.40
1	Processing fee	2.50
	Subtotal	51.55
	GST	5.15
	Total	**56.70**

Total costs (including all visits and patient samples):

Test	Qty	patients	Total
Full pathology costs as above =$56.70	2	150	$17,010.00
All bloods apart from OGTT= $44.17	2	150	$13,251.00
One off project establishment fee	1	n/a	$110.00
TOTAL COSTS			**$30,371.00**

Payment details: NSW pathology will send invoices on a monthly basis (usually around 7th of each month) to the liveplus.study@sydney.edu.au email address. The account to be charged will be Hopewood project (RC 44072, PC D1760).

2-DEPARTMENT OF RADIOLOGY (CT SCAN):

Total costs (including all visits and patient samples):

Test	Qty	patients	Total
CT Scan=$300	1	150	$45,000.00
TOTAL COSTS			**$45,000.00**

Payment details: The department of radiology will send invoices on a quarterly basis to the liveplus.study@sydney.edu.au email address. The account to be charged will be Hopewood project (RC 44072, PC D1760).

Institution payment processing details

Payee Name:	*Sydney Local Health District*
Payee Address:	*Sydney Local Health District (SLHD)* *c/- District Finance* *Level 8, KGV Bldg 13, Royal Prince Alfred Hospital* *Missenden Rd, Camperdown, 2050*
Bank:	*Westpac Banking Corporation*
Branch:	*181 Miller Street North Sydney, NSW 2060*
Account Name:	*SLHD General Fund*
BSB Number:	*032099*
Account Number:	*520802*
SWIFT No:	*WPACAU2S*
Remittance advice:	*SLHD-RPAHREMMIT@health.nsw.gov.au*

RPA PHARMACY

It has been agreed that the following fees will be paid to RPA Hospital Pharmacy. The RPA Pharmacy will raise a journal transfer for payment quarterly.

Fee Description	Unit price
Metoprolol 50mg Tablets	$0.01 per tablet
Glyceryl Trinitrate 300mcg sublingual tablets	$0.15 per tablet
Ivabradine 5mg tablets	$0.21 per tablet

DocuSign Envelope ID: 84749869-BA24-47BE-96B0-BAD5527BC396

Schedule 3: Study Protocol Identification

Full Title:	A randomised controlled trial to evaluate an intensive lifestyle program for reversal of coronary heart disease (LIfestyle VulnErable PLaqUe Study (LIVEPLUS)
Version Number:	X20-0229 (v4.0)
Date:	03 / 11 / 2020
List of Key attachments:	Protocol

DocuSign Envelope ID: 8474986B-BA24-47BE-96B0-BAD5527BC396

Schedule 4: Special Conditions

Please Paste/Enter Text Below

Nil.

Appendix H

Author contribution statement for Chapter 3

DocuSign Envelope ID: F41F1160-212A-4636-A46A-6B7A9B02D733

Author Contribution Statement

Chapter 3 of this thesis is published as outlined below. By signing below, I confirm that Sayan Mitra was the co-author and contributed to the design, resources development, and manuscript writing for the following article:

> S. Cassidy, C.M. Kroeger, T. Wang, **S. Mitra**, C. Liu, R.V. Ribeiro, A. Dai, J. Lau, R. Huang, A. Masedunkas, S. Jose, N. Liu, L. Avery, J. Yang, M. McGrady, S.N. Lo, J. George, P.A. Cistulli, L. Khor, R. Kozor, M. Ugander, I. Wilcox, I. Hunyor, and L. Fontana. Impact of an Intensive Lifestyle Program on Low Attenuation Plaque and Myocardial Perfusion in Coronary Heart Disease: A Randomised Clinical Trial Protocol. Nutrition and Healthy Aging, 2022: 9-22, DOI: 10.3233/NHA-210146

Name	Signature	Name	Signature
Sophie Cassidy		Leah Avery	
Cynthia M. Kroeger		Jessica Yang	
Tian Wang		Michele McGrady	
Sayan Mitra		Serigne Lo	
Chen Liu		Jacob George	

Rosilene V. Ribeiro	DocuSigned by: [redacted]	**Peter Cistulli**	DocuSigned by: [redacted]
Aimee Dai	DocuSigned by: [redacted]	**Lynn Khor**	DocuSigned by: [redacted]
Jonathan Lau	DocuSigned by: [redacted]	**Rebecca Kozor**	DocuSigned by: [redacted]
Robin Huang	DocuSigned by: [redacted]	**Martin Ugander**	DocuSigned by: [redacted]
Andrius Masedunkas	DocuSigned by: [redacted]	**Ian Wilcox**	DocuSigned by: [redacted]
Shane Jose	DocuSigned by: [redacted]	**Imre Hunyor**	[redacted]
Na Liu	DocuSigned by: [redacted]	**Luigi Fontana**	DocuSigned by: [redacted]

Appendix J

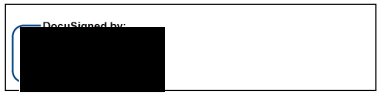
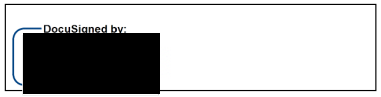
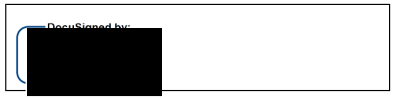
Author contribution statement for Chapter 6

DocuSign Envelope ID: C28585D4-0C8F-4766-9B53-D3BBAC441654

Author Contribution Statement

Chapter 6 of this thesis is published as outlined below. By signing below, I confirm that Sayan Mitra was the co-author and contributed to the design, resources development, and manuscript writing for the following article:

> **S. Mitra**, C.M. Kroeger, J. Xu, L. Avery, A. Masedunskas, S. Cassidy, T. Wang, I. Hunyor, I. Wilcox, R. Huang, B. Chakraborty, L. Fontana. Testing the Effects of App-Based Motivational Messages on Physical Activity and Resting Heart Rate Through Smartphone App Compliance in Patients With Vulnerable Coronary Artery Plaques: Protocol for a Microrandomized Trial. JMIR Research Protocols, 2023;12:e46082, DOI: 10.2196/46082

Name	Signature	Name	Signature
Sayan Mitra		Sophie Cassidy	
Cynthia M. Kroeger		Tian Wang	
Jing Xu		Imre Hunyor	
Leah Avery		Ian Wilcox	
Andrius Masedunkas		Robin Huang	

Bibhas Chakraborty

DocuSigned by:
[redacted]

Luigi Fontana

DocuSigned by:
[redacted]

Appendix K
LIVEPLUS recruitment fliers

THE UNIVERSITY OF SYDNEY

ARE YOU INTERESTED IN LIVING HEALTHIER?

About Our Study

The purpose of this 12-month study is to determine whether a comprehensive lifestyle intervention (5:2 pescovegetarian diet, physical activity, and stress reduction training) improves cardiovascular health in people with coronary heart diesease

Potential Benefits

Reduction in body (fat) weight, blood pressure, glucose, cholesterol, and inflammation. No cost. Included dietary, physical activity, and stress reduction coaching, heart testing, body composition, and blood labs

Now Enrolling

Ages 18-85
Normal to overweight
Non-smoker
Vulnerable plaque on CT scan

[redacted]
Dr Cynthia Kroeger
Trial Coordinator
liveplus.study@sydney.edu.au

Principal Investigator
Luigi Fontana, MD, PhD, FRACP