Sedentary time glycaemic control and type 2 diabetes

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Sedentary Time, Glycaemic Control and Type 2 Diabetes

Submitted by

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Bachelor of Clinical Exercise Physiology
Bachelor of Applied Science of Exercise and Sports Nutrition

A thesis (by publication) submitted in total fulfillment of the requirements of the degree of

Doctor of Philosophy

Behaviour, Environment and Cognition Research Program
Mary MacKillop Institute for Health Research
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Melbourne, Victoria

2nd of July 2022
Statement of authorship and sources

To the best of my knowledge no other person’s work has been used in this submission without due acknowledgment.

The research featured in this thesis involving human research participants and data received approval by the relevant ethics committee. For all research, written and informed consent was obtained and archived.

Included in this thesis is published work and/or work in preparation for publication in scientific journals. These publications have been co-authored. Contributions to each scientific work have been acknowledged in the thesis and approved by higher degree research body.

Christian John Brakenridge

Date: 02/07/2022
Acknowledgements

It’s not often that you are granted the opportunity to unabashedly provide gratitude to the people that made it all happen, like in those conversations you might exchange with coworkers at the end of a work Christmas party. So here goes.

To my supervisors who provided unwavering support,

David Dunstan, thank you for having me on board, which from the outset might have been a leap of faith. Before your invite, truth be told I was disillusioned with my career. For you to so generously provide an offer filled me with such a deep and profound sense of hope – hope that I could grow as a person and eventually make something of myself that I could be proud of. You have been there with me every step of the way throughout this candidature, and I will always admire your ability to lead the lab and foster an equal and collaborative work environment.

Alison Carver, thank you for being so reliable and kind throughout the candidature, also for giving me the confidence in the final stages towards submission. Neville Owen, it’s often awe-inspiring hearing you pull the right phrase out of the ether. You have improved my ability to express myself through writing and oration immeasurably, and ultimately this is the defining feature of a researcher. Thanks for always being so generous and open for discussion, whether academic or otherwise, and thanks too for fixing my bike. Genevieve Healy, it’s no understatement to say that you have been the key player in all my research roles to date.

Towards the end of my time at the University of Queensland you tried to set me up with a role aiming to investigate sedentary behaviour within a chronic disease management context, with me ultimately taking another route. To then deliver on that original promise some five years later in the form of PhD candidature makes you a hero of mine. Without your instinct for good science and brevity during my PhD candidature, I wouldn’t have reached this far.

To my Baker Institute lab mates,

Resident PhD students at the time of my commencement: Michael Wheeler, Frances Taylor, and Ashleigh Homer, thank you for simply showing me how it’s done. It’s rare to find people simultaneously so generous and intelligent. Frankie, Ash, and Mel Townsend, my lab sisters
who have been with me throughout my candidature. It’s inspiring to know that we will cross paths again and we will always have this shared experience to reflect on. Thank you for always having my best interests at heart and continually batting for me as one of your own. Ruth Grigg and Kym Rickards, you both foster such a fantastic team-oriented environment which is great to work in. Kym, our camaraderie is the best, and our banter really makes me feel welcome in the lab in so many ways. One day the pretty figures in this thesis might make a difference too! Ruth, thank you for always prioritizing the support and wellbeing of all of us. It’s hard to think of any words that would do your unrelenting support of me in the last 3 years any justice. Parneet Sethi, you have given me confidence and taught me autonomy with my work. Once you showed me it was all possible with diligent and continued elbow grease, it was a real turning point in my PhD experience. Current PhD buddy Francis Dzakpasu, thanks for sticking with me and always leading an enviable and studious example for me to follow, I’ve sincerely enjoyed our problem-solving adventures as of late and I look forward to celebrating with you as

To the academics that were pivotal co-authors in my publications to date: Agus Salim, John Bellettiere, Sebastien Chastin, and Elisabeth Winkler. Thank you for your generosity with providing insights, technical support, and constructive critique. If it is said that if you are the smartest person in the room, then you are in the wrong room, then perhaps I have the right room with your company. I am also grateful to the UQ researchers that both created the opportunities and opened them to me specifically, in particular: Ana Goode, Brianna Fjeldsoe, Paul Gardiner, and Sjaan Gomersall. The mentoring and vote of confidence that you have provided me has made a significant difference in my life.

Students, staff, and academics including, but not limited to: Elly Fletcher, Rumya Pathmanathan, Hayley Dillon, Nick Saner, Terry Fong, Jed Morton, Ashley Bigaran, Tye Dawood, Stephanie Yiallourou, Erin Howden, and Evelyn Parr. Thanks for giving me new perspectives, evaluating my work, and being good friends. A special thank you also goes to you Vaughan Macefield, for always keeping it real and the mentorship between drinks. To my international research colleagues, Ana Pinto, Danielle Ostendorf, Shilpa Dogra, Suvi Lamberg, and Beatriz Rodriguez. I am grateful to have been invited into your world and your respective projects,
which have provided a healthy distraction from the work in this thesis. Arto Pesola, thank you for involving me with your research, which has filled me with excitement knowing that there are already new opportunities waiting for me. These were a ‘carrot at the end of the stick’ during my candidature and kept me motivated throughout.

Thanks must go to the OPTIMISE research participants that gave up their time, their blood, permitted health coaching, and responded to millions of surveys. I am grateful to all of you for letting me be a part of your story and letting me well and truly understand your health.

To my close friends and family, of which there are too many to name here. Thank you for always being supportive and encouraging of my career pursuits.

Charlotte, you opened the door for me to the world of research. Thank you for showing me that completing a PhD was surmountable, and not necessarily a monolithic task. You’ve supported me from day one, and I’m lucky to have you as my sister always pushing me to do my best. Mum, you have always provided unconditional love and shared pride of my achievements, that has meant a lot to me and was the best final encouragement in these last few months. Dad, thank you for developing in me an inquisitive and curious mind, and instilling in me a strong sensibility for things technical and technological. Thank you both for bestowing me with the creativity required to come up with some of the ideas in this thesis, and always pushing me to pursue my passion. To Alex, Callum, Sam, Sam, and Nam, a great deal of the intelligence that I can claim has come from our friendship, having held strong over the many years. Thanks for continuing to encourage growth by being the sounding board to my ideas and opinions.

Finally, there’s my darling partner Missy Lewis. Missy, you have supported me through what were and continue to be the most challenging of times. You have championed my wins and provided solidarity with my losses. I am extremely grateful for your selflessness and sacrifice to be a part of this journey. You are the love of my life.
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* Tables and figures presented in the papers included
Abstract

Background

An estimated 537 million adults globally have diabetes (of which over 90% have type 2 diabetes), contributing substantial impact to their health and future risk of disease. Excessive sedentary time – too much sitting – has now been identified as a distinct behavioural target for the management of type 2 diabetes. Glycaemic control is a key management consideration for reducing the risk of cardiometabolic diseases and diabetes complications. However, the associations of sedentary time with glycaemic control, and the potential benefits of replacing sedentary time with alternatives (e.g., with standing or stepping), along with the impacts of COVID-19 on lifestyle behaviours are unclear. Such information is necessary to help inform the development of randomised controlled trials aiming to reduce sedentary behaviour in people with type 2 diabetes to improve glycaemic control.

Aims

The overarching aim of this thesis is to better understand the role of sedentary time and its alternatives in people with type 2 diabetes. Specific objectives are to:

- Understand associations of sedentary behaviour and its main alternatives – standing and stepping, with glycaemic control and related cardiometabolic risk markers in those with and at risk of type 2 diabetes
- Determine how relationships of glycaemic control and related cardiometabolic risk markers with sedentary behaviour and main alternatives may differ between those with or at risk of type 2 diabetes.
- Describe the development of a multicomponent sedentary behaviour reduction intervention in adults with type 2 diabetes.
- Investigate the longer-term changes in sedentary behaviour and physical activity in people with type 2 diabetes and explore the impact of COVID-19 lockdown restrictions on these behaviours.
**Methods**

Data for this thesis were drawn from three studies: the Australian Diabetes, Obesity and Lifestyle (AusDiab) study, the Maastricht Study, and the OPTIMISE Your Health Study. Across two countries (Australia, Netherlands), 3,047 participants either with type 2 diabetes, at higher risk of type 2 diabetes, or with normal glucose metabolism were investigated. Key measures of interest were glycaemic control (glycosylated haemoglobin; HbA1c), fasting and OGTT blood draws (plasma glucose and insulin), and other related cardiometabolic biomarkers relevant to diabetes management (e.g., lipids, triglycerides, waist circumference, insulin sensitivity). In all studies, free-living sedentary time and activity were objectively assessed with device measures including the research grade activPAL™ inclinometer and a consumer wearable Fitbit™, which facilitated the measurement of longer-term observation periods. Activity data collected were analysed with a range of regression methods, including compositional data analysis.

**Key Findings**

The epidemiological findings demonstrated that compositions of both waking and the full 24hr time with greater sitting time were associated detrimentally with indices of glycaemic control and related cardiometabolic risk markers, with direct implications for diabetes management. Compositions with greater sitting, and less standing had detrimental associations only in those at higher risk of diabetes (≥5.7% HbA1c), suggesting that interventions may be of greater benefit to those with more-impaired glycaemic control. These findings were further corroborated in a cohort of people with type 2 diabetes, with findings suggesting that more time spent standing or stepping in lieu of sitting time is associated with greater glycaemic control benefits. Importantly though, only variations in sitting and stepping time in a daily composition were associated with glycaemic and insulin sensitivity outcomes (fasting and 2-hour post-load glucose, HbA1c, and insulin sensitivity) in people with type 2 diabetes, suggesting that stepping time should ideally replace sitting time for more favourable changes in diabetes-related outcomes. Potential offsets in time spent in sedentary behaviour by time spent standing and stepping are presented, with an indication of progressively beneficial associations with diabetes-related outcomes up until a particular threshold.
Longitudinal findings suggest that the COVID-19 lockdown restrictions were associated with significant changes to physical activity and sedentary behaviours in office workers with type 2 diabetes. Overall, intervention trial participants monitored for months preceding and during the lockdown restrictions reduced their light and fairly active intensity minutes and increased their sedentary minutes and sedentary bout duration. Some participants maintained or improved their longitudinal pattern of behaviours despite the restrictions, providing additional insight. These factors may have relevance and implications for adherence to the intervention in the randomised control trial (the OPTIMISE Your Health study) described in this thesis. In future, the analytical approaches devised and used in the studies reported in this thesis can test outcomes of this trial and determine how sedentary behaviour may be addressed to improve glycaemic control in those living with type 2 diabetes.

Conclusions

This thesis expands current knowledge on sedentary behaviour within free-living contexts and in people at risk of and with type 2 diabetes. Favourable time-use compositions associated with beneficial glycaemic control and related cardiometabolic risk markers have been identified using novel methodology. These compositions require corroboration by more robust study designs, including by the sedentary behaviour intervention trial described. Further, the COVID-19 pandemic provided a novel opportunity to explore longer-term physical activity and sedentary behaviours, the findings of which suggested increased sedentary behaviours and decreased active behaviours in participants with type 2 diabetes following lockdown restrictions. In this context, addressing high levels of sedentary behaviour remains a public health priority, particularly in people with type 2 diabetes.
Publications, Presentations & Awards

Peer-review publications related to thesis


Manuscripts related to thesis in preparation for scientific journal


Additional peer-reviewed publications during candidature


**Conference presentations related to thesis**


Additionl invited presentations and written works related to thesis

• Rise and Recharge: Balancing sedentary behaviour for health benefit. Presented at the Early-Mid Career Research Seminar Series at Monash University, April 2022.

• ABC Illawarra interview on sedentary behaviour and diabetes management. Interviewed live on ABC talk-back radio, December 2021.

• COVID saw us sitting longer – and diabetes rose globally by 16% in 2 years. Time to get moving. The Conversation article, December 2021.

• Using the Fitbit to understand the long-term impact of COVID-19 lockdown on activity levels amongst intervention trial participants with type 2 diabetes. Presented at the Melbourne Centre for Data Science Seminar Series at The University of Melbourne, December 2020.

• Associations with glycemic outcomes of 24-hr activity time-use composition: variations by level of diabetes risk Presented internally at Baker Heart and Diabetes Institute Monday meeting, July 2020.

• The Optimise Your Health Trial: Reducing Sitting Time in Office Workers with Type 2 Diabetes. Presented internally at Baker Heart and Diabetes Institute Monday meeting, February 2020.

Print media releases related to thesis are available in Appendix F

Awards received during candidature

• Harold Mitchell Travelling Fellowship. Competitive travel, conference and laboratory visit support to Finland provided by Harold Mitchell Foundation with the Baker Heart and Diabetes Institute. Awarded $5,000.

• Winner, Best Overall Presentation. Geraldine Naughton Student Research Presentation Awards – Australian Catholic University, online. Awarded $500.

Grant application and involvement during candidature

• Academy of Finland: “OPTIMUS: A Randomized Controlled Trial to Influence Sustained Glycaemic Control by Reducing Muscle Inactivity Time in Middle-Aged and Older Office Workers with Type 2 Diabetes” (Pesola A, Owen N, Dunstan D, Juutinen Finni T, Healy GN,
Brakenridge CJ, Lamberg S); AU $1,109,565; 2021 – 2024. **AWARDED.**

- **Baker Seed Grant:** “The Integration of Lifestyle into Personalised Medicine Approaches: A machine learning-based algorithm for high-resolution and cost-effective characterization of sedentary behaviour” (Salim A, Brakenridge CJ, Owen N, Dunstan D); AU $95,000; 2022 – 2023.

More information on grant applications is available in Appendix G
# List of Abbreviations and Nomenclature

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<tbody>
<tr>
<td>Accelerometer</td>
<td>A device that measures acceleration forces</td>
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<tr>
<td>ABS</td>
<td>Australian Bureau of Statistics</td>
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<tr>
<td>Actigraph</td>
<td>Wrist worn accelerometer</td>
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<tr>
<td>ActivPAL</td>
<td>Thigh affixed accelerometer produced by activPAL™</td>
</tr>
<tr>
<td>AUD</td>
<td>Australian dollar</td>
</tr>
<tr>
<td>AusDiab</td>
<td>Australian Diabetes, Obesity and Lifestyle Study</td>
</tr>
<tr>
<td>BMI</td>
<td>Body Mass Index</td>
</tr>
<tr>
<td>CoDA</td>
<td>Compositional Data Analysis</td>
</tr>
<tr>
<td>CRP</td>
<td>C-reactive protein</td>
</tr>
<tr>
<td>CVD</td>
<td>Cardiovascular Disease</td>
</tr>
<tr>
<td>DEXA</td>
<td>Dual-energy X-ray Absorptiometry</td>
</tr>
<tr>
<td>EMG</td>
<td>Electromyography</td>
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<tr>
<td>FMD</td>
<td>Flow-mediated dilation</td>
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<tr>
<td>FPG</td>
<td>Fasting plasma glucose</td>
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<td>GLUT4</td>
<td>Glucose transport protein</td>
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<tr>
<td>HbA1c</td>
<td>Glycosylated haemoglobin</td>
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<tr>
<td>HDL</td>
<td>High-density lipoprotein</td>
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<tr>
<td>HOMA</td>
<td>Homeostasis Model Assessment</td>
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<tr>
<td>LDL</td>
<td>Low-density lipoprotein</td>
</tr>
<tr>
<td>LPA</td>
<td>Light-intensity physical activity</td>
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<tr>
<td>MET</td>
<td>Metabolic equivalent</td>
</tr>
<tr>
<td>MVPA</td>
<td>Moderate to vigorous intensity physical activity</td>
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<td>OGTT</td>
<td>Oral Glucose Tolerance Test</td>
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<td>PLG</td>
<td>Post-load plasma glucose</td>
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<td>Term</td>
<td>Description</td>
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<tr>
<td>Prolonged sitting</td>
<td>Sitting accumulated in prolonged bouts (≥30 minutes)</td>
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<tr>
<td>Sedentary behaviour</td>
<td>Waking behaviour 1.5 METS or less sitting or reclined</td>
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<td>Type 1 diabetes</td>
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<tr>
<td>T2D</td>
<td>Type 2 diabetes</td>
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<tr>
<td>UKPDS</td>
<td>United Kingdom Prospective Diabetes Study</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Introduction

Type 2 diabetes is one of the largest contributors to disease burden in Australia and globally (1,2). Acceptable management of blood glucose (i.e., glycaemic control) is the primary consideration. Poor glycaemic control leads to increased risk of diabetes-related complications and additive burden on the health care system (3). Addressing modifiable lifestyle factors is a cornerstone in the management of glycaemic control. These include modifying diet, cigarette and alcohol consumption, weight loss, and increasing physical activity. Current physical activity guidelines recommend at least 150 minutes of moderate-intensity exercise per week, and 2 – 3 sessions (≥60 minutes) of resistance exercise. However, consistent evidence shows that physical activity levels are low in people with diabetes, with many reporting no engagement in moderate- to vigorous-intensity physical activity (MVPA) (4,5) or insufficient levels to meet guidelines (6).

Sedentary behaviour (i.e., time spent sitting) is increasingly being considered as a modifiable lifestyle factor that influences glycaemic control (7) and can increase all-cause mortality risk, particularly in those who are also inactive (not meeting physical activity guidelines (8)). People living with type 2 diabetes engage in higher amounts of sedentary behaviour compared to those without, averaging 10 hours per day of sitting (9). This suggests that interventions to reduce sedentary time may be a potential target for health promotion in this population. Due to the compositional nature of a 24-hour day, reductions in sedentary time will inherently lead to increases in time spent in other activities. However, it is currently unclear what the relative benefit of the different replacement activities (i.e., standing, stepping) may be in those with type 2 diabetes, and further, the extent to which these behaviour changes can be maintained long term – particularly in the face of unexpected barriers such as the COVID-19 pandemic.

This thesis aims to address key knowledge gaps in the lifestyle management of type 2 diabetes by increasing understanding of the potential benefits of reducing sedentary behaviour and increasing physical activity for glycaemic control and risk factors for cardiometabolic disease. It begins with a focused literature review (Chapter 1) and methods chapter (Chapter 2) providing the scientific background, rationale, context, and methodology for the four primary research
chapters (Chapters 3 – 6). To conclude, a discussion chapter (Chapter 7) synthesises the findings and expands on their collective relevance to the field, elaborates on strengths and limitations of the thesis, and discusses the clinical and public health implications with identification of directions for future research.

Prior to this thesis, there was limited evidence, using robust measures, regarding the associations of sedentary behaviour and its alternatives with glycaemic control and diabetes management. To address this gap, cross-sectional analyses were undertaken in adults with type 2 diabetes from two population-based datasets: the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study and the Maastricht Study from the Maastricht University (Netherlands). These studies have gathered some of the most comprehensive data of free-living device-measured sitting, standing, and stepping time in adults with type 2 diabetes.

Another key gap in the literature is the lack of longitudinal and experimental evidence on sedentary behaviour in people type 2 diabetes, including understanding how the COVID-19 pandemic has influenced sedentary behaviour and physical activity in people with type 2 diabetes. Chapter 5 details the protocol of a randomised controlled trial titled “Optimise Your Health”; a large-scale study that is investigating how long-term reduction in sedentary behaviour impacts glycaemic control. Chapter 6 focuses on the long-term activity patterns of a convenience sample of adults with type 2 diabetes and how they were impacted by the lockdowns related to the COVID-19 pandemic.

Chapter 7 discusses the clinical implications of the research, and the potential for its translation to the management of people with type 2 diabetes. According to these concepts, the primary findings are contextualised, and future research opportunities are suggested. As per guidelines for thesis by publication, each chapter is summarised to highlight key messages of each publication. Citations and formatting for each paper are self-contained and as per journal bibliography requirements. Other citations used throughout this thesis are provided in the references section at the end.
Chapter 1: Literature Review

Chapter 1 provides a scientific context to the aims of this thesis – to better understand the role of sedentary time and its alternatives in people with type 2 diabetes. Section 1.1 outlines the burden of type 2 diabetes and the importance of addressing modifiable lifestyle factors, and with evidence provides a rationale to underpin novel and improved management approaches. Section 1.2 describes the relationship of physical activity to type 2 diabetes. Section 1.3 describes the epidemiology of sedentary behaviour, describing the numerous adverse impacts on glycaemic control and related cardiometabolic health and the implications for type 2 diabetes management. Section 1.4 outlines how the COVID19 pandemic affected populational physical activity and sedentary behaviour levels as well as people with type 2 diabetes.

An overall summary is provided, identifying the evidence gaps and from this, the primary research objectives are derived.

1.1 The burden of diabetes and the importance of addressing modifiable risk factors

Diabetes is defined by the body’s impaired ability to produce or respond to insulin, resulting in insufficient metabolism of blood glucose. In 2021, there was an estimated 537 million adults (aged 20 – 79) living with diabetes globally (2), a prevalence that has more than tripled since previous estimates in 2000. Type 2 diabetes represents 90 – 95% of all diabetes cases (2) and is characterised by insulin resistance and high blood sugar (hyperglycaemia). It is a progressive disease often worsening in prognosis over time. In Australia, an estimated 5.3% of the population (1.3 million) had diabetes in 2020 (1). It is the fastest growing chronic condition in Australia (1). Reported data from the Australian Bureau of Statistics (ABS) 2011-2012 health survey (10) indicate that in Australia there is one undiagnosed person to every four diagnosed. Global estimates suggest this is even higher with almost half of all adults living with diabetes (44.7%; 239.7 million) being undiagnosed (11).

The global health expenditure attributed to diabetes in adults has expanded from AUD 232 billion in 2007 to 966 billion in 2021 (2). In Australia, type 2 diabetes constitutes the 12th largest
contributor to disease burden (2015), and accounts for 2.2% of total disease burden, costing Australians AUD 6 billion per year (1). Further estimates attribute the burden of high plasma glucose levels (which additionally include prediabetes and undiagnosed diabetes), to constitute 4.7% of the Australian chronic disease burden (1). For the average person with type 2 diabetes, the financial burden has been estimated to be $4025 per year and can increase up to $9645 in the event of diabetic complications (3). In 2015, 18,100 Australians were absent from the labour market due to diabetes. This financial impact (12) extends to the proliferation of welfare payments and further loss in taxation revenue, namely as a result of less productive life years in people with type 2 diabetes (13).

Diabetes was associated with 10.5% of all deaths in Australia in 2018 (1). The most prevalent cause of death was due to cardiovascular disease complications (56% of diabetes-associated deaths). Diabetes is associated with increased oxidative stress, coagulability, endothelial dysfunction, and autonomic neuropathy, which may contribute directly to macrovascular pathology (14). In 2020, 57% of all people reported living with diabetes in Australia also reported comorbid cardiovascular disease (15). In addition to cardiovascular disease, people with diabetes have considerably higher risk of other chronic conditions including: depression (16); Alzheimer’s and dementia (17); asthma (18); chronic obstructive pulmonary disorder (19); hyperthyroidism (20) and many others. A unique consideration for diabetes is the manifestation and progression of microvascular diabetic complications, which develop as a product of chronic and untreated hyperglycaemia (21). These microvascular complications include: retinopathy – the leading cause of blindness; nephropathy, and neuropathy; and eventually macrovascular (e.g., CHD, Stroke) complications develop (22).

1.1.1 Diabetes diagnosis and glycaemic control

Diabetes is diagnosed through determination of current glycaemic control status, which is paramount for establishing current risk for adverse health outcomes. The current measures for interpreting glycaemia include fasting plasma glucose (FPG), Oral Glucose Tolerance (OGTT), and glycated haemoglobin (HbA1c). A FPG measurement requires a person to have blood drawn and collected in a fasted state (typically over 9 hours without food). OGTT requires a
person to present fasted before ingesting a standardised 75g glucose, and then blood glucose is measured at successive intervals, typically with the 2 hour results reported (23). Together these measures provide insight into a person’s typical blood glucose levels pre-prandial (fasted) and post-prandial (fed) and can be used to indicate insulin sensitivity. Abnormal results on either FPG or OGTT reflect impaired fasting glucose (IFG), impaired glucose tolerance (IGT), or a diabetes diagnosis. Glycated haemoglobin (HbA1c) also requires a blood draw but does not need the person to present fasted. It captures average glycaemia over the last 12 weeks and is insensitive to daily variability in blood glucose (23,24).

Various targets have been determined by the American Diabetes Association (ADA) to determine a diagnosis and corresponding health risk (Table 1; ADA 2018) (25). Management of these aforementioned biomarkers is essential to slow the progression of disease and to prevent impaired fasting or impaired glucose tolerance from progressing to type 2 diabetes. In 1999-2000, 16.4% of Australian adults were identified as having either impaired fasting glucose or impaired glucose tolerance (26), indicating that there is in fact a large cohort of people in Australia who are have a heightened risk for the development of type 2 diabetes.

Table 1. American Diabetes Association classification for normal, impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and diabetes.

<table>
<thead>
<tr>
<th></th>
<th>Fasting Blood Glucose (mmol/L)</th>
<th>Oral Glucose Tolerance Test (2h mmol/L)</th>
<th>Glycated Haemoglobin (HbA1c%)</th>
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<tbody>
<tr>
<td>Normal</td>
<td>&lt;5.56</td>
<td>&lt;7.78</td>
<td>&lt;5.7%</td>
</tr>
<tr>
<td>IFG, IGT (Prediabetes)</td>
<td>≥ 5.56 - &lt;7</td>
<td>≥ 7.78 - &lt;11.1</td>
<td>≥ 5.7 &amp; &lt;6.5%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>≥ 7</td>
<td>≥ 11.1</td>
<td>≥ 6.5%</td>
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To diagnose type 2 diabetes, ADA recommends a positive 2h post-prandial value measurement for OGTT and HbA1c (27). Glycaemic control is a term that is relative to the individual and relates to the improvement of these blood glucose measurements. There is substantial evidence that improving glycaemic control is associated with reduced macrovascular disease
and microvascular disease. Large prospective trials, in a range of cohorts featuring both type 1 and type 2 diabetes, have demonstrated that disease and mortality endpoints favour intensive glycaemic control (28). The strongest evidence is the reduction of microvascular disease (29), especially retinopathy, and nephropathy disease incidence and progression. Extended observation periods have also demonstrated that even after intervention, and resumption of glycaemia equivalent to control participants’ levels, that intensive treatment results in diminished risk of myocardial infarction and delays the progression of diabetic nephropathy (30,31). The United Kingdom Prospective Diabetes Study (UKPDS) trial (31) which followed participants on intensive treatment for 10 years demonstrated the strongest evidence supporting glycaemic control as effective for reducing all-cause mortality, achieving a 10% reduction compared to the control group. Of note, intensive glycaemic control was efficacious independent of the glucose-lowering therapies (either insulin, chlorpropamide, or glibenclamide) used in this trial.

Table 2. An evidence summary of the associated risk of disease with hyperglycaemia

<table>
<thead>
<tr>
<th>Levels of evidence</th>
<th>Associated risk of disease with hyperglycaemia</th>
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| Consistent evidence – at least one systematic review     | • Microvascular disease: retinopathy, peripheral neuropathy, nephropathy and albuminuria (22)  
• Macrovascular disease: acute coronary syndrome (32)  
• Cancer: pancreas, liver, endometrium, mammary gland (33)  
• Adverse pregnancy outcomes (34)                       |
| Emerging evidence – at least one RCT                    | • Macrovascular disease: Congestive heart failure in diabetic patients after MI (35)  
• Congestive heart failure in non-diabetic populations (36)  
• Cancer: Colorectal (37); Gastric (38); Urinary tract, malignant melanomas (39)  
• Post-surgery infection (40)  
• Cognitive dysfunction (41)                              |
1.1.2 Modifiable lifestyle factors, glycaemic control, and diabetes burden

Modifiable lifestyle risk factors associated with type 2 diabetes include smoking, diet, alcohol consumption, overweight/obesity, and physical inactivity. Modifying these behaviours is acknowledged as being integral for the prevention and management of diabetes. Addressing these factors also reduces the risk of clustered comorbidity associated with type 2 diabetes (46,47).

Most interventions targeting modifiable lifestyle risk factors have attempted to modify diet and exercise participation. Many of these trials have seen prospective improvement in glycaemic control and resultant improvement in disease outcomes, although there is a paucity of evidence in people with type 2 diabetes. In the Diabetes Prevention Program trial (DPP), which recruited participants with impaired glucose tolerance, participants who were randomised to weight loss (7% weight loss target) and physical activity (target of 150 minutes/week) (48) outperformed the metformin and usual care arms in terms of glycaemic control and microvascular burden (49). In The Da Qing trial (50), participants with impaired glucose tolerance were recruited and intervention group participants improved diet, exercise, or both and were followed up for 30 years. Participants in the intervention groups delayed their diagnosis of diabetes and had lower incidence of microvascular disease. The extensive follow-up facilitated identification of fewer cardiovascular disease events, lower cardiovascular disease, and lower all-cause mortality among the intervention groups (51). The Look AHEAD (action for Health in Diabetes) trial (52) aimed to induce weight loss via changes to dietary intake and physical activity among older adults with type 2 diabetes. The study found less pronounced benefits for disease outcomes, only reduced risk of diabetic kidney disease and retinopathy. However, the intervention did result in benefit to markers predictive of disease risk such as glycaemic control, blood pressure, lipids, and a reduction in obesity (53). Whilst more research is needed in large cohorts of people with type 2 diabetes, collectively these results do suggest that lifestyle interventions that
improve glycaemic control are likely to result in improved health outcomes and some level of disease mitigation.

Both lifestyle and pharmacological interventions have demonstrated efficacy for improving glycaemic control. However, despite the clear clinical gains it is evident that substantial portions of the population (men: 31%; women: 24%) do not reach target glycaemic control levels of 7% HbA1c (54). With improvements still to be made in addressing the burden of diabetes and its associated complications, a number of investigations have explored the role of physical activity and exercise as tools to manage type 2 diabetes.

1.2 Physical activity, glycaemic control and diabetes

Physical activity is defined as any bodily movement produced by skeletal muscles that requires energy expenditure (55). Exercise is a form of physical activity that is planned and structured. Current guidelines classify adults as being physically active if they achieve 150-300 minutes of moderate-intensity physical activity, or 75-150 vigorous-intensity physical per week, and engage in at least two days of muscle-strengthening activities per week (56). Where an individual does not achieve these guidelines, they are classified as physically inactive. Aside from the benefits to disease risk, physical activity provides two direct benefits to diabetes management and glycaemic control: the enhanced stimulation of insulin-independent glucose uptake and augmentation of insulin action (57). Muscle contraction stimulates glucose uptake, independent to signaling via insulin. Every muscle contraction signals translocation of GLUT4 out of intracellular storage, and towards the plasma membrane. This in turn facilitates enhanced glucose transport into muscle and liver cells where it is stored as glycogen, which necessarily reduces the content of glucose in the bloodstream. Following repeated contractile efforts, more muscle capillaries are recruited and blood flow is maximised, in turn enabling maximal supply of blood glucose to muscle tissue (58). People with type 2 diabetes are characterised by a state of insulin resistance, indicating an impaired cell response to insulin, and thus have impaired insulin-mediated glucose uptake. Whilst the etiology is not completely understood, the state of insulin resistance is precipitated by obesity, excess lipids, and excess
visceral adiposity (59). Independent to physical activity’s role in energy expenditure and fat oxidation (60), muscular contraction leads to an improved sensitivity of muscle cells to respond to insulin-dependent glucose uptake. This confers a lasting improvement to basal insulin sensitivity, where even at rest the body becomes more effective at glucose disposal. Improved insulin sensitivity is short-lived, and will disappear after approximately 2 - 72 hours (61,62), suggesting that persistent bouts of physical activity are required to maintain insulin sensitivity (63).

Intervention trials that have resulted in increased physical activity and exercise corroborate these mechanisms by exhibiting improvement in glycaemic control. Aerobic training (-0.7% HbA1c compared to control), and resistance training (-0.5% HbA1c) improve glycaemic control (64). There is also evidence to suggest the combination of the two are superior to single modality (65). Interventions aiming for 150 minutes or more of exercise per week (-0.9% HbA1c) outperformed those with less than 150 minutes (-0.4% HbA1c) for glycaemic control (64). Physical activity and exercise not only improve glycaemic control and insulin sensitivity (66–68), but also increase energy expenditure and may contribute to weight loss, which is central to reducing the risk of diabetes comorbidity and mortality. Exercise intervention studies in people with type 2 diabetes report changes in waist circumference and weight following 12 month follow-ups (69,70). In interventions where pedometers were supplied to people with type 2 diabetes to improve physical activity, weight loss was significant albeit smaller (-0.65 kg mean difference from control) (71).

Physical activity interventions in people with type 2 diabetes have also been shown to benefit levels of low-density lipoprotein (LDL-C) (72), systolic and diastolic blood pressure (73) - especially with 150 minutes of exercise per week, and endothelial function (74). Collectively, these cardiometabolic risk marker improvements may confer considerable benefit to cardiovascular disease risk. Alongside the numerous benefits to cardiometabolic health, physical activity is known to improve depressive symptoms (75,76), aiding in the management of the disease, and cognitive function (77), which is likely an important factor with heightened Alzheimer’s and dementia disease risk in people with diabetes (78).
The American Diabetes Association has developed evidence-based guidelines (79) which recommend for adults with type 2 diabetes the following:

- Engage in 150 minutes or more of moderate-to-vigorous intensity activity per week. Activity should be spread over at least 3 days per week, aiming for no more than two consecutive days without physical activity. Where a person is physically fit, shorter durations (minimum of 75 minutes per week) of vigorous-intensity or interval training may be sufficient.
- Engage in 2 – 3 sessions per week of resistance exercise on non-consecutive days.
- Are encouraged to increase daily incidental physical activity.
- To gain more health benefit from physical activity, participation in supervised training is recommended over non-supervised programs.
- Decrease the amount of time spent in daily sedentary behavior and interrupt prolonged sitting every 30 minutes (to be discussed further in section 1.3).

1.2.1 Physical activity participation in people with type 2 diabetes

Despite the evidence suggesting a strong level of support for the benefit of physical activity in the prevention and management of diabetes, as well as other non-communicable diseases, physical activity participation is still low. Latest estimates from the World Health Organization (WHO) indicate that one in four (27.5%) of adults do not meet the aerobic exercise physical activity guideline of at least 150 minutes per week (56). In many studies, sufficient physical activity is low in people with diabetes (5,6,80). In one study (6), only 39% of people with diabetes were physically active compared to 58% of adults without diabetes. In two studies, substantial proportions of those surveyed did not engage in any (i.e.: they reported zero minutes) of physical activity (4,5). People with type 2 diabetes are frequently provided with advice from a health professional to engage in regular exercise (81), however it is known that advice to support physical activity alone is poorly associated with improvement in glycaemic control (64). Key barriers to physical activity and exercise in people with diabetes are a reported lack of motivation and lack of social support (82). Other common barriers in the literature are listed below.
• Lack of motivation (82–86)
• Low social acceptability and/or lack of social support (82,84,87,88)
• Lack of time (83,86,88–92)
• Present physical discomfort when exercising and/or fear of injury (87,91,93)
• Lack of perceived affordability and low access to resources (84,90,94)
• Perceived difficulty or challenge with engaging in activity (90,94)
• Health conditions prohibit engagement in activity (e.g. functional limitations) (87,88)

The above barriers focus solely on the engagement of people with type 2 diabetes in exercise. Broadening the perspective beyond just exercise, specifically to also include the entire gamut of physical activity intensities and sedentary behaviours in daily life, may increase the spectrum of behavioural interventions available, therefore broadening the potential for health improvement.

1.3 The role of sedentary behaviour in diabetes management

Distinct from physical inactivity which is classified as achieving insufficient physical activity per week, sedentary behaviours are increasingly being targeted as modifiable risk factors for public health improvement (95). This is in recognition to the last couple of decades which have seen the proliferation of work using computers at a desk, considerably more time spent engaged in recreational screen time, and significantly more time spent in driving in personal vehicles (96). Sedentary behaviour is defined as any waking behaviour characterized by low energy expenditure (<1.5 metabolic equivalents [METS]), and typically describes deskwork, TV viewing time, or other recreational sitting time. In research studies it is typically measured by self-report (e.g., television/screen viewing time, seated transport time), by direct observation (i.e., in experimental settings), or in field with body-worn accelerometers or inclinometers. Sedentary behaviour is accrued typically in large volumes in modern society, with sedentary time averaging 8 – 9 hours per day (97–99). Accumulating sedentary behaviour should be considered different from engaging in too little exercise, as sedentary time has stronger inverse
correlations with light-intensity physical activity, as opposed to moderate-to-vigorous intensity (100). To investigate the adverse associations of sedentary behaviour on health, many studies have accounted for the confounding association of MVPA. These investigations have demonstrated that sedentary time is associated with detrimental health outcomes independent of time spent in in MVPA, suggesting that sedentary behaviour is an independent risk factor for adverse health outcomes (101). In other analyses, only high amounts (> 60 minutes per day) of MVPA were sufficient to counter the adverse associations of a sedentary lifestyle on health (102,103).

Compared to the low sedentary behaviour levels, high sedentary time is associated with a 112% increase in relative risk of type 2 diabetes (104). The key mediators of this association are worsened glycaemic control, including fasting plasma glucose, 2h plasma glucose (105), and lower insulin sensitivity (106). Epidemiological evidence in people with type 2 diabetes supports these findings, suggesting that sedentary behaviour is not only important for the prevention of type 2 diabetes, but is also potentially a behavioural target in its management. This is important considering that people with type 2 diabetes have higher volumes of sedentary behaviour than those with prediabetes and normoglycaemic metabolism (9,107). Sedentary behaviour in cohorts with type 2 diabetes is associated with higher waist circumference, worse cardiometabolic risk score (comprising HbA1c) (108), higher LDL-C and lower high-density lipoprotein cholesterol (HDL-C), and worsened insulin sensitivity (109).

In contrast to the widespread use of self-report measures to investigate sedentary behaviour in the field, body-worn device-based measures are increasingly being used to quantify these behaviours with greater precision. These are typically in the form of pedometers and accelerometers, that measure steps and physical activity; and inclinometers, which are capable of distinguishing between postures such as sleeping, sitting, standing, and ambulation. Importantly, these device-based measures increase the objectivity of behaviour measurement, especially as they are not prone to recall bias. A review comparing the two types of measures determined that on average self-report measures underestimated sedentary time by approximately 1.74 hours/day compared to device-based measures (110). This is important
because it suggests that it may be flawed to make specific sitting time recommendations based upon self-report findings. Another strength of accelerometers and inclinometers is that they can appropriately categorise all time spent wearing the device into distinct behaviours. This is relevant to the field of sedentary behaviour as reducing sedentary time necessarily means greater time spent in other behaviours such as standing, incidental light physical activity, moderate-to-vigorous-intensity physical activity or sleeping.

Epidemiological investigations have been able to leverage use of device-based measures in cross-sectional designs and simulate the hypothetical effect of reducing sedentary behaviour into one of its alternatives, with early evidence indicating the estimated health benefit differs depending on what sedentary behaviour is reduced with (111,112). Various studies have employed an isotemporal substitution analytical approach (113) in order to determine the theoretical effect of replacing time spent sitting with time spent in another behaviour like standing. Investigations have demonstrated that replacing sedentary time with standing time is associated with improvements in risk markers that are relevant to people with type 2 diabetes such as lower (114) obesity markers (115,116), chronic-low grade inflammation (117), fasting plasma glucose, triglycerides, total/HDL cholesterol ratio and higher HDL cholesterol levels (118) and fat-free mass (116). Sedentary time replaced with physical activity, including light-intensity physical activity (LPA), moderate-to-vigorous physical activity (MVPA) or stepping (111,119) in general were associated with stronger associations than standing, and generally the greater the intensity of activity the greater the estimated benefit. For increased stepping time there is a greater amount of evidence given it is easier to interpret activity than idle and static standing time. Sedentary behaviour replaced by stepping time has been associated with lower obesity markers, triglycerides, and 2h post-load glucose levels (118). Sedentary behaviour time reallocated to LPA has been associated with beneficial triglyceride levels and improved insulin sensitivity (120). In the same investigation, MVPA replacing sedentary time was associated with improved HDL cholesterol, decreased waist circumference, triglycerides, glucose, and improved insulin sensitivity at a greater degree than when replacing sedentary time with LPA. Encouragingly, similar findings have been found in cohorts both at increased risk of impaired glucose regulation or type 2 diabetes (106,121) as well as in those with type 2
diabetes (122–124). In people with type 2 diabetes, replacing sitting time with MVPA is associated with lower waist circumference and BMI (122–124). Only one of these studies (123) used inclinometers (and thus was able to distinguish between sedentary and non-sedentary behaviours) in people with type 2 diabetes. This highlights a paucity of evidence investigating sedentary behaviour in people with type 2 diabetes and with robust device-based measures.

1.3.1 Sedentary behaviour change

To expand on the epidemiological findings and elucidate the biological impacts of sedentary behaviour, mechanistic day trials have been designed to investigate how changing sedentary behaviour influences acute health outcomes. Typically, these studies have compared experimentally induced prolonged sitting time with sitting time interrupted (e.g., with standing, light activity or MVPA). These studies attempt to not only understand the acute implications of sitting, but they also provide insight on the likely impact of the various countermeasures (activity). One of the first acute trials in people with type 2 diabetes involved comparing prolonged sitting with prolonged sitting interrupted with 3 minutes of light walking or simple bodyweight resistance exercises every 30 minutes (125). That trial demonstrated improvements in 8-hour glucose area under the curve (iAUC – reduction of 39%) and insulin levels (iAUC – reduction of 36% - 37%) compared to the uninterrupted sitting. The findings suggest that the potential efficacy and glycaemic benefit of breaking up sitting may be more pronounced in people with type 2 diabetes compared to those without (126), however this requires further confirmation in the free-living setting. A subsequent analysis (using continuous glucose monitors) shows that these benefits may persist in the following 22 hours (127). Another study compared sedentary time with breaks in sedentary time extending beyond two days of intervention. For five consecutive days, participants were advised to participate in one hour of moderate exercise, or replace five hours of sedentary behaviour with walking or standing (light-intensity activities), or advised to restrict their walking and standing time to only one hour per day (128). The light-intensity physical activity condition was associated with less time spent in hyperglycaemic glucose ranges, lower overall 24hr glucose, and lower insulin resistance. These findings may suggest that light activities spread habitually across the whole day, as opposed to
A single hour bout (characteristic of many exercise regimes), may provide considerable benefit to metabolic health.

Notwithstanding the positive findings from these experimental trials, there remains a need for these designs to be translated into long-term trials in order to understand whether reducing lifestyle sedentary behaviour may benefit long-term glycaemic control (i.e., glycosylated haemoglobin: HbA1c). However sedentary behaviour interventions are a relatively new concept, and as such have been seldom administered in clinical and non-clinical populations (129). Interestingly, intervening on sedentary behaviour may be more achievable than MVPA especially in clinical populations who have greater prevalence of exercise intolerance or mobility impairment (130). These interventions typically target workplace sitting time by modifying the office environment (e.g., height-adjustable workstation, or high table hot desk installations to encourage standing) and/or with counselling and education (group setting or with individual consultation). In pooled estimates, these trials have resulted in small benefits to weight, waist circumference, body fat, systolic blood pressure, insulin, and HDL (129). Whilst these findings demonstrate there are likely benefits in these interventions to people with type 2 diabetes, there has been limited number of randomised controlled trials evaluating this in this cohort.

Randomised controlled trials in people with type 2 diabetes (Table 3) have typically involved small sample sizes, indicative of investigations in their infancy. Generally, these interventions have successfully reduced sedentary time in their intervention groups, with stronger reductions in the short term (Δ3M SB% range -17% to -6%) compared to the long term (Δ12M SB% range -13% to 0%). This suggests that sedentary behaviour can feasibly be reduced in people with type 2 diabetes over at least a three-month period. However, the effect on cardiometabolic risk markers is mixed, and often glycaemic control is not measured despite it being a key management consideration in people with type 2 diabetes. Given that the evidence base is small, and that RCTs are resource intensive to conduct, observational trials investigating free-living sedentary behaviour (and its alternatives) can be helpful for addressing these evidence gaps and generate novel hypotheses concerning diabetes management.
<table>
<thead>
<tr>
<th>Trial</th>
<th>Design</th>
<th>Intervention</th>
<th>SB reduction</th>
<th>Health outcomes</th>
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</thead>
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<tr>
<td>Alonso-Dominguez et al. (2019); Spain (131) EMID Study</td>
<td>Two-arm RCT: control group (n=102), and intervention group (n=102). Clinically relevant outcome measures included: BMI, FPG, HbA1c, triglycerides, total serum cholesterol, LDL, HDL. Measures recorded at baseline, 3-months, and 12-months.</td>
<td>Control group received usual care and ten-minute face-to-face information on diet and PA. Intervention group received ten-minute face-to-face information on diet and PA, a phone app for physical activity self-monitoring (e.g. step counts) and health behaviour promotion, a one-hour workshop on use of the app, structured exercise (nurse-led) with five moderate intensity 4km walks over five weeks.</td>
<td>IG ΔSB min/day (95%CI) 3M: -46.8 (-66.0, -27.5)*</td>
<td>Intervention group had statistically significant differences at 3M timepoint only. At 3M only BMI differed by -0.3 kg/m², and WC differed by -2.3cm in the intervention group compared to the control group.</td>
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<tr>
<td>Balducci et al. (2019); Italy (132) The IDES_2 trial</td>
<td>Two arm RCT: control group (n=134), and intervention group (n=133). Primary outcomes: physical activity measures, and sedentary time (h/d). Secondary outcomes included HbA1c, FPG, triglycerides, HDL, LDL lipoprotein, systolic and diastolic blood pressure, glomerular filtration rate, albumin creatinine ratio, body weight, waist circumference, high-sensitivity C-reactive protein, and 10-year CHD risk score. Outcomes recorded every 4 and 12 months, finishing with 3 years follow-up</td>
<td>Both control group and intervention group participants received general PA and SB recommendations, and recommendations for improving dietary consumption, on achieving glycaemic, lipid, blood pressure, and body weight clinical management targets. The IG received an additional single individual counseling session and eight biweekly practical counseling sessions conducted by a certified exercise specialist per year for three years. Counseling began with instruction on reducing sedentary time, and increasing light activities, and then substituting it with moderate-to-vigorous-intensity physical activity.</td>
<td>IG ΔSB hour/day (95%CI) 12M: -0.9 (-1.0, -0.7)<em>; 24M: -0.7 (-0.9, -0.5)</em>; 36M: -0.3 (-0.6, -0.1)*</td>
<td>Mean difference between intervention and control groups was significant for fasting plasma glucose, systolic blood pressure, and fatal 10-year risk score. Per protocol analyses of the 36-month follow-up demonstrate significant different between groups for HbA1c. Effects with HbA1c were more pronounced in intervention participants with HbA1c greater than or equal to 8%.</td>
</tr>
<tr>
<td>Miyamoto, T., et al. (2017); Japan (133)</td>
<td>Three-arm RCT: control group (n = 10), intervention groups: non-locomotive physical activity group (N-LPA; n = 12); locomotive physical activity (LPA; n = 9). Primary outcomes: HbA1c and fasting glucose; secondary outcomes: body mass, triglycerides, LDL, total cholesterol. Outcomes recorded at baseline and at 12 weeks. Control group received no instruction. The N-LPA group was verbally instructed to increase N-LPA (domestic and occupational activities such as sit-to-stand activities or washing the dishes) and LPA group was verbally instructed to increase volume and frequency of light physical activity. Both intervention groups activity levels were supported with body-worn accelerometers that provided visual feedback on activity levels.</td>
<td>IG N-LPA SB% ± SE: BL: 47.5 ± 4.3; 12W: 41.5 ± 3.9* IG LPA SB% ± SE: BL: 49.4 ± 3.4; 12W: 44.2 ± 2.1 Only the N-LPA group reduced SB. Group changes in SB were not associated with any changes in primary or secondary outcomes. Post-hoc analyses determined that increased time spent sedentary (ΔSB) was positively associated with HbA1c% and increased total PA (ΔTPA) was inversely associated with HbA1c%</td>
<td>Eakin et al. (2014); Australia (134) Living Well With Diabetes trial</td>
<td>Two-arm RCT: control group (n=131), intervention group (n=118). Primary outcomes were MVPA, weight, HbA1c. Secondary outcomes were dietary energy intake, diet quality, waist circumference, fasting lipids, and blood pressure. Outcomes recorded at baseline, six, 18, and 24 months. The control group were mailed a summary of their results following each assessment and provided standard diabetes self-management education brochures. The intervention group received telephone delivered health coaching (27 calls over 18 months) focusing on increasing physical activity, and reducing energy intake and improving diet quality. The calls supported the initiation and maintenance of weight loss and achieving recommended HbA1c at 7%. In addition, participants were encouraged to reduce sitting time, reduce prolonged sitting, and to aim for less than 2 hours/day of screen time outside of work. IG MVPA increased at follow-up, dietary energy intake and quality score improved during the intervention. Sedentary behaviour time changes not reported. Despite increased MVPA levels in the intervention group there were no statistically significant improvements to the cardiometabolic risk markers except weight loss (kg, %), and waist circumference.</td>
</tr>
</tbody>
</table>
De Greef, K. (2010); Belgium (135)

| De Greef, K. (2010); Belgium (135) | Two arm RCT: control group (n=21), and intervention group (n=20). Primary outcomes were PA as assessed by accelerometer (minutes/day) and pedometer (steps/day). Secondary outcomes were weight, BMI, blood pressure, HbA1c, and total cholesterol and sedentary behaviour. Outcomes recorded at baseline, 13 weeks and at 52 weeks. | Control group received no instruction but to continue with guidelines and advice prescribed by their dietitian and endocrinologist. The intervention group followed a 12-week lifestyle intervention with five cognitive behavioural group sessions of 90 minutes each. Content of these sessions include increasing knowledge and benefits of PA and adverse effects of sedentary lifestyle, monitoring sedentary activities and substituting alternatives, highlighting barriers to PA and reducing SB, relapse prevention with behaviour change, and long-term action planning and goal setting. | IG SB min/day ± SD: BL: 1183 ± 90; 3M: 1111 ± 118*; 12M: 1187 ± 99. | No intervention effect on health outcomes. |

* denotes statistically significant difference in sedentary behaviour to control group

Abbreviations: RCT = randomised controlled trial; LPA = light-intensity physical activity (unless stated otherwise); MVPA = moderate-to-vigorous-intensity physical activity; SB = sedentary behaviour; SE = standard error
1.3.2 Sedentary behaviour and its alternatives in a time-use composition

Recent guidelines from countries such as Canada have shifted attention to the importance of 24-hour guidelines, with sedentary behaviour being considered as one of the component behaviours. These guidelines make formal recommendations on how much physical activity, sleep, and sitting time should be performed in relation and context to each other.

For adults aged 18 – 64, Canadian 24 movement guidelines (136) recommend the following:

- Engage in 150 minutes of moderate-to-vigorous-intensity physical activity per week.  
  ➢ *Strong recommendation, moderate quality evidence.*
- Perform muscle-strengthening activities on major muscle groups at least twice per week.  
  ➢ *Strong recommendation, very low-quality evidence.*
- Engage in several hours of light physical activities, including standing per day.  
  ➢ *Strong recommendation, with low-quality evidence support.*
- Aim for 7 – 9 hours of sleep on regular basis, with consistent sleep and wake-up times.  
  ➢ *Strong recommendation, moderate (sleep duration) to very low (sleep consistency) quality evidence.*
- Engage in no more than 8 hours of sedentary behaviour per day, break up longer periods of sitting as often as possible.  
  ➢ *Strong recommendation with very low-quality evidence.*
- Replace sedentary behaviour with additional physical activity and replace light physical activity with more MVPA while preserving sleep durations.  
  ➢ *Strong recommendation, very low-quality evidence/*

When comprising these recommendations, a key analytical limitation identified was that most of the literature that examined associations of behaviour combinations and health used statistical approaches that fundamentally treat behaviours as being independent of one another (137). However, the behaviours that compose the 24-hour day are not independent of each other, as they form a composition of fixed time (137,138). If behaviours are considered in an independent fashion, then a reduction of sitting does not inherently consider with which behaviour(s) sitting is (partially) replaced by, and as such paths (1) and (2) in Figure 1 are treated the same.
Values in graphs correspond to hours in a 24-hour day
The original composition describes 10 hours of sitting, 4 hours of standing, 2 hours of stepping, and 8 hours of sleeping. Path (1) illustrates a 2-hour reduction in sitting and a corresponding 2-hour increase in stepping time. Path (2) illustrates a 2-hour reduction in sitting and a corresponding 1-hour increase in stepping and a 1-hour increase in standing time.

Compositional data analysis (CoDA) is a statistical technique that appropriately deals with interrelated behaviours that operate in a fixed period such as the waking day, or 24-hour day. There is a lack of high quality CoDA evidence used to inform the 24-hour movement guidelines (136). With this technique, any composition of time can be tested against health outcomes and risk markers, which includes isotemporal substitution modelling (139), where one behaviour is replaced with another and the remaining behaviours are fixed.

Recent evidence has determined that compositions of behaviours are associated with cardiometabolic risk markers. One of the first study to test composition with health outcomes
(138) determined that different compositions of 24hr time are associated with cardiometabolic risk markers in different ways, with some markers (e.g., Homeostasis Model Assessment [HOMA], insulin, triglycerides) sharing similar beneficial associations with time spent in light intensity activities to time spent in moderate-to-vigorous intensity activities, suggesting intensity was less important. A key finding of this investigation (138) was that if SB replaced LIPA with stable MVPA levels, there was a higher health risk persistent in the modelling. This suggests that even those with higher MVPA levels (such as those meeting exercise guidelines) may still improve their health by reducing SB with LIPA. A finding that has subsequently been corroborated by another CoDA investigation in extremely active adults (140).

A systematic review of all compositional analyses investigations was performed (141) to support the Canadian 24hr movement guidelines. In summary, the results indicate that time spent in MVPA (especially with concordant reduction in sedentary behaviour time) was superior to all other behaviours for its association with all-cause mortality and adiposity. However, for cardiometabolic risk markers, there was a mixed consensus on whether time spent in MVPA, or LPA was associated with the best health benefits. For both the CoDA systematic review, and the 24hr movement guidelines themselves, the volume and quality of evidence was deemed very low, with prevalent evidence gaps. For example, only two studies used robust measures able to distinguish standing time from sedentary time (142,143). Only one study investigated whether the associations were moderated by the cohort studied, which entailed studying the behavioural composition across different age groups (144). Currently, little is known how chronic disease status, and in this case glycaemia, diabetes risk, or type 2 diabetes, may moderate the associations of behavioural composition with health outcomes.

1.4 COVID-19, sedentary behaviour, and diabetes

The importance of addressing sedentary behaviour in people with type 2 diabetes has never been more apparent than in the past two years. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a strain of coronavirus causing coronavirus disease 2019 (COVID-19). This first outbreak of the disease occurred in December 2019 in Wuhan, China and has had
considerable implications for the disease burden of type 2 diabetes. Australia is one of a few countries that has kept infection cases and deaths to a low level (145), in part due to strong preventative countermeasures such as community-wide lockdown restrictions. Pre-existing conditions, such as cardiovascular disease, obesity and cancer lead to a greater risk of severe COVID-19 disease outcomes (146). From the outset, studies have suggested that in people with diabetes there is a higher risk of severe complications with COVID-19. This contributes to 4-fold greater likelihood of severe and critical outcomes in those with diabetes compared to those without (147). Infection is especially concerning as it may increase the risk of diabetic kidney acidosis (148). Of particular importance for the management burden of diabetes is the observation that restrictions have contributed to both a reduction in government-subsidised medical services for chronic disease management, as well as a reduction in the formal diagnosis of diabetes (149). Women with gestational diabetes, a common precursor to type 2 diabetes, encountered a lag in diagnosis until after pregnancy, or received no diagnosis at all (150). Whilst tele-health services were provided in the midst of social distancing mandates, the evidence demonstrates that adherence to these appointments was diminished despite a perceived need by patients with diabetes (151). Therefore, the pandemic has likely contributed to an acute increase in diabetes burden and constituted as barrier to the effective clinical management of diabetes.

The pandemic and associated lockdown restrictions have contributed to considerable decline in physical activity levels (152,153) and an increase in sedentary time (154). Of concern, there is evidence that these behaviours have become more entrenched (155) or there has been a lag in them returning to normal following end to lockdown restrictions (156). Reductions in physical activity have been greater in people with obesity (156). Collectively these factors are likely to have unfavourable impacts on diabetes management and glycaemic control. This is especially alarming when in the context of the pandemic, worse glycaemic control is associated with greater severity of illness and rate of hospitalization outcomes from COVID-19 (157). Despite these factors, it is less understood how people with type 2 diabetes have been affected in relation to physical activity and sedentary behaviour by COVID-19 and associated restrictions. Many of these investigations have also typically involved single time-point questionnaires and
have not involved long term measures which are required to validly characterise lifestyle behaviour change.

1.5 Summary

Diabetes continues to increase in prevalence globally and contributes to multimorbidity and economic burden. Physical activity and exercise are considered as being key modifiable lifestyle factors integral to the management of the disease. However, the prevalence of physical inactivity (not meeting physical activity guidelines) is high, and higher still in people with type 2 diabetes. Type 2 diabetes guidelines have now identified sedentary behaviour as being another modifiable lifestyle risk factor distinct from too little physical activity. While the evidence base relating to sedentary behaviour in people with type 2 diabetes is still in its infancy, there is promising preliminary evidence showing that reducing sedentary behaviour may be efficacious for the clinical management of people with type 2 diabetes, with possible benefits to attenuating plasma glucose levels. The extent to which such changes in sedentary behaviour in the free-living setting improve the management of glycaemic control and related cardiometabolic risk markers is investigated in this thesis.

The first evidence gap to be addressed acknowledges that few studies have evaluated sedentary behaviour in people with type 2 diabetes in the free-living setting with robust measures of sitting time. In addition, compositional data analysis has been scarcely used in this population; this is needed to inform the understanding of how sedentary behaviour should be balanced or offset by healthier alternative behaviours such as standing or activity. In addition, little is known on how states of impaired glucose metabolism or type 2 diabetes may influence the relationships of sedentary behaviour and its alternatives with glycaemic control and other indices of health risk.

One of the most pragmatic ways to investigate whether reducing sedentary behaviour leads to improvements in glycaemic control is through study designs involving randomised controlled trials. However, presently few trials have specifically focused on reducing sedentary behaviour
in people with type 2 diabetes. In the trials conducted to date, few have employed long term follow-up procedures and long-term measures of glycaemic control relevant to management and comorbidity prevention. The OPTIMISE Your Health Study is a randomised controlled trial that has been designed to address these gaps, with methods and procedures described in detail in Chapter 5. Another gap in the evidence of these trials is understanding the level of long-term adherence to sedentary behaviour reductions, particularly in the face of unexpected barriers like the COVID-19 pandemic. Few studies have investigated how the COVID-19 pandemic and associated restrictions changed sedentary behaviour and activity levels in people living with type 2 diabetes.
Aims

The overarching aim of this thesis is to better understand the role of sedentary time and its alternatives in people with type 2 diabetes. Specific objectives are to:

- Understand associations of sedentary behaviour and its main alternatives – standing and stepping, with glycaemic control and related cardiometabolic risk markers in those with and at risk of type 2 diabetes.
- Determine how relationships of glycaemic control and related cardiometabolic risk markers with sedentary behaviour and main alternatives may differ between those with or at risk of type 2 diabetes.
- Describe the development of a multicomponent sedentary behaviour reduction intervention in adults with type 2 diabetes.
- Investigate the longer-term changes in sedentary behaviour and physical activity in people with type 2 diabetes and explore the impact of COVID-19 lockdown restrictions on these behaviours.

Addressing these objectives will further understanding of the associations of sedentary behaviour in people with type 2 diabetes. It will also provide insight into whether sedentary behaviour reduction has further potential to be a component of the clinical management of type 2 diabetes. The methods used in this thesis, and the findings addressing the research objectives are described in Chapters 2 – 6. Discussion concerning strengths and limitations of the work, clinical implications, research in context, and implications for future research and practice are presented in Chapter 7.
Chapter 2: Methods

This chapter details the methods of the three studies from which this thesis draws data: the Australian Diabetes, Obesity and Lifestyle (AusDiab) study; the Maastricht Study (epidemiological studies) and the OPTIMISE Your Health trial (intervention study). This detail is intended to compliment and extend on the study-specific detail provided in the relevant chapters. It includes detail on study designs, recruitment and sampling procedures, data collection, and analytical approaches applied to the body-worn device-based measures. The OPTIMISE Your Health study is described in further detail in Chapter 5.

2.1 AusDiab study methods

The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) was established to address evidence gaps on diabetes prevalence, risk factors, and associated conditions in Australia (158). The prospective cohort study was conducted in a national cohort using a clustered recruitment strategy stratified by the state and territories of Australia. The original survey began in 1999-2000, and follow-up surveys were conducted in 2004-2005 and in 2011 – 2012. In the third wave (2011-2012), a sub-sample of participants wore the activPAL™ thigh-worn monitor. This thesis uses only the data from this third wave of data collection.

2.1.1 Baseline and the first follow-up survey: protocol, procedures

Detailed methods and rationale for the AusDiab study have been published elsewhere (158). In brief, adults aged 25 years and over were originally recruited for the baseline survey across six states and the Northern Territory of Australia. Recruitment was conducted in clusters based on census collector districts, and within each state and territory six collector districts were randomly selected. Survey weighting was applied to ensure that the data was Australian population representative. Survey activities were conducted over a 21-month period between May 1999 and December 2001. The survey comprised two phases: an initial household interview followed by a biomedical examination. The household interview entailed recording
the participant’s date and country of birth, language spoken at home, marital status, level of
education, history of diabetes and high blood sugar levels. The biomedical examination was
conducted in 46 centralised local testing sites and was based on the World Health Organisation
(WHO) recommended model for diabetes and other non-communicable disease field survey
data collection (159). Examinations consisted of anthropometrics (height, weight, waist
circumference), blood (fasting, and OGTT measurements), and urine assessment. The OGTT was
performed on all participants, except for those who reported using insulin or oral
hypoglycaemic medications or were pregnant at the time of assessment. During the OGTT
participant, the research team interview administered behavioural and dietary questionnaires.

Of the baseline sample (n=11,247), the majority were female at 55.1%, and the mean age was
51.5 years (158). Using this data, prevalence of diabetes was determined to be 7.4% with 16.4%
having impaired fasting or impaired glucose tolerance. During 2004 - 2005 the AusDiab
procedures were repeated for the first follow-up (160). Participants were invited back provided
they had not refused contact, moved overseas, or withdrawn due to severe or terminal illness
or death (n = 10,788). Of these participants, 1,990 cancelled their follow-up assessment. A total
of 6,400 participants attended the on-site testing centres, 137 attended their local pathology,
and 2,261 provided self-report data only. A total of 8,798 participants were involved at the first

2.1.2 AusDiab Follow-up 2011 – 2012

Following the baseline, and an initial cohort follow-up in 2004-2005, a third follow-up phase of
AusDiab was launched in 2011 – 2012. All surviving participants who participated in the original
AusDiab survey in 1999 - 2000 were invited to the 2011-2012 follow-up study. The same
exclusions applied with participants at follow-up, whereby in in instances where they refused
contact, moved overseas, moved to a care facility, or withdrew due to severe or terminal illness
they were excluded (n=1,944). Of the 11,247 participants who were involved in the first
AusDiab study, only 6,186 participated in the AusDiab 2011-2012 survey (161). There were
small and statistically significant differences between the baseline sample and those that
attended the third follow-up. Participants in 2011-2012 follow-up were younger, more affluent, more likely to be married, and were healthier overall (161). Without survey weighting methods, the study sample was no longer Australian population representative. Participants followed the same general process as the previous two waves. Namely, they were booked to a centralised testing site (6,186). For those that could not attend, 150 attended their local external pathology laboratory, and 1,422 provided health information via telephone questionnaire only. All participants were aged at least 35 years of age by the third AusDiab wave.

A subsample of participants who attended the third phase were approached to wear the activPAL thigh-worn inclinometer. Across 46 testing sites, participants (ambulatory and not pregnant) were invited on a daily basis until five participants per day were recruited, or until there were no more monitors available. Of the 1014 participants who were invited to wear the monitor, 782 consented. Of these participants, 741 wore the monitor for at least one valid day, which was achieved by wearing the monitor on one day for at least 10 hours during the waking period. Compared to the overall AusDiab sample in 2011/2012, the participants who wore the activPAL were more likely to be younger, healthier, and in a higher socioeconomic position (118). The activPAL monitor was attached during the oral glucose tolerance test. Participants were instructed to wear the device on their midline anterior aspect of their upper right thigh, continuously during all waking hours. Following seven complete days of wear, participants were instructed to mail back the monitors in a provided post bag. Section 2.4 below describes the analytical approach applied to the activPAL data.

The Australian Diabetes Obesity and Lifestyle study is the first observational prospective study of its kind, and the first to incorporate an oral glucose tolerance test. Testing was performed across all states and the Northern Territory of Australia, featuring a diverse range of ages, ethnicities, socioeconomic backgrounds, and health factors. It also was one of the first studies of its kind to implement the activPAL thigh monitor capable of distinguishing posture and accelerometry. As a result of attrition, the third AusDiab study sample were no longer Australian population representative, although still representative of community-dwelling
adults in Australian society. The activPAL sub-sample was significantly healthier than the main sample and featured a greater proportion of people with normal glucose metabolism. For this reason, the sub-sample had less capability to objectively assess and characterise the sedentary behaviour and physical activity of people living with type 2 diabetes and impaired glucose metabolism.

2.2 The Maastricht study

The Maastricht study is an observational and prospective study with a specific focus on the aetiology of type 2 diabetes, including complications and emerging comorbidities associated with the disease (162). The study was conducted entirely in the southern region of the Netherlands (in Maastricht and surrounding municipalities). Participants were aged 40 – 75 years and living in the southern part of the Netherlands. Municipalities included Maastricht, Margraten-Eijsden, Meersen, Valkenberg, Maastricht and Heuvelland in the province of Limburg. Recruitment was completed through municipal registries as well as a regional diabetes patient registry via mail. There was deliberate oversampling of people with type 2 diabetes within this cohort. The study population having a greater proportion of people with type 2 diabetes than the general population facilitates greater statistical power to compare people with type 2 diabetes with the remaining sample. Furthermore, the sampling process provides the opportunity to understand how emergent comorbidities, quality of life, use of health care resources, and other health outcomes may differ across glucose metabolism status. The study began recruiting participants in November 2010 through to September 2013 (162), 3,451 participants were recruited. Only observational cross-sectional findings are available for investigation in this thesis.

2.2.1 The Maastricht study protocol and procedures

Participants underwent an extensive phenotyping protocol over three to four assessment visits at the Maastricht University Medical Center (162). Procedures were uniformly delivered to all
participants unless contraindicated. Questionnaires were filled out by participants via a web-
based program initially with supervision and assistance provided by the research staff. After the
participants were sufficiently familiar with the questionnaire program and questionnaires, they
were instructed to complete the questionnaires at home where feasible. Other measurements
were performed by trained research staff during three to four 4-hour visits at the Medical
Center using standardized protocols. The full examination of each participant finished within a
three-month time window. In brief, the assessments included, but were not limited to:
anthropometric assessments, fasting blood draws, urine assessment, physical function tests
(e.g., timed up and go, six minute walk test), standardized lifestyle and behavioural
questionnaires (including a food frequency questionnaire), and an oral glucose tolerance test.
On the day of the physical function tests, participants had the activPAL device attached to their
anterior mid-thigh. This necessitated the first day of observation being excluded from analysis
as it coincided with the physical tasks not representative of typical activities of daily living.
Participants were instructed to wear the device for eight consecutive days and advised not to
remove the device for reasons of simplicity with interpreting any non-wear time (162). Of all
participants recruited (n=3,451), 696 did not wear the activPAL thigh monitor, and an additional
110 had invalid activPAL data.

The main strengths of the Maastricht observational study were that it featured a diverse
sample of participants with diabetes prediabetes and normal glucose metabolism. This helps
identify how health outcomes differ by diabetes status. It is also the only observational study
that includes a substantial amount of people (n=684) with type 2 diabetes measured by the
activPAL thigh monitor. Reportedly, there were a wide range of differences in the sample, with
wide variation in lifestyle, socio-economic factors, and health. The sample is predominantly
Caucasian, which means that the potential findings from the study can be extrapolated to
western countries, however it is limited it its ability to represent more ethnically diverse and
non-Caucasian populations.
2.3 The OPTIMISE Your Health Study

The OPTIMISE Your Health study’s methods and procedures are described in greater detail in Chapter 5 of this thesis. The OPTIMISE Your Health study is a randomised controlled trial examining the effectiveness of a series of multicomponent interventions targeting sitting less and moving more and aims to improve metabolic and brain health outcomes over a duration of 18 months. More specifically, height-adjustable desks, wrist-worn physical activity trackers (Fitbit™), and behavioural health coaching support are provided to intervention-arm participants to encourage the reduction of sedentary behaviour with standing and stepping during work and across the entire day. Glycaemic control (glycosylated haemoglobin; HbA1c) and sitting time (activPAL device measured: hours/16 hour day) are key primary outcomes, with secondary outcomes encompassing relevant glycaemic measures considered including fasting plasma glucose and a 2h OGTT. Participants (n=250) are assessed at baseline, three, six, 12, and 18-months. Intervention participants receive the intervention for 12 months and are compared to controls in this time period, before entering a maintenance phase at 12 – 18 months. Control participants receive a delayed intervention at 12 months, which is an abbreviated version of the intervention modified to be more suitable for external delivery and scaling up to the wider public.

The OPTIMISE Your Health trial was suspended following COVID-19 pandemic restrictions from March to October 2020. During this time all new recruitment and in-person clinical assessments were temporarily halted. Participants who were enrolled in the trial completed their participation with COVID-safe protocols. These included remote pathology visits (HbA1c testing) where feasible, and participants being emailed a COVID-19 questionnaire that specifically surveyed lifestyle and work changes following the implementation of restrictions.

The trial has numerous strengths. It will feature a large sample and is therefore capable of addressing multiple research questions. The multicomponent intervention targets various levels of influence on behaviour (environment, intra-personal, inter-personal) and is based upon previously successful interventions that successfully reduced sitting time. Few studies have used objective assessment of sedentary time, which facilitates a more robust and valid
assessment of the relationship of sitting time to long-term glycaemic control, which is relevant to investigating the efficacy of the treatment.

2.4 Sedentary behaviour measurement and analysis

The AusDiab, Maastricht, and OPTIMISE Your Health studies all use the activPAL™ (PAL Technologies Ltd., Glasgow, UK) thigh-worn device. The activPAL is typically affixed to the anterior mid-thigh. By interpreting current thigh angle, the device is able to differentiate sitting or lying behaviours from standing, or ambulation. The device is able to interpret raw accelerometry and walking cadence. As such, walking behaviours can be additionally quantified in terms of steps per minute, which can be interpreted as light-intensity, moderate-intensity, or vigorous-intensity physical activity (163). In the studies included in this thesis, the device interpreted behaviours at 30 cycles per second (30 hz) and a new posture defined up to once a second (164), with these settings all wear time can be accurately categorised as sitting/lying, standing, or stepping. The activPAL device is reliable both between devices and within the same device used with reliability estimates ranging from 0.79 – 0.99 (165). The device also validly interprets total volume of sitting and standing time with only small differences (0.19% [0.68, - 1.06] and 1.4% [-6.2, 9.1] respectively) when compared to direct observation performed by researchers (165).

2.4.1 activPAL inclinometer data collection methods

The activPAL inclinometer requires initialisation prior to being provided to a participant. This can be undertaken up to four days in advance, allowing for domestic postage of the device. The device must also be water-proofed before provision, which is done typically using a nitrile sleeve and adhesive bandaging wrapping. The device is attached by staff or self-administered via written instructions. The manufacturers of the device recommend attachment to the midline anterior aspect of the upper thigh with the device in an upright position. Attachment to the thigh is supported with adhesive wrapping and additional wraps are provided to participants should irritation with the skin, or loss of contact occur. Depending on protocol, the activPAL devices are generally worn for seven – ten days continuously (164). Seven days of
wear allows for a minimum acceptable level of repeatability, and controls to an acceptable
degree the variation in intra-activity levels observed (166). For the three included studies in this
thesis, participants wore the activPAL thigh monitor continuously during sleep hours, which was
regimented for reasons of simplicity with defining minimal non-wear time, and as it may
improve wear time compliance (167).

The OPTIMISE Your Health study and the AusDiab study employed self-report diaries and
required participants to record their sleep periods (wake / sleep) and periods of time that they
removed the monitor. In the Maastricht study, an automated algorithm was created by
examining the outputted activPAL events files (a file that timestamps when a behaviour is
performed). Algorithm rules were devised by researchers after they had observed the events
files in combination with the proprietary activPAL assessment of waking/sleeping period. The
algorithm’s performance within the sample was subsequently compared to a small subsample
of participants (n=177) who reported sleep and wake times in daily logs. These logs provided
validation to the automated method and indicated good agreement, determining only a 0.02
hour difference with sleep logs (168). The final determination of sleep periods, whether from
diaries or through automated processes resulted in these sleep periods being reclassified.

Another commonly employed criterion to ensure the activPAL™ data is valid is by ensuring that
each participant has sufficient wear time for a given day. In the case of AusDiab, a day was valid
if the participant wore the device for ≥10 hours in the waking period. The Maastricht study
excluded days with <10 hours waking time, or ≤14 hours on the final day of observation. The
OPTIMISE trial uses these hour criteria and additionally identifies an invalid wear day when the
majority (>95%) of the day is composed of one behaviour, indicating a malfunctioned or
stationary (i.e., non-worn) device. Invalid wear days are removed during data processing.
Participants may be excluded from subsequent analyses depending on whether they meet a
minimal threshold of valid days, with four to seven valid days being a typical minimum
requirement (164). Once these data cleaning methods have been correctly applied, the
activPAL events files are processed further to determine behaviour variables across available
valid days. In this process activPAL time is compartmentalized into waking behaviours
(composed of sitting, standing, stepping totals) and sleep. These variables can be averaged across the valid days to determine an average day of daily behaviours. Statistical analysis programs can be applied to these variables facilitating analytical approaches such as Compositional Data Analysis which requires a constrained (time spent can only be in one of the selected behaviours) and finite (behaviours sum to a universal total, e.g., 24 hours or 16 hour waking day) composition of time use.

2.4.2 Compositional data analysis

Compositional data analysis approaches are well established in statistics, originally being performed to deal with spurious correlation works in the late 1800s (169). The analytical technique was developed further by John Aitchison in the 1980s (170), and subsequently has been used for geochemistry (171), nutrition (172), and more recently in health behaviour epidemiology (138) as referred to in section 1.3.2 of Chapter 1. Compositional data refers to a set series of parts or components that combine to form a finite total. Often the compositional data is normalized to equal a discreet total, such as adding up to 1, or 100%. A composition with d components $x_i$ normalized to 100% is:

$$\sum_{i=1}^{d} x_i = 100\%$$

Behaviours and their time-use ($T$) within the day are inherently compositional in nature, that is they sum up to a finite amount of time; or 100% of the day.

$$T_{sleeping} + T_{sitting} + T_{standing} + T_{stepping} = 24 \text{ hours} = 100\%$$

As the 24hr day is constrained to these four behaviours, there is no room for undefined time. The composition of the day may be additionally defined as just the waking period as:

$$T_{sitting} + T_{standing} + T_{stepping} = 100\%$$

These compositions may also be normalized to 16 hours, accounting for a standardized eight hours of sleeping, however what is relevant is that the set of behaviours combine to form a universal whole. This scale invariance infers that each component is a vector in proportion to one another. That is, if one behaviour component is lower, the remaining behaviour(s) must be
proportionally higher. By synthesizing data from the activPAL thigh-worn monitor, all participants have a composition of behaviours normalized to the entire day (24 hours, as in Chapter 3) or the waking day (16 hours, as in Chapter 4). An individual’s behaviours are transformed into interrelated vectors in an Aitchison’s simplex (173); and thus proportions of a finite composition. From this, the mean composition of a population can be determined. Geometric means are used for normalised and proportional data.

The geometric mean of a population refers to a specific location in simplex space, made up of $d$ components, with no variance (e.g. confidence interval) of the individual behavioural components seen with traditional arithmetic analyses. Instead, variance in one behaviour must be in relation to time spent in the other co-behaviours. As such a variation matrix can describe the population variance. This is performed between two behaviours by calculating the natural log of the mean ratio, for example: $\ln(\text{sitting} \div \text{stepping})$. Values close to zero (natural log of $1:1$) imply stronger codependence, or shared variance between the two behaviours.

### 2.4.3 Linear regression analysis with compositional data

Traditional linear models in health behaviour epidemiology aim to estimate an outcome ($Y$) as a condition of the amount of univariate or multivariate exposure. Linear regression models are characterised by the relationship of $d$ exposures $x$ to outcome $Y$ of interest:

$$E(Y \mid x) = \beta_0 + \beta_1x_1 + \ldots + \beta_dx_d$$

Considering sleeping, sitting, standing, and stepping and their estimated association with $Y$ the linear regression model would form as follows:

$$E(Y \mid \text{SitStandStepSleep}) = \beta_0 + \beta_1\text{Sit} + \beta_2\text{Stand} + \beta_3\text{Step} + \beta_4\text{Sleep} + \text{covariates}$$

Unfortunately, performing this standard linear regression analysis with adjustment for all parts will lead to high multicollinearity and often spurious results (137). Omitting one behaviour, which is typically performed in multivariate regression models, will lead to inconsistent regression estimates depending on which behaviour is removed (139). Another limitation is that standard regression assumes unconstrained space, where behaviour totals are able to vary into
the infinity. Isometric log-ratio (ilr) transformations allow for isometric mapping of the simplex and preserves it in real space. The simplex, containing \( d \) parts is mapped to dimensional real space as \( d - 1 \). Therefore, the linear regression model using isometric log ratios (\( z \)) is as follows:

\[
E (Y \mid z) = \beta_0 + \beta_1 z_1 + \beta_2 z_2 \ldots + \beta_{d-1} z_{d-1}
\]

The model represents the composition, the resultant \( R^2 \) describes the variation in the entire composition’s as it explains the outcome of interest, and the p-value describes the statistical significance of the model. In a 4-part composition the regression coefficients \( (\beta_1, \beta_2, \beta_3) \) indicate the strength of the association of the ilr transformations \( (z_1, z_2, z_3) \) with the outcome \( (Y) \).

Considering sitting, standing, stepping and sleeping in a 4-part composition the ilr transformations would be as follows:

\[
z_1 = \sqrt{(3/4)} \ln(\text{sitting} / \sqrt[3]{\text{standing} \times \text{stepping} \times \text{sleeping}})
\]

\[
z_2 = \sqrt{(2/3)} \ln(\text{standing} / \sqrt{\text{stepping} \times \text{sleeping}})
\]

\[
z_3 = \sqrt{(1/2)} \ln(\text{stepping} / \sqrt{\text{sleeping}})
\]

The regression coefficient \( \beta_1 \) represents the association of time spent in sitting relative to the remaining behaviours in the simplex remaining constant. The coefficient \( \beta_2 \) represents standing relative to stepping and sleeping remaining constant, and coefficient \( \beta_3 \) represents stepping relative to sleeping remaining constant. As time spent in behaviours is always relative to time not spent in the remaining behaviours, the order of isometric log ratios can be re-ordered to investigate the ratio in question, this is achieved without any changes to the model’s fit or statistical significance as described earlier.

2.4.4 Isotemporal substitution and other CoDA methods

Isotemporal substitution has been widely used in behavioural research to investigate how one behaviour relates to another relative to the outcome investigated (113). Using this analytical approach on observational data, allows one to investigate the hypothetical effect of reducing one behaviour for another. In compositional data analysis, the simplex and quantities within
each component are under complete control. This means that any composition with set component quantities can be compared with a reference composition (commonly the geometric mean or centre) in terms of an outcome of interest (Y). Isotemporal substitution can be applied within this framework, varying one behaviours time-use with another, whilst the remaining behaviours remain fixed. To perform this, the ilr coordinates in the linear regression equation are reconfigured to investigate variation in time between two components. This approach, and transformation has been described in detail elsewhere (139). This approach considers two compositions: the geometric mean as reference, and the new altered composition.

Considering the previously described ilr coordinates: z1, z2, z3; these are reconfigured according to previously devised methods (139). Depending on which two behaviours are considered for isotemporal substitution, and their position in the isometric log-ratio will determine the set of operations required for isotemporal substitution transformation. Below follows an example to determine the estimated association (ΔY) of increasing standing time with a concurrent decrease in sitting time as follows:

\[ Δz1 = -\frac{1}{2} \ln(1 + Δ \text{Time} / \text{stand}) + \frac{1}{2} \ln (1-Δ \text{Time} / \text{sit}) \]
\[ Δz2 = \frac{1}{2} \ln(1 + Δ \text{Time} / \text{stand}) \]
\[ Δz3 = 0 \]

And using the Δ ilr coordinates in the original linear regression model as follows:

\[ ΔY = β_1Δz1 + β_2Δz2 + β_3Δz3 \]
\[ ΔY = β_1 -\frac{1}{2} \ln(1 + Δ \text{Time} / \text{Stand}) + \frac{1}{2} \ln (1-Δ \text{Time} / \text{sit}) + β_2\frac{1}{2} \ln(1 + Δ \text{Time} / \text{stand}) \]

As the estimated difference in outcome (ΔY) from the mean is determined through linear estimates of the same model, the constant (β0), included covariates (e.g., age, sex, smoking status), and any ilr coordinate that do not contain one of the two behaviour components undergoing isotemporal substitution are cancelled out (z3). The delta outcome (ΔY) is expressed in relative terms from the geometric mean using either percentages or absolute units.
from the mean outcome estimate (e.g., Δ%: -5%, or Δ glucose: -5 mmol/L), or normalised to standard deviations (+/- SD) from the mean.

Compositional data analysis is commonly presented in a cartesian system by way of ternary phase diagram. The ternary diagram conveys a three-component composition with three axes, all possible combinations of the three components are represented within the finitely bordered simplex. These graphics are commonly created in the R statistical analyses program such as with packages “ggtern” (174) and “ggplot2” (175). Graphical illustration methods such as density plots can depict a population’s sample density and geometric means with respect to the three components (Figure 2; Panel 1) (176). Density plots can also illustrate how participants changed their composition following intervention (Figure 2; Panel 2) (177). Heatmaps can be overlayed on top of these ternary diagrams to denote how a given composition is associated with an outcome variable (Figure 2; Panel 3) (178). McGregor et al. (2018) (179) took advantage of the constrained nature of three dimensional composition and graphically presented the work using two dimensional space (Figure 2; Panel 4). Time not spent in LPA or MVPA are necessarily spent in sedentary behaviour given the constrained nature of the analyses. This work has been adapted in Chapter 4. The heatmaps in this thesis were created by artificially generating a series of equidistant composition values in simplex space and determining the associated outcome of these composition coordinates are estimated using the model. These values are generated from the population’s geometric mean and employ mahalanobis distance methods to control the variance and omit outliers from significantly altering the graphical depictions. Ultimately these values are then used to visually illustrate how a range of compositions are associated with a health outcome of interest.
2.4.5 Employing data from wrist-worn consumer devices

Consumer-grade physical activity trackers are becoming increasingly popular (181). These devices use similar technology to that of research grade accelerometers, suggesting that the
analytical techniques currently applied to wrist-worn tri-axial research accelerometers (182,183) can be transferred to the consumer-grade devices. A benefit of the consumer-grade devices is that they provide continuous surveillance of behaviours over greater periods of time than traditional research-grade activity monitors. This means consumer-grade activity trackers can readily identify changes in physical activity and sedentary levels as they occur on a continuous basis.

In this thesis, continuous Fitbit™ (Fitbit Inc, San Francisco, CA, USA) activity data was captured in the months preceding, and during the COVID-19 pandemic lockdown restrictions in Australia in the OPTIMISE Your Health intervention participants. Participants wore the device continuously because of their participation in the OPTIMISE intervention. Fitabase© (Small Steps Labs LLC, San Diego, CA, USA; www.fitabase.com) is a third-party proprietary database that automatically collects all Fitbit data. Steps, metabolic equivalents (METs), physical activity intensities, and sedentary behaviour were extracted from the Fitabase database at minute intervals. The data was processed to generate the following dependent variables: steps/day, METs/day, physical activity intensity minutes (lightly, fairly, and very active minutes) and sedentary behaviour minutes per day. Physical activity and sedentary behaviour bouts were ranked according to their bout duration (mins), and normalised as a proportion of total time spent in the respective activity intensity type, and from this a weighted median bout duration was determined according to previously devised accelerometry methods (184), providing the “usual” bout duration of each of these behaviours. The main independent variable of interest was lockdown time indicator with two states: either prior to lockdown restrictions (before March 23rd, 2020) or after them. Variables were incorporated into generalised least squares regression models except the steps/day variable which was incorporated into a negative binomial regression model. Regression models were performed within each participant, and then meta-analysed to provide overall estimates. Using these regression models, it was possible to determine whether the COVID-19 lockdown restrictions were associated with longer term sedentary behaviour and physical activity changes in participants involved in the OPTIMISE Your Health trial.
Further methodological information pertaining to the use of the Fitbit in the OPTIMISE Your Health trial is available in Chapter 5, and more information pertaining to the Fitbit’s data collection and analysis are available in Chapter 6.
Chapter 3: Contrasting compositions of sitting, standing, stepping, and sleeping time: associations with glycaemic outcome by diabetes risk

3.1 Introduction
The research identified in Chapter 1 covers an overview of the many studies investigating the role and influence of sedentary behaviour on health. These include hypothesis-generation epidemiological studies, experimental trials, and some preliminary randomised controlled trials. Recent reviews and evidence (141) have highlighted a need for sedentary behaviour research to investigate the role of sedentary behaviour in distinct cohorts such as those with chronic diseases. In addition, a recent meta-analysis (185) suggests that in an acute experimental setting, response to prolonged sedentary behaviour differs by level of insulin resistance, or metabolic impairment. Chapter 3 presents a research publication that has aimed to investigate the role of sedentary behaviour in people with an elevated risk of type 2 diabetes and compare them to people at lower risk. These comparisons increase our understanding of sedentary behaviour, and importantly identify whether targeting sedentary behaviour could have utility in chronic disease management settings.

The first paper of this thesis, presented here in section 3.2, uses compositional data analysis to examine the associations of 24hr time-use with glycaemic control, and compares these associations between people at lower risk and higher risk of type 2 diabetes. This investigation was conducted in a large sample of community-dwelling Australian adults. Further summary and implications of the findings are presented in section 3.3.
3.2 Manuscript

This manuscript was published in the peer-reviewed journal International Journal of Behavioral Nutrition and Physical Activity in December 2021. Description and extent of contributions are detailed in Appendix A. This manuscript was published and can be reproduced under the terms of Creative Commons Attribution license 4.0

Citation:
Contrasting compositions of sitting, standing, stepping, and sleeping time: associations with glycaemic outcome by diabetes risk

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Abstract

Background: Recent evidence suggests that prolonged sitting and its adverse impact on glycaemic indicators appear to be proportional to the degree of insulin resistance. To investigate this finding in a free-living context, we aimed to examine associations of device-measured 24-h time-use compositions of sitting, standing, stepping, and sleeping with fasting glucose (FPG) and 2 h post-load glucose (2hPLG) levels, and to examine separately the associations with time-use compositions among those at lower and at higher risk of developing type 2 diabetes.

Methods: Cross-sectional analyses examined thigh-worn inclinometer data (activPAL, 7 day, 24 h/day protocol) from 648 participants (aged 36-80 years) at either lower (< 39 mmol/mol; < 5.7% HbA1c) or higher (≥ 39 mmol/mol; ≥ 5.7% HbA1c) diabetes risk from the 2011-2012 Australian Diabetes, Obesity and Lifestyle study. Multiple linear regression models were used to examine associations of differing compositions with FPG and 2hPLG, with time spent in each behaviour allowed to vary up to 60 min.

Results: In general, the associations with the FPG within the time-use compositions were small, with statistically significant associations observed for sitting and sleeping (in the lower diabetes risk group) and standing (in higher diabetes risk group) only. For 2hPLG, statistically significant associations were observed for stepping only, with findings similar between lower (β = −0.12 95%CI: −0.22, −0.02) and higher (β = −0.13 95%CI: −0.26, −0.01) risk groups. Varying the composition had minimal impact on FPG; however 1 h less sitting time and equivalent increase in standing time was associated with attenuated FPG levels in higher risk only (Δ FPG% = −1.5 95%CI: −2.4, −0.5). Large differences in 2hPLG were observed for both groups when varying the composition. One hour less sitting with equivalent increase in stepping was associated with attenuated 2hPLG, with estimations similar in lower (Δ 2hPLG% = −3.8 95%CI: −7.3, −0.2) and higher (Δ 2hPLG% = −5.0 95%CI: −9.7, −0.0) risk for diabetes.

Conclusions: In middle-aged and older adults, glycaemic control could be improved by reducing daily sitting time and replacing it with stepping. Standing could also be beneficial for those at higher risk of developing type 2 diabetes.

Keywords: Time-use, Diabetes risk, Glycaemic control, Sedentary behaviour
**Background**

Clinical practice guidelines for the prevention of type 2 diabetes emphasise lifestyle management as the first priority for those identified with elevated risk [1]. A primary focus has been on promoting regular participation in moderate-to-vigorous intensity physical activity. More recently, addressing sedentary (sitting) time has been included in guidelines [2] based on emerging observational and acute experimental evidence regarding the detrimental relationships of high volumes of time spent sitting with risk for type 2 diabetes [3] and its precursors [4], and the potential benefits of replacing sitting time with physical activity and/or standing [5–7].

Consideration of 24 h time-use as a composition of distinct yet competing activities (sitting, standing, stepping, and sleep) is increasingly being adopted in observational research to examine associations with health outcomes and risk biomarkers [8–10]. This has been made possible by the use of continuously-worn activity-monitor devices that collect time- and date-stamped information, enabling the 24 h period to be categorised entirely into the sum of time spent in different behaviours. This has led to the creation of integrated movement guidelines, that have made recommendations on how to best utilise the 24 h for greatest health benefit [11]. There have been numerous studies that have suggested that time spent sitting [7], standing [12], in physical activities [13], and in sleep [14] can have distinct associations with glucose outcomes. However, the majority of these studies did not differentiate by posture (instead, they did so using device acceleration thresholds). Nor have they considered these behaviours as interrelated exposures [15], where spending time in one behaviour will necessarily mean less time undertaken in the remaining behaviours within the same 24 h period.

Findings from recent laboratory-based trials suggest that the detrimental impacts of prolonged sitting time on blood glucose may be proportional to the degree of underlying insulin resistance [16], but it is not known if this is manifested in the free-living context. Furthermore, it is unclear if changing sitting, standing, and activity levels have differential impact depending on underlying risk for developing type 2 diabetes. This has important implications for the tailoring of public health advice, and for clinical practice guidelines targeting vulnerable populations.

To address these evidence gaps, compositional data analyses (CoDA) were used to examine the associations with fasting plasma glucose (FPG) and 2 h post-load glucose (2hPLG) of device-measured components of 24 h time-use (sitting, standing, stepping, and sleeping) in the free-living context in middle-aged and older Australian adults. Compositions with varying time spent between components were compared between those at lower and higher risk for type 2 diabetes.

**Methods**

**Participants and setting**

The Australian Diabetes, Obesity and Lifestyle Study (AusDiab) baseline study methods and response rates are described in detail elsewhere [17]. In brief, the baseline study was a national population-based survey of 11,247 adults aged ≥25 years in 1999–2000. A stratified cluster sampling approach was undertaken, with strata selected based upon the six states and the Northern Territory of Australia. Subsequent follow-ups occurred in 2004–2005 (n = 6400) and 2011–2012 (n = 4614). At the 2011/2012 follow-up, a sub-sample of participants were invited to wear an activity monitor as described elsewhere [7]. Eligible participants (ambulatory, and not pregnant) were recruited daily in a consecutive manner until either a quota was reached (n = 5) or no more monitors were available. Of the 1014 approached, 782 consented to wearing the monitor, and 741 wore the monitor for at least one valid day. For these analyses, the following exclusions were applied: those with less than four valid monitor-wear days (n = 21), those with known diabetes (diagnosed by physician and taking hypoglycaemic medication or insulin) at the assessment (n = 37); those pregnant (n = 2); and those with missing covariates (n = 33). A small number of participants missed assessment of 2hPLG (n = 8) and FPG (n = 1) in the oral glucose tolerance test (OGTT) assessment. Thus, the final cross-sectional study was conducted with 647 for the FPG analysis and 640 for the 2hPLG analysis. The sample was stratified into two groups according to their HbA1c (glycated hemoglobin) levels: lower risk for diabetes (<39 mmol/mol, <5.7% HbA1c), and higher risk (≥39 mmol/mol, ≥5.7 HbA1c). This was conducted a priori and based on experimental research suggesting that behaviours are associated with varied glucose outcomes depending on the degree of dysmetabolism [16]. Stratification is also in accordance with the American Diabetes Association’s diagnosis classification for prediabetes [18].

**Data collection**

On the day of recruitment, participants followed standard protocols as per the main AusDiab study procedures [19]. Following an overnight fast (minimum 8 h), participants underwent biochemical and anthropometric assessments and completed a series of questionnaires at their local testing site. FPG and HbA1c were taken initially, followed by a standard 2 h 75-g OGTT [20]. The activity monitor was put on either on the day of the assessment or the following day. Questionnaires...
(self-completed and interviewer administered) were used to collect data on confounding variables.

Device-measured sitting, standing, stepping, and sleep time

The time-use composition was derived from measurements using the activPAL3 activity monitor (PAL Technologies Limited, Glasgow, UK; version 6.4.1); this device has been shown to be accurate and reliable for use with adults and older adults [21]. Each monitor was initialised with the default settings (20 Hz) and waterproofed by covering it in a nitrile sleeve and then encased in transparent Hypafix. It was then secured anteriorly to the participant’s right thigh at the approximate midline. Participants were instructed to wear the monitor continuously for seven consecutive days (24h/day, keeping the device attached for showering/bathing), and to record in a standardised diary their sleep and monitor removal time (if it did occur). The device was mailed back to the AusDiab research staff in a reply-paid envelope at completion. Monitor data were processed using SAS 9.3 (SAS institute Inc., Cary, NC, USA). An invalid wear day was considered to be when monitor wear time was less than 80% of waking hours, or less than 10 h if the participant’s diary was missing sleep and wake times. Invalid wear days were excluded from data analysis. If sleep and wake times were not reported in the diary they were estimated using an automated algorithmic method [22], which demonstrated almost perfect agreement for most participants (median kappa 0.94 in 88% of participants). Sleep time was deduced by subtracting all waking behaviour and unworn monitor time from 24h. Across all valid days, the average time spent in sitting, standing, stepping, and sleeping within a 24h period was calculated.

Glycaemic measures

Blood samples were collected via venipuncture with whole blood collected into fluoride-oxalate containing tubes for the analysis of plasma glucose, and EDTA containing tubes for the analysis of HbA1c. All blood specimens were centrifuged on-site in order to separate plasma, which was then immediately aliquoted for testing and storage. Storage entailed either the immediate transport of the sample to a central independent laboratory (Healthscope Pathology) or to the site freezer where it was kept at −20°C and subsequently at −80°C within 1 to 2 weeks after collection. HbA1c was measured with liquid chromatography method (Bio-Rad Variance Hemoglobin Testing System; Bio-Rad, Hercules Ca, USA). FPG and 2hPLG were measured by the hexokinase method using a Siemens Advia 2400 (Siemens AG, Munich, Germany).

Other measures

Backwards elimination was performed on a set of confounders previously identified in the activity monitor subsample (covariate elimination where \( p > 0.2 \)) [7]. Variables excluded were contraceptive medication, ethnicity, employment status (blue collar, white collar, unemployed), occupation type (manager, professional, technician, service worker, clerical worker, sales worker, machinery, labourer worker, labourer, never worked), fibre intake, and marital status. Smoking status and menopausal status were excluded, however given their potential for modifying glucose metabolism; they were added back into the confounder adjusted models. Confounders used for all models included: age, menopausal status (self-reported pre, peri, post-menopausal status, or male), education attainment, income category, smoking category, depression status [23], diet quality [24], energy intake, alcohol and calcium intake. These analyses did not account for confounding by adiposity as it was considered on the causal pathway and thus a mediator of the relationships. A separate analysis with adjustment by waist circumference revealed similar magnitude and direction for all relationships.

Statistical analyses

Analyses were conducted using Stata 14.2 (StataCorp LP, College Station, TX, USA) and R version 3.6.1. Group characteristics were compared using analysis of variance for continuous variables, and by chi-square tests for categorical variables. In the linear regressions, glucose outcomes were log transformed which improved normality of residuals. Multicollinearity among confounders were assessed using variance inflation factor (VIF) methods, all models had VIF values below 2.5.

The CoDA method procedure has been described in detail previously [9, 25]. The 24h day (1440min) examined was finitely comprised of sitting, standing, stepping, and sleeping time-use components. Daily totals of all activities were calculated into geometric means per diabetes risk group using Aitchison’s perturbation method (“acomp” function in R package: Compositions). Means were transformed into isometric log ratios and compared between higher and lower risk groups. In order to explain significant group difference, geometric means were first computed as a log ratio (higher/lower risk), and then bootstrapped (as described by Gupta et al. [26]) to calculate the percentage difference (difference between two log ratios) between the two geometric means with upper and lower limits of 95% confidence intervals. Overall group difference was determined with Hotelling’s test (R package: “Hotelling”).
The compositional modeling employs isometric log ratios (ilr) of the behaviour components. In brief, the outcome (log glucose) is dependent on the sum of composition isometric log ratios and covariates through a regression model.

\[
E(y|ilr) = \beta_0 + \beta_1 ilr1 + \beta_2 ilr2 + \beta_3 ilr3 + \text{effect of other covariates}
\]

Where ilr1, ilr2 and ilr3 are the coordinates of the ilr-transformed composition. The coefficient \( \beta_1 \) is the main interest here as it reflects the effect of time spent in one behavior relative to the other three. For example, to assess the effect of time spent sitting relative to stepping, standing, and sleeping, we would use ‘sitting’ as the reference behavior when performing the ilr transformation and compute ilr1 as:

\[
ilr1 = \sqrt{\frac{(3/4)\ln(sitting)}{\sqrt{(standing \times step \times sleeping)}}}
\]

To assess the interaction with diabetes risk, an interaction between ilr-transformed variables (ilr1, ilr2, ilr3) and diabetes risk group was added to the model and the interaction coefficient with ilr1 was examined for statistical significance. To test an outcome's association with relative time spent in the other behaviours, the ilr-transformed variable was recalculated using that behaviour as reference and the above procedures were repeated. For all behaviours, associations were tested in unadjusted and confounder-adjusted models. The models were then used to estimate the expected log FPG and 2hPLG values with set compositions.

New compositions were made by adding and subtracting 15, 30, 45, and 60 min from the geometric mean values. The difference (delta) between the estimated log glucose value of the new composition and the estimated value of the geometric mean composition was calculated using R package “deltacomp” [10, 27]. Confidence intervals were determined using the standard error of the delta estimate. The estimated differences were then back-transformed and presented as percentage difference from the original glucose value. For each of the behaviours, there was no requirement to adjust them from zero time as every participant participated in at least 1 min in each of the behaviours. All hypothesis testing was two-tailed and the type I error for all statistical analyses were set at 5%.

**Results**

**Characteristics of participants**

Table 1 describes the characteristics of participants with lower and higher diabetes risk. Compared to the lower risk, the higher risk participants were more likely to be older, and to include post-menopausal women, and earn less. There were no significant differences in behaviours between the lower risk and higher risk for smoking, energy intake, or dietary quality. Alcohol intake was greater in the lower risk (15.5 g) compared to the higher risk (11.5 g).

**Geometric means for the 24 h day**

Table 2 shows the geometric means of sitting, standing, stepping, and sleeping for the lower and higher risk participants. For both the lower and higher risk, sitting occupied the largest proportion of the day and stepping the smallest. When considering group geometric means and variance intervals comparing the two risk groups, all percentage differences intersected zero; therefore, there were no statistically-significant differences between groups. The comparisons using Hotelling’s test confirmed no statistically significant difference between the overall compositions with \( p \)-value > 0.05.

**Compositional linear regression modelling**

The associations of log glucose outcomes with time spent in each behaviour (and consequently less time in remaining behaviours) are presented for both the lower and higher diabetes risk participants unadjusted and confounder adjusted in Table 3. In the confounder adjusted model, for lower risk all associations with FPG were weak, with statistically significant associations observed for sitting (\( \beta = 0.04 \ 95\%CI: 0.00, 0.08 \)) and stepping (\( \beta = -0.06 \ 95\%CI: -0.12, -0.00 \)) only. Associations with FPG were also weak in the higher risk, with the only statistically significant association being with standing time (\( \beta = -0.07 \ 95\%CI: -0.12, -0.01 \)). However, the direction of the relationships of standing and sleeping with FPG were opposite between groups (\( p < 0.01 \) for interaction); this was the only statistically significant interaction by diabetes group observed. For 2hPLG, statistically significant associations were observed for stepping only, with associations similar for the lower (\( \beta = -0.12 \ 95\%CI: -0.22, -0.02 \)) and higher (\( \beta = -0.13 \ 95\%CI: -0.26, -0.01 \)) risk groups. Notably, there was a positive association with 2hPLG and sleeping time in the high risk group (\( \beta = 0.17 \ 95\%CI: 0.04, 0.39 \)); however, this finding did not reach statistical significance.

**Comparison of compositions with varying time spent between behaviours**

New compositions were made by adding and subtracting time from geometric mean values. The new compositions’ estimated glucose values were then compared to original mean values in lower and higher risk. Figure 1 illustrates varying totals of sitting, standing, and stepping, and Table 4 shows 60 min composition variations between two select behaviours.
Small differences in estimated fasting glucose outcomes were found when varying the compositions from geometric means. In lower risk, increasing sleeping by 60 min and decreasing sitting by 60 min (Sit → Sleep) was associated with decreased FPG: −1.1%Δ FPG (95% CI: −2.0, −0.2). Lower sitting time, and higher standing time were associated with lower FPG in higher risk only. In higher risk, 60 min more standing, and equivalent less time sitting (Sit → Stand) was associated with reduced FPG: −1.5%Δ FPG (95% CI: −2.4, −0.5). This suggests that standing may be more advantageous for the higher risk group (Fig. 1A). Increased standing time by 60 min, and 60 min less sleeping time (Sleep → Stand) was associated with greater FPG in the lower risk group (1.1%Δ FPG (95% CI: 0.0, 2.2)) and reduced FPG in the higher risk group (−1.8%Δ FPG (95% CI: −3.5, −0.2)).

The estimated differences in 2hPLG when varying the compositions were greater than in FPG. For example,

### Table 1 Sample characteristics stratified by lower and higher risk for diabetes

<table>
<thead>
<tr>
<th></th>
<th>Diabetes Risk</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lower Risk (n = 376)</td>
<td>Higher Risk (n = 272)</td>
<td></td>
</tr>
<tr>
<td>HbA1c, mmol/mol 95% CI</td>
<td>36 (36–37)</td>
<td>41 (41–41)*</td>
<td></td>
</tr>
<tr>
<td>HbA1c%, 95 CI</td>
<td>5.4 (5.4–5.5)</td>
<td>5.9 (5.9–5.9)*</td>
<td></td>
</tr>
<tr>
<td>FPG, mmol/L (sd)</td>
<td>5.2 (0.5)</td>
<td>5.5 (0.9)*</td>
<td></td>
</tr>
<tr>
<td>2hPLG, mmol/L (sd)</td>
<td>5.2 (1.3)</td>
<td>6.0 (2.3)*</td>
<td></td>
</tr>
<tr>
<td>Socio-demographic</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years (sd)</td>
<td>56.0 (9.8)</td>
<td>60.2 (9.3)*</td>
<td></td>
</tr>
<tr>
<td>Women, n (%)</td>
<td>198 (52.7%)</td>
<td>165 (60.7%)</td>
<td></td>
</tr>
<tr>
<td>Education, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High school or less</td>
<td>93 (24.7%)</td>
<td>95 (34.9%)*</td>
<td></td>
</tr>
<tr>
<td>Technical / Vocational</td>
<td>184 (48.9%)</td>
<td>116 (42.6%)*</td>
<td></td>
</tr>
<tr>
<td>Bachelor degree or higher</td>
<td>99 (26.3%)</td>
<td>61 (22.4%)*</td>
<td></td>
</tr>
<tr>
<td>Income, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No income, or not reported</td>
<td>22 (5.9%)</td>
<td>17 (6.2%)</td>
<td></td>
</tr>
<tr>
<td>$1-39,999 per year</td>
<td>65 (17.3%)</td>
<td>66 (24.3%)</td>
<td></td>
</tr>
<tr>
<td>$40,000-79,999 per year</td>
<td>91 (24.2%)</td>
<td>71 (26.1%)</td>
<td></td>
</tr>
<tr>
<td>≥ $80,000 per year</td>
<td>198 (52.7%)</td>
<td>118 (43.4%)</td>
<td></td>
</tr>
<tr>
<td>Menopause, n (%) women</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>88 (44.4%)</td>
<td>117 (70.9%)*</td>
<td></td>
</tr>
<tr>
<td>Peri-menopausal</td>
<td>37 (18.7%)</td>
<td>20 (12.1%)*</td>
<td></td>
</tr>
<tr>
<td>Pre-menopausal</td>
<td>73 (36.9%)</td>
<td>28 (17.0%)*</td>
<td></td>
</tr>
<tr>
<td>Known depressive symptoms, n (%)a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>23 (6.1%)</td>
<td>29 (10.7%)</td>
<td></td>
</tr>
<tr>
<td>Behaviour</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status, n (%)b</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current smoker</td>
<td>28 (7.4%)</td>
<td>18 (6.6%)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>139 (37.0%)</td>
<td>97 (35.7%)</td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>209 (55.6%)</td>
<td>157 (57.7%)</td>
<td></td>
</tr>
<tr>
<td>Dietary Intake</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Energy, mcals/day</td>
<td>1.7 (0.65)</td>
<td>1.7 (0.67)</td>
<td></td>
</tr>
<tr>
<td>Dietary quality score</td>
<td>65.7 (12.4)</td>
<td>67.2 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Alcohol, g/day</td>
<td>15.5 (19.1)</td>
<td>11.5 (15.3)*</td>
<td></td>
</tr>
<tr>
<td>Calcium, g/day</td>
<td>0.9 (0.3)</td>
<td>0.9 (0.3)</td>
<td></td>
</tr>
</tbody>
</table>

Table displays mean (standard deviation), or sample n (%)

*Indicates significant difference between stratified groups with p < 0.05

a Known depressive symptoms indicated when CESD score ≥ 10

b Smoking status: Current smoker: smokes now, and ≥ 100 cigarettes in lifetime, Ex-smoker: does not currently smoke and ≥ 100 cigarettes in lifetime, Non-smoker: smoked < 100 cigarettes in lifetime and does not currently smoke
Table 2  Geometric means of behaviours in those with lower and higher risk for diabetes

<table>
<thead>
<tr>
<th>Diabetes Risk</th>
<th>Lower Risk (n = 376)</th>
<th>Higher Risk (n = 272)</th>
<th>Percentage Difference (95% CI)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Geometric means, mins/1440a</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sitting</td>
<td>526.4 (36.6%)</td>
<td>530.7 (36.9%)</td>
<td>0.49% (−4.44, 5.41)</td>
</tr>
<tr>
<td>Standing</td>
<td>287.1 (19.9%)</td>
<td>288.5 (20.0%)</td>
<td>−3.90% (−9.36, 1.59)</td>
</tr>
<tr>
<td>Stepping</td>
<td>120.6 (8.4%)</td>
<td>116.0 (8.1%)</td>
<td>−0.21% (−2.20, 1.84)</td>
</tr>
<tr>
<td>Sleeping</td>
<td>505.8 (35.1%)</td>
<td>504.8 (35.1%)</td>
<td>0.80% (−2.56, 4.08)</td>
</tr>
</tbody>
</table>

a Geometric means expressed as minutes conducted within a 1440 min composition (percentage rounded to complete number)

b Percentage difference refers to the log ratio difference between each behaviour per group converted into percentage. Positive estimated difference indicates that the higher risk has a greater level of the given component; negative estimated difference indicates the lower risk has a greater level of the given component.

Percentage difference and 95% confidence intervals were determined with bootstrapping. Behaviours with confidence intervals that intersect zero should be considered to not differ by diabetes risk group

Table 3  Associations of behaviours with glucose biomarkers overall and in lower and higher risk for diabetes

<table>
<thead>
<tr>
<th>Behaviours (y1)</th>
<th>FPG</th>
<th>2hPLG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td>Lower Risk (β) (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>β (95% CI)</td>
</tr>
<tr>
<td>Unadjusted model</td>
<td>Sitting</td>
<td>0.05* (0.01, 0.08)</td>
</tr>
<tr>
<td></td>
<td>Standing</td>
<td>-0.05* (-0.08, -0.02)</td>
</tr>
<tr>
<td></td>
<td>Stepping</td>
<td>-0.02 (-0.04, 0.01)</td>
</tr>
<tr>
<td></td>
<td>Sleeping</td>
<td>0.02 (-0.03, 0.07)</td>
</tr>
<tr>
<td>Confounder adjusted model</td>
<td>Sitting</td>
<td>0.04* (0.01, 0.08)</td>
</tr>
<tr>
<td></td>
<td>Standing</td>
<td>-0.03 (-0.06, 0.01)</td>
</tr>
<tr>
<td></td>
<td>Stepping</td>
<td>-0.02 (-0.05, 0.01)</td>
</tr>
<tr>
<td></td>
<td>Sleeping</td>
<td>0.00 (-0.05, 0.05)</td>
</tr>
</tbody>
</table>

β (95% CI) presented with 95% confidence interval (CI). Coefficient corresponds to association of time spent in the behaviour with log glucose outcome

All confounder adjusted models adjusted for age, menopausal status (pre, peri, post-menopausal, male), education attainment, income category, smoking category, depression, diet quality, energy intake, alcohol, and calcium intake

a* p-value interaction indicates where association is statistically different by diabetes risk

*Indicates a statistically significant association, and statistically significant interaction by diabetes risk using p < 0.05 in two tailed analyses

less stepping, and more sitting time was associated with large differences in 2hPLG from mean values (Fig. 1D) in both risk groups. The greatest estimated glucose differences were observed when increasing sleep by 60 min, and decreasing stepping by 60 min which were associated with similar values in lower risk (7.8%Δ 2hPLG (95%CI: 0.9, 15.1)) and higher risk (10.8%Δ 2hPLG (95%CI: 2.4, 19.9)). While the estimates suggest that the higher risk group had more pronounced differences from the mean, the overlapping confidence intervals equated to no significant difference between risk groups with estimations of Δ 2hPLG.

Discussion

This is one of few studies to use a postural-based approach to identify sitting, standing, stepping and sleeping time with compositional data analysis methods [28, 29]. We showed that in this sample of middle-aged and older Australian adults, behaviours composing 24 h time-use were associated with biomarkers of glucose control, with some potential differences for those at lower risk and higher risk for diabetes. Compositions that had greater sitting, and lesser equivalent stepping time were most detrimental, however this association did not differ significantly by diabetes risk group. Compositions with greater sitting, and lesser equivalent time standing had small but statistically significant detrimental associations for those with higher risk for diabetes only. These findings may have important practical implications. For example, a person at higher risk of diabetes may improve glycaemic control not only with physical activity, but with greater levels of standing time (albeit more modestly so), which can be achieved over the course of the 24 h day.

Interestingly, compositional modeling showed the increase to 2hPLG levels with 60 min more sitting (lower risk: + 6.9% 95CI%: 0.6, 13.5; higher risk: + 9.1% 95CI%: 0.6, 18.5) outweighed the attenuation of 2hPLG with
**Fig. 1** Comparing compositions with varying totals of sitting, standing, and stepping and their associated glucose outcomes in lower and higher risk for diabetes. Graphs A and B denote compositions with varying time spent sitting (more sitting time and less standing indicated to the left of the x-axis) and standing (more standing time and less sitting indicated to the right of the x-axis) and estimation of fasting, and 2 h plasma glucose dependent on composition. Graphs C and D denote compositions with varying time spent sitting and stepping. Graphs E and F denote compositions with varying time spent standing and stepping. The associated glucose outcomes at a given composition are compared to the glucose outcomes at the geometric mean. Difference in glucose between new composition and original are denoted by Δ FPG% and Δ 2hPLG%.

**Table 4** Varying composition by 1 h and using linear regression models to estimate glucose

<table>
<thead>
<tr>
<th>Varying compositions by 60 min&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Δ FPG%</th>
<th>Δ 2hPLG%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lower Risk (n = 375)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Higher Risk (n = 272)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sit → Sleep</td>
<td>−1.1% (−2.0, −0.2)</td>
<td>0.3% (−1.2, 1.8)</td>
</tr>
<tr>
<td>Sit → Stand</td>
<td>0.0% (−0.8, 0.7)</td>
<td>−1.5% (−2.4, −0.5)</td>
</tr>
<tr>
<td>Sit → Step</td>
<td>−0.6% (−1.9, 0.7)</td>
<td>−1.4% (−3.4, 0.7)</td>
</tr>
<tr>
<td>Stand → Sleep</td>
<td>−1.1% (−2.2, 0.0)</td>
<td>2.1% (0.3, 3.9)</td>
</tr>
<tr>
<td>Stand → Sit</td>
<td>−0.1% (−0.9, 0.7)</td>
<td>1.7% (0.6, 2.9)</td>
</tr>
<tr>
<td>Stand → Step</td>
<td>−0.7% (−2.4, 1.1)</td>
<td>0.4% (−2.2, 3.1)</td>
</tr>
<tr>
<td>Step → Sleep</td>
<td>−0.3% (−2.6, 1.9)</td>
<td>2.5% (−0.8, 5.9)</td>
</tr>
<tr>
<td>Step → Sit</td>
<td>0.7% (−1.4, 2.8)</td>
<td>2.1% (−1.2, 5.6)</td>
</tr>
<tr>
<td>Step → Stand</td>
<td>0.7% (−1.8, 3.2)</td>
<td>0.7% (−3.1, 4.5)</td>
</tr>
<tr>
<td>Sleep → Sit</td>
<td>1.1% (0.2, 2.1)</td>
<td>−0.4% (−1.9, 1.1)</td>
</tr>
<tr>
<td>Sleep → Stand</td>
<td>1.1% (0.0, 2.2)</td>
<td>−1.8% (−3.5, −0.2)</td>
</tr>
<tr>
<td>Sleep → Step</td>
<td>0.5% (−1.0, 2.1)</td>
<td>−1.7% (−3.7, 0.3)</td>
</tr>
</tbody>
</table>

Values expressed as the percentage difference (95% CI) between the new composition’s estimated glucose value and the original geometric mean glucose value (Δ FPG% or Δ 2hPLG%) for each diabetes risk group

<sup>a</sup> Compositions tested varied by 60 min from geometric means, for example, “Sit → Stand” denotes 60 minutes subtracted from sitting time and added to standing time geometric means.
60 min more stepping (lower risk: $-3.8\%$, 95CI%: $-7.3, -0.2$; higher risk: $-5.0\%$, 95CI%: $-9.7, -0.0$), indicating a potential ceiling effect of benefit from daily stepping. Similar asymmetric relationships have been observed in compositional analyses before [9, 10, 29, 30], and previously hypothesised to be either relevant to the outcomes and behaviours observed, or to be inherent to the compositional data. For the present findings, it may suggest that higher daily sitting deconditions glycaemic control at greater levels than what is achieved by stepping to improve it. The relationship of time-use and glycaemic control should be investigated further to confirm these findings.

Standing was inversely associated with FPG in the higher risk group only. Whilst there is evidence of standing being beneficially associated with mortality [31–33], many investigations purport that most, if not all glucose change is induced by reallocation time to movement [6, 29, 34], potentially as standing produces only marginal increments in muscle activity and energy expenditure [28]. The reason why the findings are exclusive to the higher risk group is unclear. However, previously standing has been demonstrated to reduce glucose levels in an overweight and obese cohort [12], and chronic muscular inactivity is more likely to induce hepatic insulin resistance in those with familial predisposition for type 2 diabetes [35], indicating that the finding may be inherent to the group studied. Future studies should investigate the extent to which standing, without ambulation is associated with beneficial metabolic outcomes, and clarify whether there is greater benefit to those more vulnerable to chronic diseases such as people with metabolic impairment or at higher risk of type 2 diabetes.

Recent experimental findings have reported that the most exaggerated postprandial glucose responses to prolonged sitting are evident in those with poorer underlying glycaemia, and insulin resistance [16]. When skeletal muscles are inactive, GLUT4 expression is down-regulated [36]; this leads to less contractile-mediated glucose uptake and more circulating glucose in the bloodstream. Being at higher risk for diabetes may increase susceptibility to insulin resistance, thus impairing the action of insulin mediated glucose disposal [37]. Therefore, those at higher risk for diabetes may have diminished capacity for homeostatic control of glucose when exposed to high volumes of sitting during the day. Considering mean estimates only, those with higher risk did exhibit a propensity for greater levels of 2hPLG with compositions higher in sitting and lower in stepping, and greater relative attenuation of 2hPLG levels with compositions higher in stepping and lower in sitting when compared to the lower risk (Fig. 1D). However, the overlapping confidence intervals suggest no significant difference by risk group for these relationships. Interestingly, compositions with higher stepping, and less sleeping were associated with reduced 2hPLG too. Evidence outlining favorable sleep duration supports $7 - 8$ h per day, and sleep time that extends beyond this duration is associated with less beneficial health outcomes [11]. Given the mean sleeping period for both risk groups was $>8.4$ h per day, it is not unfeasible that excessive sleep durations, especially in place of daily physical activity, may be less favourable for glycaemic control. These findings however should be interpreted with caution given the cross-sectional study design, where reverse causation (i.e. worsened metabolism provokes longer sleep durations) cannot be ruled out. Future studies incorporating larger sample sizes, and a longitudinal study design should investigate these findings further.

Compositions that had 60 min more stepping time and equivalent reduction in sitting time had comparable associations with glucose outcomes to those that have previously been reported in a physical activity intervention. Gong et al. [38] determined that physical interventions achieved significant 2hPLG reductions when comparing the standardised mean differences to controls (SMD: $-0.42$, 95% CI: $-0.63, -0.20$). The results of the present study are comparable, albeit of lower magnitude, for both lower (SMD: $-0.16$ 95% CI: $-0.19, -0.13$) and higher risk (SMD: $-0.13$ 95% CI: $-0.15, -0.10$) when comparing more physically active compositions to the original geometric mean composition. Difference in magnitudes may be explained by physical activity interventions specifically involving participants in more intensive, and controlled experimental approaches as opposed to the free-living context of the present study.

Recent public health and clinical practice guidelines now emphasise the importance of not only reducing total sedentary time, but also increasing total physical activity through moving more throughout the day – ’sit less and move more’ [3]. Our findings suggest that for glucose outcomes, this approach may be of greater importance in those at higher risk for development of diabetes, which is aligned with landmark diabetes prevention trials primarily targeting those at elevated risk [39]. A recent systematic review by Hadgraft et al. [40] evaluated a large sample of sedentary behaviour change interventions and determined only small benefit of reducing sedentary time on FPG. Given the findings of the present study, the small benefit to glucose levels may be explained by the majority of included studies recruiting the general population (therefore not necessarily at high risk of chronic disease), as well as having a degree of heterogeneity between intervention components and
intervention messaging. Notably, most of the intervention trials in the systematic review resulted in increased standing behaviours only, as opposed to changes to stepping levels. Future interventions should target the replacement of sedentary behaviour with both standing and stepping behaviours, and target those at elevated risk of diabetes.

The main strengths of this study were the measurement of 24 h posture time-use with device-based measures in the free-living context, as well the interpretation of this with a CoDA technique. The participants were recruited from the general Australian population, indicating that these findings may apply to a broader population, however it should be noted that this study’s subsample of participants were on average healthier than the main sample [7]. By using the activPAL device it was possible to accurately interpret postures such sitting, standing, and stepping, which has rarely been applied to a cohort at risk of diabetes. However, findings do need to be considered in the context of the limitations. Notably, cross-sectional analyses preclude causal inference. Another limitation is that selection bias may be present as stratification by diabetes risk group at 39 mmol/mol HbA1c may lead to reduced glucose outcome variability (and a greater chance of type 2 error); however there were similar estimates with 2hPLG between groups for sitting and stepping. The CoDA modeling did not account for patterns of time (e.g. short or long periods of sitting /or stepping), intensity (light, moderate, or vigorous intensity), nor sleep quality, which are known to have independent associations with cardiometabolic biomarkers [8, 41, 42]. There may have been some errors in the sleep estimate as sleep onset was self-reported or automatically estimated rather than objectively measured.

Conclusion
In conclusion, these findings from an examination of 24 h time-use (composed of sitting, standing, stepping and sleeping) in participants going about their normal daily lives, suggest that in middle-aged and older adults, glycaemic control could be improved by reducing daily sitting time and supplementing it with standing or stepping, especially so in those at higher risk of developing type 2 diabetes.

Tables
See Tables 1, 2 and 3.

Abbreviations
2hPLG: 2 h post-load glucose; AusDiab: The Australian Diabetes, Obesity and Lifestyle Study; CoDA: Compositional data analysis; FPG: Fasting plasma glucose; HbA1c: Glycated Haemoglobin; ilr: Isometric log ratio; OGTT: Oral glucose tolerance test; VIF: Variance inflation factor.

Acknowledgements
The authors acknowledge the participants and research staff involved with AusDiab, and Kelsie M Full, Elisabeth Winkler, Dorothea Dumuid, and Ty Stanford for offering statistical analysis advice.

Authors’ contributions
CB conducted analysis and wrote the manuscript. DD, GH, NO, were involved in the conception of the present study’s design, advised on the analyses, and editing of the manuscript. AC was involved in editing of the manuscript. PS was involved in and advised on the analyses. SC, JB, AS, advised on the analyses. The authors read and approved the final manuscript.

Funding
We are grateful for the funding support from the National Health and Medical Research Council (NHMRC grants 233220 and 1007344), Australian Government Department of Health and Ageing, Abbott Australasia Pty Ltd, Alphapharm Pty Ltd., Amgen Australia, AstraZeneca, Bristol-Myers Squibb, City Health Centre-Diabetes Service-Canberra, Department of Health and Community Services—Northern Territory, Department of Health and Human Services—Tasmania, Department of Health—New South Wales, Department of Health—Western Australia, Department of Health—South Australia, Department of Human Services—Victoria, Diabetes Australia, Diabetes Australia Northern Territory, Eli Lilly Australia, Estate of the Late Edward Wilson, GlaxoSmithKline, Jack Brockhoff Foundation, Janssen-Cilag, Kidney Health Australia, Marrian & FH Flack Trust, Menzies Research Institute, Merck Sharp & Dohme, Novartis Pharmaceuticals, Novo Nordisk Pharmaceuticals, Pfizer Pty Ltd., Pratt Foundation, Queensland Health, Roche Diagnostics Australia, Royal Prince Alfred Hospital, Sydney, Sanofi Aventis, sanofi-synthelabo, and the Victorian Government’s OIS Program. DD, GH, NO are supported by the NHMRC Fellowships scheme. Funding for JB came from a program project (PO1 AG052352) supported by the US National Institute on Aging. The funders of this study had no role in the data analysis or interpretation of the results.

Availability of data and materials
Datasets are available on request to corresponding author.

Declarations
Ethics approval and consent to participate
Protocols were approved by the Alfred Health Ethics Committee (approval no. 39/11). All participants provided written informed consent.

Consent for publication
Not applicable.

Competing interests
No relevant conflicts of interest to disclose.

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Received: 25 March 2021 Accepted: 5 October 2021
Published online: 04 December 2021

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3.3 Summary and implications of the findings

This manuscript in section 3.2 has reported on the extent to which inter-related behaviours conducted during the average 24hr period are associated with glucose outcomes. A novel approach was the application of this analytical method with stratification by level of diabetes risk. By categorising participants according to risk status and using interaction terms with compositional data analysis (CoDA), the influence of present metabolic impairment status on the relationships could be determined, the findings suggest that those at higher risk of developing diabetes may differ from healthier participants when exposed to sedentary behaviour interventions.

This manuscript determined that 24hr compositions, composed of sitting, standing, stepping, and sleeping were associated with fasting and 2h plasma glucose levels. There were only minor differences seen in those at higher risk for diabetes compared to those at lower risk. These were mainly between standing and sitting, and sitting and sleeping, for fasting plasma glucose levels. These findings may indicate that only in those at higher risk are fasting glucose levels likely to be influenced by replacing sitting with standing behaviours, whereas in people with lower risk of diabetes, these metabolic factors may be less likely to be improved by sedentary behaviour interventions.

Increasing stepping time and decreasing sitting time was associated with the greatest differences in 2h plasma glucose and estimated delta glucose. However, the difference of one extra hour of stepping time made relative to the mean did not differ by diabetes risk group. On one hand, this finding generally disagrees with the evidence determined within the Dempsey at al. (186) meta-analysis, which reported that people with impaired metabolic health attained a greater proportional benefit when reducing sitting time as measured by OGTT. On the other hand, it is possible that the sampling employed in this CoDA analysis failed to recruit a sufficient number of participants with significant metabolic disease. Whilst the findings indicate that the risk groups did not differ for 2h glucose in OGTT, in every single relationship, the higher risk group exhibited greater estimated difference in glucose levels following modification to 24hr time. With more extensive sampling methods, more comprehensive metabolic health
measures, and the inclusion of people with type 2 diabetes, the difference by diabetes risk hypothesised in this thesis might have been realised.

A key clinical implication from this study is that, even for those at higher risk of developing diabetes, there is likely potential to improve glycaemic control with modifications of 24hr time spend. These are likely best realised by trading sitting time with stepping time. However, there are also positive implications for trading sitting time with standing time, especially for fasting plasma glucose levels. Diabetes and metabolic diseases are progressive in nature, which might suggest that lifestyle changes may become ineffective as metabolism worsens, however, encouragingly this study supports the potential for lifestyle intervention to be even more efficacious in prevention and management of metabolic diseases.

Determining the therapeutic utility of sedentary behaviour reduction across states of metabolic health (insulin sensitivity, insulin resistance, glycaemia), warrants further investigation. This could be achieved by sampling a more diverse range of metabolic health profiles, including more people with type 2 diabetes, prediabetes, and more people with normoglycaemic metabolism for comparisons. Aspects of these evidence gaps are addressed in the following chapter (Chapter 4), examining data from a study with a large number of participants with type 2 diabetes, for whom device-derived measures of sitting, standing, and stepping are available.
Chapter 4: Potential impacts of sedentary and active time use compositions on metabolic health

4.1 Introduction
The Maastricht Study is the largest observational study to date to employ activPAL thigh worn monitors, allowing for the valid and objective measurement of sedentary behaviour in a free-living setting. In addition, the study aimed to oversample people with type 2 diabetes, therefore increasing the capability to observe the pathophysiological processes associated with the disease; and allow for increased power for comparisons between people with type 2 diabetes and people with impaired fasting, impaired glucose tolerance, and normal glucose metabolism.

Taking the analytical approach with compositional data analysis developed in Chapter 3 and applying it to the sample of Maastricht study participants (n=2,388), 684 of which had type 2 diabetes. Not only would this increase the diversity of the sample, helping to answer previous research hypotheses in Chapter 3, but the enhanced sample size may also lend itself to more in depth epidemiological investigations also with compositional data analyses. In addition to analysing isotemporal one-to-one compositional transformations, this manuscript aimed to understand how the entire time-use composition was associated with cardiometabolic and glycaemic control risk markers. This included evaluating the association of combined modifications to standing and stepping simultaneously, which is increasingly becoming a feature of modern sedentary behaviour interventions that target the reduction of sitting with both standing and ambulatory activity.

Chapter 4 uses compositional data analysis techniques to examine the associations of daily time-use with glycaemic control and related cardiometabolic risk markers and compares these associations between people with normal glucose metabolism, prediabetes, and type 2 diabetes. How sedentary behaviour should be balanced with standing and stepping is investigated, as well as combined associations of standing and stepping in lieu of sitting time-use. The observations are made in a large sample of community-dwelling adults from the
southern regions of the Netherlands. Further summary and implications of the findings are presented in section 4.3.

4.2 Manuscript

This manuscript is in its final stages of author review and sign-off and will be submitted to a scientific journal. Description and extent of contributions are detailed in Appendix A. Supplementary materials referenced in the manuscript are presented in Appendix B.

Citation:
Potential impacts of sedentary and active time use compositions on metabolic health

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Abstract

Background/Objective

The balance of time spent across the day in sitting, standing and stepping can impact markers of metabolic health. However, the time use composition balances associated with benefit are undefined, and it is unclear if these associations may vary by diabetes status.

Research Design and Methods

Using compositional data analysis (CoDA), we examined thigh-worn activPAL data (eight days, continuous wear protocol) from participants aged 40 – 75 years in the Maastricht Study; 1341 who were normoglycaemic (NGM); 363 with prediabetes; and 684 with type 2 diabetes (T2D). Multiple linear regressions examined cross-sectional associations of waking-hours’ time-use (sitting, standing, and stepping) with five cardiometabolic risk markers: waist circumference (WC), fasting (FPG) and 2h plasma glucose (2hPLG), glycated haemoglobin (HbA1c), and Matsuda index (ISI-M); and a clustered cardiometabolic risk (CMR) score. Compositional isometric log-ratio coordinates with generalised additive splines characterized ratios of sitting to standing and sitting to stepping. Isotemporal substitution (+/-30 min) and combined substitutions were used to estimate associations with risk markers and the CMR score. Variation by diabetes status on the compositional associations was investigated.

Results

Lower sitting with higher active time use (both standing or stepping) were beneficially associated with all outcomes, with associations stronger for stepping. Associations varied by diabetes status, with stronger associations observed for those with T2D (WC, FPG, 2hPLG, HbA1c) and prediabetes (WC) compared to the NGM group. Spline models of time-use with CMR depicted a progressively decreasing relationship for stepping/sitting plateauing at 0.55/1 (4.4h stepping per 8h sitting time-use) and for standing/sitting at 0.82/1 (6.6h standing per 8h sitting time-use), with similar relationships observed for the other risk markers.

Conclusions

Daily time use compositions with higher standing and stepping time were associated with more favourable cardiometabolic health and glycaemic control, particularly among those with T2D. Overall, compositions that balanced sitting time with higher stepping and/or standing time were progressively beneficial, with suggestion of a potential plateau of benefit for the reduction of sedentary behaviour within daily time-use composition.
**Introduction**

Guidelines from the American Diabetes Association (1) now include a joint recommendation to increase physical activity and reduce sedentary behaviour (defined as any waking behaviour in a sitting or lying posture below 1.5 metabolic equivalents (2)). These recommendations are supported by observational evidence (3) and the findings of acute experimental studies (4), which have demonstrated that reducing time spent sedentary (e.g., breaking up sitting every 30 minutes with light intensity physical activities (5), alternating standing and sitting every 30 mins (6), or a combination of the two (7)) improves cardiometabolic health. However, when observing free-living populations of adults, it has been shown that these active interruptions to sedentary behaviour are seldom achieved and are even less prevalent in people with diabetes (8). Investigating the balance of different compositions of time-use in physical behaviours (i.e. sitting, standing and stepping) and how they relate to indicators of metabolic health, can further inform interventions to help adults meet health recommendations.

The application of continuous measurement approaches, such as those collected via a thigh-worn inclinometer, when used in conjunction with compositional data analysis (CoDA), facilitates the investigation of free-living sedentary behaviour and its interrelationship with standing and stepping behaviours in a time-use composition. With this approach, it is possible to simulate and model the potential impacts of different daily activity compositions with cardiometabolic risk markers and health outcomes. Although well established in other fields, such as geochemistry (9) and nutrition (10), application of CoDA is relatively new to the physical activity field (11). There has also been very limited application of this methodology in regard to understanding different risk profiles, including in people with, or at risk of, diabetes (12). This is noteworthy as the health risks of sedentary behaviour may be more pronounced in people with T2D (4,13).

To address these evidence gaps, we examined compositions of sitting, standing, and stepping and their associations with cardiometabolic risk and glycaemic control markers. Associations were examined overall, as well as by diabetes status (normoglycaemia, prediabetes, T2D). We hypothesised that compositions with higher sitting time would be adversely associated, and higher standing and stepping time beneficially associated with markers of glycaemic control and cardiometabolic risk; and, that these associations would be stronger in people with type 2 diabetes and prediabetes than in the group with normoglycaemia.
Methods

Study population

Data were obtained from the Maastricht study (14), which is an ongoing observational study of eligible adults aged between 40 and 75 years old living in the Southern Netherlands. The rationale and study methodology have been described previously (14). In brief, recruitment was conducted through mass media campaigns, municipal registries and the regional diabetes patient registry. Participants were recruited and stratified according to diabetes status in an effort to investigate the etiology and pathophysiology of diabetes, with an oversampling of individuals with known T2D status. The current report includes cross-sectional data from 3,451 participants who were recruited between November 2010 and September 2013; all examinations were performed on each participant within 3 months of consent. Exclusions were applied if they had missing data on the following covariates (n=334): sex, age, education category, smoking status, and/or food frequency diet score. Participants who had invalid activPAL activity monitor data (n=100) (see below) or did not wear the device (n=601) were excluded. Participants with type 1 diabetes or “other diabetes” such as latent autoimmune or steroid induced diabetes, or diabetes following pancreatectomy were excluded (n=28) leaving 2,388 participants for the present analyses.

The Maastricht study was approved by the institutional medical ethical committee (NL31329.068.10) and Minister of Health Welfare and Sports of the Netherlands (permit no. 131088-105234-PG). Written informed consent was obtained from all participants. The manuscript was written in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines (15).

Sitting, standing, stepping

Daily behaviours, i.e., sitting, standing and stepping, were measured using the activPAL3™ inclinometer (PAL technologies Limited, Glasgow, UK; version 6.4.1). The device was attached directly to the skin on the front of the right thigh with transparent 3M Tegaderm™ tape and was waterproofed with a nitrile sleeve. Participants were instructed to wear the monitor for eight consecutive days continuously and without removal. To avoid inaccurately identifying non-wear time, participants were asked not to replace the device once removed. Data were uploaded using the activPAL software and processed using customised software written in MATLAB R2018b (MathWorks, Natick, USA). An automated algorithm was used to determine waking time and has been described elsewhere (16). The first measured wear day was excluded from analyses, because it coincided with the clinical assessment, which involved a physical function battery and was therefore not a true representation of typical day behaviours. Data from the final wear day, containing ≤14 hours, were also excluded for each
participant. Data were included for analyses if there was at least one valid wear day which constituted ≥10h of waking time for any given day. The total amount of time spent sitting, standing, and stepping was recorded and divided by the number of valid wear days to derive average daily totals.

Cardiometabolic risk-marker outcomes

Outcomes were waist circumference, fasting glucose, 2h post-load glucose, HbA1c, the Matsuda index and a clustered cardiometabolic risk score. Waist circumference was measured manually with a tape measure at the midway between the lower rib margin and the peak of the iliac crest to the nearest 0.5cm. Fasting samples were assessed using standard enzymatic hexokinase reference method for plasma glucose. Glycosylated haemoglobin (HbA1c) was measured with ion-exchange high performance liquid chromatography. All included participants underwent a standardised 2h oral glucose tolerance test (OGTT), as described previously (14), where blood draws subsequent to fasting were collected at 15, 30, 45, 60, 60, 90, and 120 minutes. Two-hour postload glucose (2hPLG) was informed by the OGTT and all seven time-points of glucose and insulin concentrations informed the calculation of the Matsuda index (17). Matsuda Index (ISI-M) was calculated using fasting and mean glucose and insulin values as: ISI-M=10,000/(Glucosefast × Insulinfast × Glucosemean × Insulinmean)½. The clustered cardiometabolic risk score (CMR) was calculated using five cardiometabolic markers including waist circumference, fasting plasma glucose, triacylglycerol, HDL-cholesterol, and average blood pressure as per previously devised methods (18,19). Fasting blood samples were used for the laboratory assessment of HDL cholesterol and Triacylglycerol. Average systolic and diastolic blood pressure was calculated from three office measurements of the right arm after a 10-min rest period using non-invasive blood pressure monitor (OMROW 705IT; OMRON, Kyoto, Japan). The average blood pressure outcome was calculated by adding the systolic and diastolic measures together and dividing the value by two. Triacylglycerol, HDL-cholesterol, and fasting plasma glucose were log-transformed. All variables were then standardised according to the mean (z = (value – mean) / SD). The risk score was then calculated by summing all the scores (with HDL added in inverse) and dividing the sum by five. Higher CMR is relative to the sample mean and is indicative of higher cardiometabolic disease risk (18).

Covariates

Covariates for confounder adjustment were extracted from questionnaires administered during the baseline assessment. Covariates were selected a priori and evaluated using a directed acyclic graph (DAG) for inclusion into the statistical models. Included covariates were sex, age, education (low, medium, high), smoking history
Regression, and variables which, FPG between 6.1 and -ero. ent only sex estithesize significantly uidel rence mean sleep time tti effect ser greater adheodo on t. FPG <7.0 mm L
modellin steppi hours (R behaviog, standing de walki.
All analyses were impred fasting glucose (FPG <7.0 mmol/l and 2hPLG between ≥7.8 and <11.1 mmol/l) and/or impaired fasting glucose (FPG between 6.1 and 6.9 mmol/l and 2hPLG <7.8 mmol/l)), and T2D was defined where fasting plasma glucose ≥7.0 mmol/l and 2h plasma glucose ≥11.1mmol/l. Normal glucose metabolism was defined as below the prediabetes and T2D cut points.

Statistical analyses

All analyses were conducted using R statistical analysis software version 4.0.0. Characteristics of the overall study population were summarized as mean (standard deviation (SD)), and categorical variables as numbers and percentages. Outcome variables were summarized as mean (SD; distribution) or median (non-normal) with inter-quartile range (IQR). Outcome variables that displayed non-normal distribution were transformed using natural logarithm.

Compositional data analysis methodology has been described in detail previously (11). There were no behaviour (sitting, standing or stepping) totals equaling zero. Geometric means were used to describe mean daily time spent in activities for the overall sample using Aitchison’s perturbation method (“ acomp” function in R package Compositions). In the present study, we constrained all behaviours to a heuristic waking period of 16 hours (mean sleep time in sample was 8.27 hours) to specifically investigate combinations of sedentary behaviour with the other activPAL assessed behaviours undertaken during waking hours - standing and stepping. To investigate time-use and the associations with the chosen outcome variables, linear regression modelling of isometric log ratios (ilr) was performed. In brief, the outcome is dependent on the sum of
composition isometric log ratios and covariates through a regression model. Within this model, isometric log ratios map the compositional data into real space. For a three-part composition, ilr1 and ilr2 are the coordinates of the ilr-transformed composition. To test the association of increasing sitting relative to remaining behaviours: standing and stepping we ordered the equation such that the $\beta_1$ coefficient reflects the effect of time sitting relative to the other two behaviours. Therefore, ilr1 is equal to:

(1) ilr1: $$(\text{sitting vs. standing, stepping}) = \sqrt{(2/3)ln(sitting / \sqrt{stand * step})}$$

To consider the relationship of the individual behaviours in relation to one another, we used the second coefficient $\beta_2$. In this case, ilr2 considers increasing stepping time relative to standing time:

(2) ilr2: $$(\text{stepping vs. standing}) = \sqrt{(1/2)ln(stepping/standing)}$$

The regression model can be reordered as per the permutation principle (11) and give the same fit regardless of order. The ilr2 coordinates for standing vs. sitting and stepping vs. sitting were investigated for curvilinear properties using a generalised additive linear spline. Splines for $z^2$ were compared to their linear models using AIC criterion. Inflection points in the splines were determined from derivative calculation, where derivative 95% confidence intervals intercepted zero. The isometric log ratio models were used to perform isotemporal substitution methods (with R package: deltaxcomp (23)) whereby 30 minutes in one behaviour was substituted for 30 minutes in another. This method which has been explained in detail elsewhere (24), produces an estimated difference in the risk marker value from the outcome value at the geometric mean.

To visualise the associations of manipulating multiple behaviours in the composition, an equally spaced dataset was produced to predict the outcome based on a complete range of compositions based on the original sample (with open-source code available on opencoda.net). The dataset was visualised with heatmap graphs. Each point on the heatmap indicates a quantity of time spent in standing (x-axis), stepping (y-axis), and sitting (the remaining time; i.e. 16hr – [standing time + stepping time]). For example, when standing and stepping are equal to zero, sitting time consequently represents 16hrs (100%) of waking behaviours. For each heatmap, the estimated outcome value when increasing stepping time by 30 minutes and decreasing sitting time by 30 minutes was depicted as ‘Direction A’. ‘Direction B’ depicted how much standing time was required for the same outcome. Direction A and B magnitudes were then halved to generate ‘Direction C’, representative of combined higher standing and stepping time with concurrent lower sitting time.
Results

Sample

Table 1 shows the characteristics of participants with stratification by diabetes status. A total of 2,388 adults were examined. Overall, the sample was: predominantly male; former smokers; and, had higher education levels. Cardiometabolic risk markers and CMR worsened sequentially from the normoglycaemic group to prediabetes, to T2D. Four out of five participants with T2D used glucose-lowering medication. The geometric mean proportions of 16-hour time use indicate that sitting time occupied the greatest proportion of the day across all strata. The prediabetes and T2D groups had higher sitting levels, and lower standing and stepping levels compared to the normoglycaemia group.
Table 1. Sample characteristics of participants stratified by diabetes status.

<table>
<thead>
<tr>
<th>Category</th>
<th>Overall</th>
<th>NGM</th>
<th>Prediabetes</th>
<th>T2D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sample number (n)</td>
<td>2,388</td>
<td>1,341</td>
<td>363</td>
<td>684</td>
</tr>
<tr>
<td>Age (mean (SD))</td>
<td>60.1 (8.1)</td>
<td>58.2 (8.1)</td>
<td>62.1 (7.2)</td>
<td>62.7 (7.7)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>Male</td>
<td>1224 (51.3)</td>
<td>548 (40.9)</td>
<td>196 (54.0)</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>1164 (48.7)</td>
<td>793 (59.1)</td>
<td>167 (46.0)</td>
</tr>
<tr>
<td>Education, n (%)</td>
<td>Low</td>
<td>802 (33.6)</td>
<td>359 (26.8)</td>
<td>133 (36.6)</td>
</tr>
<tr>
<td></td>
<td>Medium</td>
<td>671 (28.1)</td>
<td>381 (28.4)</td>
<td>96 (26.4)</td>
</tr>
<tr>
<td></td>
<td>High</td>
<td>915 (38.3)</td>
<td>601 (44.8)</td>
<td>134 (36.9)</td>
</tr>
<tr>
<td>Smoking history, n (%)</td>
<td>Never</td>
<td>847 (35.5)</td>
<td>539 (40.2)</td>
<td>105 (28.9)</td>
</tr>
<tr>
<td></td>
<td>Former</td>
<td>1241 (52.0)</td>
<td>643 (47.9)</td>
<td>219 (60.3)</td>
</tr>
<tr>
<td></td>
<td>Current</td>
<td>300 (12.6)</td>
<td>159 (11.9)</td>
<td>39 (10.7)</td>
</tr>
<tr>
<td>Glucose-lowering med., n (%)</td>
<td>Yes</td>
<td>545 (22.8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Diet score (mean (SD))</td>
<td>83.77 (14.71)</td>
<td>85.66 (14.41)</td>
<td>82.91 (14.92)</td>
<td>80.53 (14.60)</td>
</tr>
<tr>
<td>WC (cm) (mean (SD))</td>
<td>94.75 [86.00, 104.00]</td>
<td>89.30 [82.25, 97.25]</td>
<td>97.75 [90.17, 105.00]</td>
<td>104.67 [96.50, 114.03]</td>
</tr>
<tr>
<td>FPG (mmol/L) (median [IQR])</td>
<td>5.50 [5.10, 6.60]</td>
<td>5.10 [4.90, 5.50]</td>
<td>6.00 [5.50, 6.30]</td>
<td>7.60 [6.80, 8.60]</td>
</tr>
<tr>
<td>HbA1c (mmol/L) (median [IQR])</td>
<td>38.00 [35.00, 44.00]</td>
<td>36.00 [34.00, 38.00]</td>
<td>38.00 [35.00, 42.00]</td>
<td>50.00 [45.00, 56.00]</td>
</tr>
<tr>
<td>CMR (median IQR)</td>
<td>-0.05 [-0.52, 0.48]</td>
<td>-0.37 [-0.76, -0.02]</td>
<td>0.14 [-0.23, 0.46]</td>
<td>0.67 [0.31, 1.03]</td>
</tr>
<tr>
<td>Geometric means, h/16h (%)</td>
<td>Sitting</td>
<td>9.7 (60.8%)</td>
<td>9.3 (58.3%)</td>
<td>9.7 (60.6%)</td>
</tr>
<tr>
<td></td>
<td>Standing</td>
<td>4.3 (27.0%)</td>
<td>4.6 (28.5%)</td>
<td>4.3 (27.0%)</td>
</tr>
<tr>
<td></td>
<td>Stepping</td>
<td>2.0 (12.2%)</td>
<td>2.1 (13.3%)</td>
<td>2.0 (12.4%)</td>
</tr>
</tbody>
</table>

For outcome measures, mean (SD range) was used for normally distributed measures, or median (IQR range) for non-normally distributed measures
Abbreviations: WC = waist circumference; FPG = fasting plasma glucose; 2hPLG = 2h plasma glucose; HbA1c = glycated haemoglobin; CMR = clustered cardiometabolic risk score
Geometric means refers to average time spent in the composition behaviours during waking time. These composition proportions are standardised to 16 hours for improved interpretation.
**Compositional associations with cardiometabolic risk markers**

All cardiometabolic risk markers were associated with the time-use composition ilrs (model p-values <0.001). Associations of time spent sitting in the composition with independent variables are presented in Table 2. Sitting vs. other behaviours (ilr1) tested the association of sitting time relative to time spent in standing and stepping. Standing vs. sitting (ilr2) tests the association of standing time relative to time spent sitting. As the coefficients correspond to the linear relationship of the logarithmically transformed ratios (ilr1 and ilr2 parameters) with glycaemic control and cardiometabolic risk markers they lack direct interpretation.

For the overall sample, sitting time was consistently associated with adverse cardiometabolic health and for time spent stepping was superior to time spent standing in its beneficial associations. Adjustment by waist circumference resulted in the attenuation of all effect estimates, though they remained statistically significant for FPG and 2hPLG outcomes. Each model was tested for interaction by sex (Supplementary 1 – complete linear regression table) with only the model for HbA1c being statistically significant, suggesting that the adverse association of sitting in lieu of stepping time was attenuated in female participants. Effect sizes were additionally compared between diabetes status groups using interaction terms, with and without adjustment for waist circumference (Supplementary 1 – complete linear regression table). A statistically significant coefficient for diabetes status interaction indicated that the effect size was significantly different by diabetes status. For waist circumference, the association of stepping relative to sitting and standing had statistically significant interaction terms, indicating more pronounced associations in prediabetes and T2D groups. Fasting plasma glucose, HbA1c, and their association with sitting and stepping also had a statistically significant interaction term with T2D only. The relationship of sitting and standing time with CMR significantly differed when comparing only the prediabetes group with NGM, with less pronounced effect sizes in those with prediabetes than the other groups. Associations were not significantly different according to diabetes status for 2h post-load glucose and Matsuda index. Adjustment by waist circumference had very minor influences on interaction by diabetes status.
Table 2. Associations of time-use composition with glycaemic control and cardiometabolic risk markers

<table>
<thead>
<tr>
<th></th>
<th>Sitting vs Other Behaviours$^a$</th>
<th>Stand vs. Sit$^b$</th>
<th>Step vs Sit$^b$</th>
<th>Step vs Stand$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\beta$ [95% CI]$^c$</td>
<td>$\beta$ [95% CI]$^c$</td>
<td>$\beta$ [95% CI]$^c$</td>
<td>$\beta$ [95% CI]$^c$</td>
</tr>
<tr>
<td>WC, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>0.41 [-2.99, 3.8]</td>
<td>3.59 [-0.25, 7.44]</td>
<td>-4.29 [-8.05, -0.54]</td>
<td>-7.89 [-12.7, -3.07]</td>
</tr>
<tr>
<td>Model 1 #T2D</td>
<td>1.79 [-0.75, 4.34]</td>
<td>0.6 [-2.36, 3.56]</td>
<td>-3.71 [-6.4, -1.02]</td>
<td>-4.32 [-7.86, -0.77]</td>
</tr>
<tr>
<td>FPG, mmol/L$^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.12 [0.1, 0.15]</td>
<td>-0.08 [-0.1, -0.05]</td>
<td>-0.14 [-0.16, -0.11]</td>
<td>-0.06 [-0.09, -0.03]</td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>-0.02 [-0.06, 0.03]</td>
<td>0.01 [-0.04, 0.06]</td>
<td>0.02 [-0.03, 0.07]</td>
<td>0.01 [-0.05, 0.07]</td>
</tr>
<tr>
<td>Model 1 #T2D</td>
<td>0.05 [0.02, 0.08]</td>
<td>-0.02 [-0.06, 0.02]</td>
<td>-0.07 [-0.1, -0.03]</td>
<td>-0.05 [-0.1, 0]</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.06 [0.03, 0.08]</td>
<td>-0.03 [-0.06, -0.01]</td>
<td>-0.07 [-0.09, -0.04]</td>
<td>-0.03 [-0.06, 0]</td>
</tr>
<tr>
<td>2hPLG, mmol/L$^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.27 [0.21, 0.32]</td>
<td>-0.17 [-0.23, -0.11]</td>
<td>-0.29 [-0.35, -0.24]</td>
<td>-0.13 [-0.2, -0.05]</td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>-0.03 [-0.1, 0.05]</td>
<td>0.07 [-0.02, 0.17]</td>
<td>-0.02 [-0.1, 0.07]</td>
<td>-0.09 [-0.2, 0.02]</td>
</tr>
<tr>
<td>Model 1 #T2D</td>
<td>-0.02 [-0.09, 0.05]</td>
<td>0.04 [-0.03, 0.12]</td>
<td>-0.01 [-0.08, 0.06]</td>
<td>-0.06 [-0.15, 0.04]</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.15 [0.1, 0.2]</td>
<td>-0.09 [-0.15, -0.03]</td>
<td>-0.17 [-0.22, -0.12]</td>
<td>-0.08 [-0.15, -0.01]</td>
</tr>
<tr>
<td>HbA1c, mmol/L$^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.11 [0.08, 0.13]</td>
<td>-0.05 [-0.08, -0.02]</td>
<td>-0.13 [-0.16, -0.11]</td>
<td>-0.08 [-0.11, -0.05]</td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>0.00 [-0.04, 0.05]</td>
<td>0.00 [-0.05, 0.05]</td>
<td>0.00 [-0.05, 0.05]</td>
<td>0.00 [-0.06, 0.07]</td>
</tr>
<tr>
<td>Model 1 #T2D</td>
<td>0.06 [0.03, 0.09]</td>
<td>0.00 [-0.04, 0.04]</td>
<td>-0.11 [-0.14, -0.07]</td>
<td>-0.11 [-0.15, -0.06]</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.05 [0.03, 0.07]</td>
<td>-0.01 [-0.03, 0.01]</td>
<td>-0.07 [-0.09, -0.05]</td>
<td>-0.06 [-0.09, -0.03]</td>
</tr>
<tr>
<td>ISI-M$^c$</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>-0.34 [-0.46, -0.23]</td>
<td>0.16 [0.03, 0.29]</td>
<td>0.44 [0.32, 0.55]</td>
<td>0.28 [0.13, 0.43]</td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>-0.08 [-0.37, 0.21]</td>
<td>0 [-0.33, 0.32]</td>
<td>0.14 [-0.17, 0.46]</td>
<td>0.15 [-0.26, 0.56]</td>
</tr>
<tr>
<td>Model 1 #T2D</td>
<td>0.01 [-0.23, 0.25]</td>
<td>-0.1 [-0.37, 0.18]</td>
<td>0.07 [-0.18, 0.32]</td>
<td>0.17 [-0.15, 0.49]</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.07 [-0.18, 0.04]</td>
<td>-0.03 [-0.14, 0.09]</td>
<td>0.15 [0.04, 0.26]</td>
<td>0.17 [0.03, 0.31]</td>
</tr>
<tr>
<td>CMR, sd</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.49 [0.43, 0.56]</td>
<td>-0.31 [-0.39, -0.24]</td>
<td>-0.54 [-0.61, -0.47]</td>
<td>-0.23 [-0.32, -0.14]</td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>-0.12 [-0.28, 0.03]</td>
<td>0.21 [0.03, 0.38]</td>
<td>0.00 [-0.17, 0.18]</td>
<td>-0.20 [-0.42, 0.02]</td>
</tr>
<tr>
<td>Model 1 #T2D</td>
<td>-0.03 [-0.14, 0.09]</td>
<td>0.04 [-0.09, 0.18]</td>
<td>0.01 [-0.11, 0.13]</td>
<td>-0.03 [-0.2, 0.13]</td>
</tr>
</tbody>
</table>

FPG = Fasting plasma glucose; 2hPLG = 2h glucose measure in oral glucose tolerance test; HbA1c = glycated haemoglobin; ISI-M = Matsuda Index described in methods; CMR = clustered cardiometabolic risk score.

$^a$ Coefficient for ilr1 parameter, representative of higher levels of sitting time and lower levels of remaining behaviours

$^b$ Coefficient for ilr2 parameter, representative of higher levels of time spent in first behaviour, and lower levels of time spent in the second behaviour

$^c$ Outcomes transformed with natural logarithm

Model 1 = adjusted for age, sex, education, smoking status, and dietary intake score.

Model 2 = Model 1 + adjusted for waist circumference, except the waist circumference outcome itself and CMR which were comprised of waist circumference.

Interaction terms indicated by ‘#’ diabetes status (Prediabetes, T2D) added to test their independent moderation on the coefficient estimates.

Associations statistically significant (p<0.05) are labelled in bold.

**Compositional isotemporal substitution modeling**

Table 3 depicts the estimated difference from the mean for risk markers when modifying time spent in one
behaviour with the other behaviour. Consider the mean sample composition, behaviours in the numerator have their composition quantity increased by 30 minutes, and behaviours in the denominator have a concurrent decrease. The associated difference in estimated risk marker between the new composition and the mean composition is depicted in the overall sample as well as by diabetes status. Overall, higher stepping levels with lower proportional levels of sitting or standing was beneficially associated with all risk markers. Increasing stepping time, in lieu of sitting time, was associated with more favourable associations with risk markers. Higher standing time with lower levels of sitting time was significantly beneficially associated with waist circumference, FPG, 2hPLG, and CMR only. In the stratified analysis, standing was not significantly associated with any risk marker in the prediabetes group. The estimated difference in risk markers were most pronounced in the T2D group, especially when compared to the normoglycaemic group, for waist circumference, FPG, 2hPLG, and HbA1c markers.

**Table 3. Estimating the difference incurred to glycaemic control and cardiometabolic risk markers with isotemporal substitution of behaviour time-use**

<table>
<thead>
<tr>
<th>Compositional isotemporal substitution + 30 mins / -30 mins</th>
<th>Overall (n=2388)</th>
<th>NGM (n=1341)</th>
<th>Prediabetes (n=363)</th>
<th>T2D (n=684)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WC, cm + stand / - sita Δ [95%CI]b</td>
<td>-0.38 [-0.51, -0.26]</td>
<td>-0.33 [-0.47, -0.19]</td>
<td>0.00 [-0.32, 0.32]</td>
<td>-0.34 [-0.59, -0.09]</td>
</tr>
<tr>
<td>+ step / - sita Δ [95%CI]b</td>
<td>-1.39 [-1.61, -1.17]</td>
<td>-0.70 [-0.95, -0.46]</td>
<td>-1.31 [-1.89, -0.73]</td>
<td>-1.37 [-1.83, -0.92]</td>
</tr>
<tr>
<td>+ step / - standa Δ [95%CI]b</td>
<td>-1.00 [-1.30, -0.71]</td>
<td>-0.37 [-0.69, -0.04]</td>
<td>-1.32 [-2.1, -0.55]</td>
<td>-1.03 [-1.65, -0.4]</td>
</tr>
<tr>
<td>FPG, mmol/Lc + stand / - sita Δ [95%CI]b</td>
<td>-0.03 [-0.04, -0.01]</td>
<td>-0.01 [-0.01, 0.00]</td>
<td>0.00 [-0.02, 0.02]</td>
<td>0.00 [-0.04, 0.03]</td>
</tr>
<tr>
<td>+ step / - sita Δ [95%CI]b</td>
<td>-0.11 [-0.14, -0.09]</td>
<td>0.00 [-0.01, 0.01]</td>
<td>0.02 [-0.01, 0.05]</td>
<td>-0.11 [-0.17, -0.04]</td>
</tr>
<tr>
<td>+ step / - standa Δ [95%CI]b</td>
<td>-0.09 [-0.12, -0.05]</td>
<td>0.01 [-0.01, 0.02]</td>
<td>0.03 [-0.02, 0.07]</td>
<td>-0.10 [-0.19, -0.01]</td>
</tr>
<tr>
<td>2hPLG, mmol/Lc + stand / - sita Δ [95%CI]b</td>
<td>-0.06 [-0.10, -0.03]</td>
<td>-0.02 [-0.04, 0.00]</td>
<td>-0.01 [-0.06, 0.04]</td>
<td>0.03 [-0.07, 0.13]</td>
</tr>
<tr>
<td>+ step / - sita Δ [95%CI]b</td>
<td>-0.26 [-0.32, -0.20]</td>
<td>-0.04 [-0.07, -0.01]</td>
<td>-0.11 [-0.20, -0.01]</td>
<td>-0.20 [-0.38, -0.03]</td>
</tr>
<tr>
<td>+ step / - standa Δ [95%CI]b</td>
<td>-0.20 [-0.28, -0.12]</td>
<td>-0.02 [-0.06, 0.02]</td>
<td>-0.10 [-0.22, 0.03]</td>
<td>-0.24 [-0.48, 0.00]</td>
</tr>
<tr>
<td>HbA1c, mmol/Lc + stand / - sita Δ [95%CI]b</td>
<td>-0.07 [-0.16, 0.01]</td>
<td>0.01 [-0.05, 0.06]</td>
<td>-0.01 [-0.14, 0.12]</td>
<td>0.19 [-0.02, 0.39]</td>
</tr>
<tr>
<td>+ step / - sita Δ [95%CI]b</td>
<td>-0.78 [-0.92, -0.63]</td>
<td>0.02 [-0.08, 0.12]</td>
<td>0.06 [-0.18, 0.30]</td>
<td>-1.07 [-1.43, -0.71]</td>
</tr>
<tr>
<td>+ step / - standa Δ [95%CI]b</td>
<td>-0.71 [-0.91, -0.5]</td>
<td>0.01 [-0.12, 0.14]</td>
<td>0.07 [-0.25, 0.40]</td>
<td>-1.27 [-1.77, -0.77]</td>
</tr>
<tr>
<td>ISI-M, indexc + stand / - sita Δ [95%CI]b</td>
<td>0.01 [-0.01, 0.04]</td>
<td>0.01 [-0.04, 0.06]</td>
<td>0.01 [-0.05, 0.07]</td>
<td>-0.01 [-0.04, 0.03]</td>
</tr>
<tr>
<td>+ step / - sita Δ [95%CI]b</td>
<td>0.17 [0.12, 0.22]</td>
<td>0.15 [0.05, 0.24]</td>
<td>0.14 [0.02, 0.26]</td>
<td>0.11 [0.05, 0.18]</td>
</tr>
<tr>
<td>+ step / - standa Δ [95%CI]b</td>
<td>0.15 [0.08, 0.22]</td>
<td>0.14 [0.02, 0.26]</td>
<td>0.13 [-0.02, 0.30]</td>
<td>0.12 [0.03, 0.21]</td>
</tr>
<tr>
<td>CMR, SD + stand / - sita Δ [95%CI]b</td>
<td>-0.02 [-0.02, -0.01]</td>
<td>-0.01 [-0.02, -0.01]</td>
<td>0.00 [-0.01, 0.01]</td>
<td>-0.01 [-0.02, -0.00]</td>
</tr>
<tr>
<td>+ step / - sita Δ [95%CI]b</td>
<td>-0.07 [-0.08, -0.06]</td>
<td>-0.04 [-0.05, -0.03]</td>
<td>-0.05 [-0.07, -0.02]</td>
<td>-0.05 [-0.07, -0.03]</td>
</tr>
</tbody>
</table>
Alternatives to sitting visualised in heatmap composition and stratified by diabetes status

As a visual example and support to the isotemporal substitution modelling in Table 3, the relationship of CMR with the daily composition, as composed of three components: sitting, standing and stepping is illustrated for the overall sample in Figure 2, and separately for NGM, prediabetes, and T2D in Supplementary Material 3. These heatmaps depict the joint associations of displacing sitting time with varying quantities of standing and stepping. Any time not spent in standing or stepping necessarily is spent sitting as a feature of the constrained simplex (preserving the constrained 16 hour waking time). In the overall sample for CMR, time spent standing or stepping in lieu of sitting time are beneficially associated. The heatmaps also suggest that varying combinations of both standing and stepping levels are beneficial (Direction C as example), dependent on the risk marker investigated. For instance, compositions with higher standing (+0.75 hours) and stepping time (+0.25 hours) are associated with similar estimated associations in CMR as +0.5 hours of stepping time. For other risk markers such as HbA1c, +1.75 hours of standing with +0.25 hours of stepping are required for similar differences in HbA1c as +0.5 hours of stepping time.
Figure 1 - Combined proportions of standing and stepping relative to sitting and associations with clustered cardiometabolic risk score

Heatmap compositions of waking day as composed of standing and stepping time. Remaining proportion of day made up of sitting time (not illustrated), therefore where stepping time = 0; and standing time = 0; sitting time = 16hrs.
Mean Composition Reference denotes the sample’s mean composition across the three components as per Table 1 geometric means for the overall sample.
Red space corresponds to adverse associations of CMR (difference from the mean), and blue space corresponds to beneficial associations of CMR.
Direction A) denotes 30mins higher stepping time from the mean composition reference.
Direction B) denotes higher standing time from the mean composition reference that is associated with similar levels of associated risk marker.
Direction C) denotes a equidistant combination of A and B, a combination of higher standing and stepping time from the mean composition.
Combined associations for all risk markers are available in Supplementary Material 3.

*Isometric log ratios described using spline modeling*

The ilr coordinates for z2, standing vs. sitting, and stepping vs. sitting and their association with risk markers
are visualized as generalised additive splines in Figure 1 for the overall sample. The cardiometabolic risk markers were normalised to distance from sample mean for comparison. Risk markers are depicted with their real values across z2s (and including confidence intervals) in Supplementary Material 2. The splines depict similar relationships to that observed in the linear regression estimates with some nuances. Time spent stepping, relative to sitting, had stronger associations with the risk markers than time spent standing relative to sitting. Greater time spent standing was required to achieve similar associations to that of stepping time and this was consistent across all risk markers and CMR scoring. In the overall estimates, CMR and the risk markers exhibited curvilinear relationships. For the clustered cardiometabolic risk score, the curvilinear trend indicated progressively decreasing CMR estimations, reaching a point of diminishing returns once sufficient displacement of sitting time had occurred. For the standing vs. sitting relationship, derivative estimations suggests that this occurred at stand : sit (z2) = 0.823, and for step : sit (z2) = 0.553. Similar curvilinear trends exist for each individual risk marker, with the displacement of sitting time with standing requiring greater quantity of time than the displacement of sitting time with stepping.

The generalised additive splines were also stratified according to diabetes status (Supplementary Material 2). These should be interpreted with caution given a smaller sample size when stratifying, where the precision may be reduced and thus the interpretability of the relationships. However, the findings are generally consistent with the linear regression estimates in Table 2. Stronger effect estimates were observed for the glycaemic outcomes in the T2D group only, with very weak and non-significant associations of fasting plasma glucose, 2h Plasma Glucose, and HbA1c in the prediabetes or NGM group. Both prediabetes and T2D groups had stronger associations of waist circumference with stepping vs. sitting compared to NGM.
Figure 2 – Curvilinear relationships of isometric log ratios with glycaemic control and cardiometabolic risk markers

<table>
<thead>
<tr>
<th>Standing: sitting z2 and CMR</th>
<th>Standing: sitting z2 and risk markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image of standing and sitting CMR analysis" /></td>
<td><img src="image2.png" alt="Image of standing and sitting risk marker analysis" /></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stepping: sitting z2 and CMR</th>
<th>Stepping: sitting z2 and risk markers</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image3.png" alt="Image of stepping and sitting CMR analysis" /></td>
<td><img src="image4.png" alt="Image of stepping and sitting risk marker analysis" /></td>
</tr>
</tbody>
</table>

Relationships of ilr coordinates z2 with CMR depicting 95% confidence intervals. Spline inflection point depicted by red dot.

Inflection points (red dot) occurred at stand: sit (z2) = 0.823, and step: sit (z2) = 0.553 for CMR.

Confidence intervals are depicted individually per risk marker for WC, FPG, 2hPLG, HbA1c and ISI-M in supplementary material 2.
Discussion

These cross-sectional findings in a large, free-living sample of middle-aged to older adults, showed that time spent in sitting, standing, and stepping and their interrelated associations differed according the respective cardiometabolic risk markers and diabetes status. All three components had stronger associations with risk markers in the prediabetes and T2D group, suggesting that people with impaired metabolism may see a greater proportional benefit to their disease risk with reduced sedentary behaviour. Whilst the associations differed according to risk marker (and therefore potential therapeutic benefit), our findings suggest that low stepping time and high sitting time can be compensated with higher standing time, albeit with a greater amount required than for stepping time. For example, as demonstrated in Table 3 and Figure 1, approximately three times as much standing time in a time-use composition appeared necessary to illicit a similar estimated difference in CMR as stepping time. Overall, we found that the ratios of standing and stepping to sitting are potentially curvilinear, suggesting that displacing sitting time is beneficial up to a certain level, at which point there are diminishing returns for cardiometabolic risk mitigation.

Our findings corroborate other observational analyses performed in prediabetes and diabetes populations. Sedentary behaviour is broadly acknowledged as being adversely associated with cardiometabolic health (25,26). Less time spent sedentary and more time in physical activity is associated with improved plasma glucose (27), insulin sensitivity (27–29), insulin, fat percentage, triglycerides and cholesterol (29). These studies largely suggest that moderate to vigorous-intensity physical activity (MVPA) is beneficial for cardiometabolic health, however still acknowledge that reduction of sedentary time through the adoption of regular light physical activity to be an important consideration irrespective of exercise levels (30). Our study extends this knowledge by additionally investigating HbA1c, fasting plasma glucose, ISI-M and CMR which are relevant to diabetes management and prevention. It also considers the role of standing as a distinct alternative (along with stepping) to sitting and analysing combinations of these alternatives to sedentary behaviour in a compositional framework. The compositional findings corroborate previously described joint associations of self-reported TV viewing time and MVPA, subsequently used to inform physical activity guidelines (31).

Similar findings have also been evident in acute experimental and field-based intervention trials. Studies in people with T2D that have acutely substituted sitting time with light activities have reported improvements in glucose iAUC, triglycerides, insulin (32), and increases insulin sensitivity (33), and these benefits may be augmented in people with T2D relative to those without (34). Reducing sitting time through a combination of light activity and standing time has also been demonstrated to have positive effects on insulin sensitivity in post-menopausal women (7). Our study corroborates these findings and suggests that the effect seen in these trials may be translatable to the free-living setting, including to the improvement of longer term measures like
HbA1c. A review of field based sedentary behaviour interventions determined that reductions in sitting (approx. sedentary behaviour reduction range: 0 – 132 minutes) corresponded with modest decreases in waist circumference, improvements to cardiometabolic risk (through systolic blood pressure and HDL cholesterol), and improved insulin sensitivity (35). Across all reviewed trials, there were no changes with fasting glucose and HbA1c, potentially as there were limited studies featuring people with T2D. Given the present findings, changes in these outcomes through reductions in sedentary behaviour may be more attainable in people with impaired glucose metabolism or people with T2D. Alternatively, these trials predominantly reduced sedentary time with standing, with only modest associations observed with glycaemic outcomes (35). Collectively, the evidence suggests that, in addition to replacing sitting with standing time, sedentary behaviour interventions may need to be directed towards incorporating more ambulatory behaviours to facilitate greater benefits in glucose metabolism.

Compositions lower in sitting time and higher in standing time were associated with beneficial CMR levels. Participants with high standing time in their composition had estimations up to -0.4 to -0.6 ΔCMR. These estimated scores have been shown to be associated with considerable reduction in prospective cardiovascular events (36). Notably, stepping of any intensity was included. Additional benefit, especially to glycaemic control, may come with the study of more active behaviours, including those of higher intensity (37). In line with this, it has been suggested that a ‘stair-case’ intervention approach could be considered when attempting to improve daily composition of waking behaviours, starting with reducing sedentary time with standing time, and then substituting in behaviours that are more active (38).

The findings from the present analysis could be used to further inform time-use activity guidelines. Current 24-hr activity guidelines (39) recommend specific quantities of time to be spent in MVPA (150 mins/week), sedentary behaviour (<8 hrs/day), and sleep (7-9 hrs/day), but are less defined in their recommendations on how exactly sedentary behaviour should be balanced across the day. The current findings illustrate a curvilinear relationship, suggesting that compositions lower in sitting time plateau in beneficial association for cardiometabolic disease risk. Similar curvilinear and diminishing returns have been observed with relationships of step count and MVPA with mortality (40,41). Extrapolating the findings to 8h of sitting, up until 4.42 hours of stepping or 6.56 hours of standing were associated with lower risk for cardiometabolic disease before associations plateaued. The findings suggest that sedentary behaviour reduction into standing or stepping may be of greater relative benefit to groups with high volumes of sedentary time. Prospective research should be performed to corroborate our findings, potentially investigating the effect of a range of different daily composition interventions (including different physical activity intensities) and their benefit for cardiometabolic risk and glycaemic control.
A key strength of this study is the use of compositional data analysis in a large sample of people including those with T2D, prediabetes and normoglycaemia for comparison. All analyses were informed by data from a posture sensing activity monitor, able to accurately collect continuous measurements over multiple days. Notably, this is one of few studies (27,42) to consider standing in a composition of time-use. Few studies (27,43) have ascertained the relationship between composition of daily behaviours with an array of risk markers indicative of subsequent disease risk, such as 2h post-load glucose and insulin sensitivity (ISI-M) which are resource intensive to collect. These observational trials have the potential to address novel hypotheses in the absence of more sophisticated prospective studies. However, a number of limitations need to be considered. The analyses are cross-sectional in nature, therefore precluding causal inference about the potential for composition changes to benefit risk markers. Prospective observational and intervention trials are needed to confirm the causal nature of the present findings. The analyses do not consider the intensity of activity, including higher intensities of physical activity (e.g., MVPA). Bout lengths, for example sedentary behaviours accumulated in prolonged bouts or activity accumulated in short bouts, were not considered, which might have unique implications for cardiometabolic health (44–46).

Conclusion

Findings from this cross-sectional study provide some initial observational evidence that could help to inform how much sedentary behaviour may need to be balanced by its alternatives - standing and stepping - in a time-use composition to improve metabolic risk. Higher time use in more upright and active behaviours (standing; stepping) was beneficially associated with cardiometabolic health, up to a certain level. Compositional data analysis methods are uniquely disposed to identify how sitting could be optimally balanced with standing and stepping in a time-use composition and interpret the association with health outcomes with relevance for diabetes management and prevention. Longer-term interventions investigating a range of daily time-use compositions focusing on the reduction of sedentary behaviour are needed to confirm these theoretical findings.

Acknowledgements

Conflict-of-interest statement

No conflicts of interest to declare
Funding

This study was supported by the European Regional Development Fund via OP-Zuid, the Province of Limburg, the Dutch Ministry of Economic Affairs (grant 31O.041), Stichting De Weijerhorst (Maastricht, the Netherlands), the Pearl String Initiative Diabetes (Amsterdam, the Netherlands), the Cardiovascular Center (CVC, Maastricht, the Netherlands), CARIM School for Cardiovascular Diseases (Maastricht, the Netherlands), CAPHRI Care and Public Health Research Institute (Maastricht, the Netherlands), NUTRIM School for Nutrition and Translational Research in Metabolism (Maastricht, the Netherlands), Stichting Annadal (Maastricht, the Netherlands), Health Foundation Limburg (Maastricht, the Netherlands), and by unrestricted grants from Janssen-Cilag BV (Tilburg, the Netherlands), Novo Nordisk Farma BV (Alphen aan den Rijn, the Netherlands), and Sanofi-Aventis Netherlands BV (Gouda, the Netherlands). DD, GH, NO are supported by the NHMRC Fellowships scheme and the Victorian Government’s OIS Program.

Contributions

CB conducted the study analysis and wrote the manuscript. DD, GH, NO, AC, were involved in the conception of the present study’s design, advised on the analyses, and editing of the manuscript. FD was involved in editing of the manuscript. AK, BDG, NCS were involved in original acquisition of the data, provided advice on the design, and provided critical review of the manuscript. SJPME, HHCMS, HB were involved in original acquisition of the data, and provided expert review of the manuscript. All authors read and approved the final manuscript.

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Supplementary Material

Supplementary Material 1. Complete linear regression associations of time-use composition with glycaemic control and cardiometabolic risk markers

Supplementary Material 2. Linear and generalised additive spline modelling and splines stratified by diabetes status

Supplementary Material 3. Combined proportions of standing and stepping and associations with glycaemic control and cardiometabolic risk markers
4.3 Summary and implications of the findings

The manuscript in section 4.2 examines how different compositions of sitting, standing, and stepping are associated with cardiometabolic biomarkers and glycaemic control risk markers. Compositions higher in sitting time were associated with detrimental glycaemic control and related cardiometabolic risk markers. Higher standing and stepping, or the combination of both were associated with beneficial outcomes, with greater time spent in standing required than for stepping for similar associated benefits. Higher stepping time and lower sitting time was associated with more pronounced associations in people with type 2 diabetes, particularly for the glycaemic control measures, corroborating the findings in Chapter 3. The associated benefit of lower sitting and higher standing or stepping in a composition was curvilinear in relationship, also similar to the findings in Chapter 3. In this manuscript, this was explored across the entire composition of time-use, with total sitting time considering in ratio to total standing and stepping time. The coefficients for sitting and standing, and for sitting and stepping, were curvilinear, and had inflection points demonstrating thresholds of decreasing associated benefit. These inflection points suggest an upper limit of associated benefit with the reduction of sedentary behaviour, and a potentially a target for sedentary behaviour interventions.

In future, experimental trials could examine the impact of inducing a composition of time-use that favours sedentary behaviour reduction for an array of upright and ambulatory behaviours. Alternatively, a randomised controlled sedentary behaviour intervention trial that aims to reduce sedentary behaviour via increases to both standing and stepping could corroborate the findings of this manuscript. If sufficiently powered, the study could examine a range of compositions and their distinct effect on cardiometabolic health and glycaemic control.

The methodological approach used in this manuscript could be applied prospectively to examine changes across multiple behaviours that compose daily time-use. The following chapter (Chapter 5) provides an account of the key attributes of such a trial, written by the candidate as a first-author paper.
Chapter 5: Sitting Less and Moving More for Improved Metabolic and Brain Health in Type 2 Diabetes: ‘OPTIMISE Your Health’ Trial Methodology

5.1 Introduction

There is mounting epidemiological and experimental evidence demonstrating that lower sitting time and higher time spent in physical activity improves intra-day glucose levels, and insulin sensitivity in people with type 2 diabetes. However, without longer-term trials that interface with the lifestyle, it is unknown how these controlled or hypothetical findings extend to free-living conditions. Further, it is less understood whether these interventions on sedentary behaviour would improve the clinical management in people with type 2 diabetes and provide sustained glycaemic control. The OPTIMISE Your Health trial aims to address this research gap.

The insights gathered from observational epidemiological work, such as that conducted in Chapter 3, and 4 in this thesis have the capacity to inform the design and delivery of these sedentary behaviour interventions. For instance, findings from Chapter 3 ascertain the hypothetical effect of reducing sitting by 1 hour for OGTT 2hPLG and fasting glucose estimates. Findings from Chapter 4 describe how sedentary behaviour should be ideally displaced by its alternatives, and thus describe beneficial combinations of sitting, standing, and stepping.

For some further context, I have been working on the OPTIMISE trial as a clinical researcher since it began recruiting in 2019, which I have been involved in running the clinical assessments and collecting data, providing behavioural health coaching support to participants in the intervention, and being fundamentally involved in the ongoing development of the trial which has evolved from being a six-month trial to an 18-month trial during my PhD. The observational study findings that I have produced during my candidature have been used to inform participants on the efficacy of reducing sedentary behaviour, and to help me think more conceptually about their time-use within the day during the health-coaching. In addition, the CoDA analytical methods used in Chapters 3 and 4 are very likely to be used in harnessing the results of the trial, especially given that it aims to intervene on multiple behaviours (sit less, and move more), and across multiple contexts.
The third paper of this thesis, presented in here in Chapter 5 section 5.2, describes the methodology and protocol of the OPTIMISE Your Health study. This trial is still ongoing and is currently being conducted in desk working adults with type 2 diabetes in the city of Melbourne, Australia. Further summary and implications of the manuscript are presented in section 5.3.

5.2 Manuscript

This manuscript was published in the peer-reviewed journal BMC Public Health in May 2022. Description and extent of contributions are detailed in Appendix A. Ethics approval to conduct this study was originally attained on the 14th of August 2018. Ethics approval certificates are available for review in Appendix C. Supplementary materials are listed in Appendix D and accessible through https://doi.org/10.1186/s12889-022-13123-x. This manuscript was published and can be reproduced under the terms of Creative Commons Attribution license 4.0

Citation:
Sitting less and moving more for improved metabolic and brain health in type 2 diabetes: ‘OPTIMISE your health’ trial protocol

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Abstract
Background: Clinical practice guidelines recommend that adults with type 2 diabetes (T2D) sit less and move more throughout the day. The 18-month OPTIMISE Your Health Clinical Trial was developed to support desk-based workers with T2D achieve these recommendations. The two-arm protocol consists of an intervention and control arms. The intervention arm receives 6 months health coaching, a sit-stand desktop workstation and an activity tracker, followed by 6 months of text message support, then 6 months maintenance. The control arm receives a delayed modified intervention after 12 months of usual care. This paper describes the methods of a randomised controlled trial (RCT) evaluating the effectiveness and cost-effectiveness of the intervention, compared to a delayed intervention control.

Methods: This is a two-arm RCT being conducted in Melbourne, Australia. Desk-based workers (≥0.8 full-time equivalent) aged 35–65 years, ambulatory, and with T2D and managed glycaemic control (6.5–10.0% HbA1c), are randomised to the multicomponent intervention (target n = 125) or delayed-intervention control (target n = 125) conditions. All intervention participants receive 6 months of tailored health coaching assisting them to ‘sit less’ and ‘move more’ at work and throughout the day, supported by a sit-stand desktop workstation and an activity tracker (Fitbit). Participants receive text message-based extended care for a further 6-months (6–12 months) followed by 6-months of non-contact (12–18 months: maintenance). Delayed intervention occurs at 12–18 months for the control arm. Assessments are undertaken at baseline, 3, 6, 12, 15 and 18-months. Primary outcomes are activPAL-measured sitting time (h/16 h day), glycosylated haemoglobin (HbA1c; %, mmol/mol) and, cognitive function measures (visual learning and new memory; Paired Associates Learning Total Errors [adjusted]). Secondary, exploratory, and process outcomes will also be collected throughout the trial.

Discussion: The OPTIMISE Your Health trial will provide unique insights into the benefits of an intervention aimed at sitting less and moving more in desk-bound office workers with T2D, with outcomes relevant to glycaemic control, and to cardiometabolic and brain health. Findings will contribute new insights to add to the evidence base on initiating and maintaining behaviour change with clinical populations and inform practice in diabetes management.

Trial registration: ANZCTR12618001159246.
Background

Type 2 diabetes (T2D) is a major cause of premature mortality and morbidity due to cardiovascular, renal, ophthalmic and neurological diseases [1]. Adults with T2D have a heightened risk of absenteeism and inability to work, which increases with diabetes duration [2]. For those with T2D, the clustering of chronic conditions, such as cardiovascular disease and dementia, can substantially impact quality of life [3]. Significantly, those with T2D have a 73% increased risk of developing dementia [4]. Diagnosis of T2D is associated with an earlier onset of dementia by an average of 2.5 years, and as such has been identified as a key modifiable risk factor for dementia in later life [5]. Within this context, greater emphasis has been directed to mid-life prevention initiatives in T2D [6]. Optimising glycaemic control is a primary management consideration to reduce and prevent the impact of multiple morbidities [7], including dementia [8].

Participation in regular physical activity is considered a core element for glycaemic control and diabetes management [9]. However, estimates indicate that only one in four adults with T2D achieve the minimum physical activity levels recommended, while one in three with T2D report doing no moderate or vigorous intensity physical activity at all [10]. Furthermore, recent evidence shows that those with T2D can spend some 10 h of their waking hours in sedentary behaviours (sitting, lying or reclining) with low energy expenditure, an amount significantly greater than those without T2D [11]. The detrimental impacts of sedentary behaviour on health are broad [12], including an increased risk of premature mortality [13]. Sedentary time is also associated with poorer glycaemic control in people with T2D [14].

Epidemiological evidence demonstrates that replacing periods of sitting, particularly prolonged sitting time, with stepping is associated with improved glucose and insulin metabolism [15, 16], and lower occurrence of metabolic syndrome [17]. Recent experimental studies in adults with T2D have also shown that interrupting prolonged sitting with frequent short bouts of light-intensity physical activity (e.g., walking, simple resistance or muscle strengthening activities) can lead to substantial reductions in acute post-meal glycaemic responses [18]. In the free-living setting, interrupting sitting time with regular standing or light-intensity activities has resulted in improved 24-h glucose levels compared to engaging in structured exercise alone [19].

To date, controlled intervention trials designed to support adults to reduce their sedentary time have typically targeted the environment (such as through installing sit-stand workstations), the individual (such as through education and prompts), or a combination of both [20]. A recent meta-analysis found that both multicomponent and single-component interventions typically reduced sitting time by 30–60 min per day, predominantly achieved by replacing sitting with standing [21]. Importantly, a dose-response effect has been observed in workplace setting-based interventions, with the higher the exposure to the intervention, the greater the reduction in sitting time, with minimal evidence of either compensation or generalisation outside of the intervention setting [22]. Therefore, initiatives aimed at further reducing time spent sitting and increasing overall physical activity should target behaviours across the whole day, together with consideration of the contexts where the bulk of sitting time occurs (e.g., workplace, domestic).

In addition to understanding such behaviour changes, it is important for intervention trials to evaluate effects of the behaviour change on biological attributes associated with the risks and complications of T2D. The findings of a meta-analysis of interventions targeting sedentary behaviour reductions alone or in combination with increases in physical activity has shown promising, albeit modest, beneficial effects on weight, waist circumference, percent body fat, systolic blood pressure, insulin and HDL levels [23]. However, to date, studies of working age adults have had limited representation of those with clinical conditions such as T2D [23]. Furthermore, there is a paucity of studies intervening for 12 months or more and few have included maintenance evaluations from which to consider sustainability and longer-term effectiveness. As T2D contributes to higher risk for dementia over the lifespan, evaluating maintenance and the potential for long term sustainability of behaviour change is a key consideration.

The OPTIMISE Your Health trial (trial duration – 18 months) is examining the effectiveness of a series of interventions targeting sitting less and moving more across multiple contexts (see footnote). The interventions target behavioural, metabolic and brain health outcomes, and each phase evaluated for cost-effectiveness. The respective interventions are: a 6-month multicomponent intervention; a 6-month extended care intervention; and an abbreviated intervention delivered to delayed intervention controls. This manuscript provides an overview of the OPTIMISE Your Health trial, including the aims,
intervention methods and evaluation protocols and contingency with the COVID-19 pandemic.

FOOTNOTE: The OPTIMISE Your Health trial was originally conceived as a 6-month trial inclusive of an intensive sedentary behaviour reduction intervention. By leveraging the merits of the original grant, and seeking to investigate the longer term implications for dementia risk in people with T2D, a second research grant was awarded to the team which allowed for an expanded protocol with extended care to 12 months as well as assessment of maintenance until 18 months post baseline. Finally, a third research grant was secured to explore an abbreviated intervention: OPTIMISED, to be delivered to delayed intervention control participants at 12–18 months with the aim of informing rapid scale-up. More information is available in electronic supplementary material (Additional file 1).

Aims and hypotheses
The trial aims to determine the effectiveness, for office workers aged 35–65 years with T2D, of a multi-component intervention with extended care (compared to a control condition, on primary and secondary outcomes. Secondary aims are to:

• assess maintenance of outcomes after cessation of study contact (with participants retaining the activity tracker and workstation components only)
• conduct an economic evaluation to determine the cost effectiveness of the intervention and to estimate the broader social and economic benefits of delaying dementia onset; and,
• develop and test (in the delayed intervention control arm) a modified version of the intervention suitable for wider-scale implementation (OPTIMISED; the abbreviated form of the intervention).

It is hypothesised (two-tailed) that:

1) The intervention and control group participants will differ in changes in the primary and secondary outcomes (0–6 months)
2) The intervention and control group participants will differ in changes in the primary and secondary outcomes (0–12 months)
3) Changes in primary and secondary outcomes achieved by completion of the intervention will be maintained at 18 months (i.e., no significant 12–18 month change)
4) The OPTIMISE intervention will be cost-effective (measured against the commonly used Australian benchmark of less than $50,000 per quality-adjusted life year gained)
5) The OPTIMISED intervention will be feasible and acceptable (primary) and result in pre-post change (12–18 months) in behaviour for delayed intervention participants.

Methods/design
The Optimise Your Health trial has been iteratively developed over time following the securing of three successive research grants (see supplementary material: Additional file 1). Each grant relates to separate trial phases and interventions with distinct aims, hypotheses, and outcome measures. Recruitment for the original OPTIMISE protocol commenced in June 2019 with 27 participants recruited and completing the 6 month original iteration. In June 2020, recruitment commenced for the extended 18 month trial, which was inclusive of all phases described above. A SPIRIT checklist for standardized protocol items was followed in writing this manuscript (Additional file 11).

Study design and randomisation
The OPTIMISE Your Health trial is a two-arm individually randomised controlled trial. Randomisation to either the intervention or delayed intervention arm is undertaken in random blocks of sizes 4–8, stratified according to whether participants are taking either 0–1 or 2+ hypoglycaemic medications. Randomisation is automated via REDCap software at the end of the baseline assessment. Due to the nature of the intervention, it is not possible to blind participants or assessors to group assignment.

The trial protocol includes five assessment time-points: baseline, 3- months, 6- months, 12-months, 15- months, and 18- months. Database(s) facilitating intervention management and data collection are undertaken through REDCap — an approved data management platform (version 11.1.25) [24]— with further data stored securely but accessibly to the multidisciplinary multinational research team through The University of Queensland’s Research Data Management System. Ethics approval for both the original and expanded protocols were granted by Alfred Health Human Ethics Committee (Melbourne, Australia), The University of Queensland Institutional Human Research Ethics Committee (Brisbane, Australia), and the University of the Sunshine Coast Human Research Ethics Committee (Sunshine Coast, Australia). The OPTIMISE Your Health trial has been registered with the Australian New Zealand Clinical Trials Registry (ANZCTR12618001159246; date of registration: 07/03/2018 URL: https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375487). The trial is undertaken in accordance with CONSORT guidelines (http://
Study setting / population
Participants are adults aged 35–65 years with clinically diagnosed and managed T2D (recent HbA1c test between 6.5 and 10.0%) who are working \( \geq 0.8 \) full time equivalent (FTE) in predominantly \(( \geq 75\% )\) desk-based work in the local Melbourne area. Participants are excluded based on the following criteria: not English speaking, pregnant, using insulin to treat their diabetes, or have high physical activity (maintained for at least 3 months: \( \geq 30 \) min of moderate-to-vigorous intensity physical activity [MVPA] per day and/or \( \geq 30 \) min of strength training on at least two separate days of the week). Complete details of the eligibility criteria are provided in the electronic
supplementary material (Additional file 3). The trial aims to recruit 125 participants per arm to satisfy sample size requirements. In-person clinical assessments are conducted at the Baker Heart & Diabetes Institute in Melbourne, Australia.

Recruitment sources
Recruitment commenced in June 2019 and is ongoing through to June 2024 using several different recruitment options, including but not limited to:

- Disseminating study promotional material into clinics and hospitals within the local community;
- Online social media advertising performed both independently and by an external third party recruitment company;
- Television and newspaper feature articles;
- Mailing people registered on the National Diabetes Services Scheme (NDSS) database; and,
- Contacting patients attending the adjacent diabetes clinic (in person or by telephone).

Screening and consent
Screening for eligibility and gaining consent involves a multistage process. Initially, potential participants are emailed a link to a brief survey containing questions concerning eligibility. Those whose surveys indicate they may be eligible receive a follow up telephone call from research personnel to confirm. Once confirmed, participants are sent further participation information (Additional file 2), and an employer permission form via email to forward to their employer, which is completed online. This employer permission form explains the relevant study requirements and informed consent for the study and permission for installation and use of a sit-stand workstation in the workplace. Participants are requested to send a photo of their current workstation setup to assist in desk installation. If a participant is self-employed or working from home they can sign the form themselves. Thereafter, participants are asked for results of any HbA1c blood test they have had in the last 4 weeks, or are provided with a pathology request slip and asked to arrange a non-fasting blood test (glycosylated haemoglobin; HbA1c%) at their nearest Melbourne Pathology centre (at no cost to the participant). Those within the eligible HbA1c% range (6.5–10.0%) are then requested to give final informed consent (written or electronic; Additional file 2) and have their baseline visit scheduled.

Impact of the COVID-19 pandemic on the trial
Intensive lockdown restrictions occurred in March 2020 leading to the suspension of recruitment. All participants enrolled in the trial during these periods were assessed according to remote COVID-safe practices. In October 2020 the lockdown restrictions ended and resumption of recruitment and the expanded protocol began.

Intervention

Background
The OPTIMISE intervention is based on the Stand Up Australia workplace intervention [25, 26]. However, it has been extended from a primarily workplace focus to include messaging targeting sitting less and moving more across the whole day. The intervention is grounded in social cognitive theory, with the key constructs targeted being: self-efficacy; socio-structural factors (barriers and facilitators); and outcome expectancies (physical, social and self-evaluative) [27]. Consistent with the socio-ecological model of sedentary behaviour [28], which highlights the multiple inter-related influences on this behaviour; the intervention targets multiple levels of influence on behaviour (environment, intra-personal, inter-personal). In contrast to the Stand Up Australia intervention [25], the OPTIMISE intervention does not specifically include workplace organisational strategies. The intervention components are informed by the Behaviour Change Wheel (BCW) and the associated COM-B system, within which capability, opportunity and motivation are postulated as interacting to stimulate behaviour change [29]. Previous feedback collected in the Stand Up Australia intervention [30] has demonstrated appropriate participant acceptance and feasibility of the key components including adaptations to the physical work environment, and the support of individual behaviour change.

Intervention targets
The key intervention messages are to “Sit Less” and “Move More”. The aim of the intervention is to support participants to achieve (by 6 months), and then to either progressively improve or maintain (at 12 and 18 months), their personalised goals for sitting less, actively breaking up sitting time, and moving more. Participants receive coaching to set incremental goals that gradually progress from their pre-existing levels at baseline towards the study targets. Key intervention targets are: at least half of daily waking time in upright postures (50% standing/stepping); at least one ‘active’ break from sitting per hour; and, at least 10,000 steps per day. An ‘active’ break is considered to be at least three minutes of walking (approximately 250 steps) or completion of simple body weight resistance exercise activities that have been adapted from previous experimental trials [18]: calf raises, squats, and single leg kickbacks, done in three sets of three 20-s bouts totaling approximately 3 minutes. Since excessive sitting and excessive standing
may both be harmful [31, 32], 50% was chosen as a level that is a simple, heuristic approach that has been safely achieved by participants in our previous trials [33] and is 2 h/day lower than the average sedentary time reached by adults with type 2 diabetes [11], assuming a 16 h waking day. Active breaks to interrupt sitting were promoted in recognition that not all sitting replacement activities have equal benefit [34, 35] with ambulation and resistance exercise showing particular benefit [36]. The 10,000 steps message is widely used in public health [37], noting benefits (including glycaemic control) for increased steps can occur below this threshold [38].

**Intervention protocol and core components**

The OPTIMISE intervention consists of health coaching (including education), a sit-stand workstation and an activity tracker (both provided by the trial) to encourage participants to sit less, as well as to move more and engage in active breaks. The intervention commences with workstation installation by third party installers approximately 2 weeks following baseline assessment. Immediately after installation, participants meet with their assigned health coach, via zoom, to discuss the intervention, demonstrate correct desk usage, and set up and demonstrate the workings of the Fitbit. The health coaching continues in person and via telephone throughout the first 6 months intensive phase (10 total contacts). They then receive tailored coaching via text message between 6 and 12 months (1–2 messages per week). Participants may seek other concomitant lifestyle interventions to manage their diabetes. After completing the trial, participants retain the sit-stand workstation and activity tracker.

**Sit-stand workstation**

Consistent with the Behaviour Change Wheel intervention functions of enablement and environmental restructuring [29], all participants are provided with an Ergotron™ WorkFit-T/TL Sit-Stand Desktop Workstation. The workstation weighs 22.5 kg and is placed on top of the existing work surface. It allows participants to easily and quietly alternate their working posture between sitting and standing whilst still interfacing with their computer. Participants are provided with either a single or dual arm monitor kit that allows their computer monitors to be directly affixed to the monitor platform. Both written and verbal ergonomic instructions are provided by the health coaches to aid in correct workstation usage [39]. Under work-at-home restrictions, the alternative protocol is for participants to take their workstations home when permitted by the employer.

**Activity tracker (Fitbit)**

In line with the Behaviour Change Wheel intervention functions of education and training, participants are provided with a Fitbit activity tracker and Fitbit smartphone application (app) for Android or Apple. The Fitbit’s main purposes are to encourage participants to move more, and to engage in active breaks from sitting. Participants are given a username and password to be used for the duration of the trial and provide permission for their data to be accessed by the project team. Upon completing the study, the account will be deactivated and participants will be instructed on how to create their own personal account. Each Fitbit is synchronized with Fitbase (Small Steps Labs, LLC; San Diego, CA, USA; http://fitbase.com), a third-party data management platform that supports top down supervision of study participants’ device usage and activity. The model of Fitbit used is the Fitbit Inspire HR, a wireless wrist-worn device that records and displays a range of outputs in real time (including daily step count, approximate resting heart rate, hourly activity / active breaks) — captured through proprietary algorithms applied to tri-axial accelerometry and heart rate (photoplethysmography) inputs — and provide vibration feedback based on the recorded data. The lithium polymer battery powers the device for approximately five days (depending on usage) before requiring recharging and collects data for up to 30 days (at which point it must be synced with the participant's smartphone).

Using the device and app real-time monitoring, participants self-monitor attainment of their self-selected stepping and active breaks goals throughout the intervention and specifically during health coaching sessions. Hourly active break reminders are sent according to the participant’s preference (up to 14 per day). These reminders are produced by the Fitbit ten minutes before each hour finishes. Participants receive a vibration alert if they have not achieved at least 250 steps in that hour (their active break, if they have chosen walking rather than resistance exercises). Other active break strategies, such as simple resistance activities may be manually recorded using the Fitbit, however these are not automatically monitored by the Fitbit itself. Health coaches remotely monitor participant adherence to steps and active break goals with Fitbase, which supports tailored feedback during coaching sessions.

**Face-to-face and telephone health coaching (0–6 months)**

The individual health coaching component targets the Behaviour Change Wheel intervention functions of persuasion, education and training. Health coaches, all of whom have at least a bachelor level of training in exercise physiology, nutrition, or nursing, are trained in the
delivery of the intervention, including motivational interviewing techniques [40]. A written script is maintained for intervention fidelity and consistency of delivery. Key aims of the health coaching are to build rapport, provide education about the importance of reducing sedentary behaviour and increasing movement throughout the day, encourage sustained self-management, and goal setting. In conjunction with the first health coaching session, participants are provided with an intervention handbook, containing written educational information and instructions (Additional file 4), an email containing basic tips to reduce sitting, a 2-min educational video describing the link between diabetes and sitting and activity levels, a video demonstrating how to perform the simple resistance activity breaks, and an activity feedback report (Additional file 5) generated from their most recent ten days of activity monitor (activPAL) wear. The health coaching consists of ten sessions (two in-person and eight via telephone; approximately 15–30 min in duration) over 6 months. Health coaches follow standardised outlines for each session set out in REDCap forms containing both the coaching script and embedded data-collection fields to further enhance intervention fidelity and collect data for process evaluation. The data collection is also used to guide subsequent health coaching sessions (e.g., goals, goal attainment). All health coaching sessions are delivered by the same health coach wherever possible and conducted at a time selected by the participant.

Coaching session 1 (face-to-face)
The first session, scheduled to take 50–60 min, occurs via video teleconferencing immediately after installation of the workstation. The session includes a brief discussion of the workstation relative to the expectations and needs of the participant, whereby the coach ensures the desk is installed to allow for correct usage habits and ergonomic positioning; demonstration of how to perform the simple resistance activities at the desk; provision, setup and demonstration of the activity tracker (see ‘Activity tracker (Fitbit)’); and, the behavior change motivational interviewing. A script of this interview is available in Additional file 7.

For the motivational interviewing, the health coach revises the participant’s personalised feedback report (Additional file 5) covering pre-existing sedentary behaviour and physical activity. Their behaviour at work, over the whole waking day, plotted by date and time is used to help set realistic goals. It is also used to identify and reflect on their “danger zones” (periods throughout the day of prolonged, unbroken sitting time), and choose relevant behavioural strategies targeting those danger zones. Participants are guided to form an action plan consisting of two goals (number of active breaks at work; total step count per day) and at least one strategy each to: sit less at work; sit less outside of work; move more during work; and, achieve the daily step count goal. Participants choose from a recommended list of strategies, or choose their own (Additional file 6). The coach supports the participant to make selections that conform to the SMART framework (Specific, Measurable, Achievable, Relevant, and Time-based), consider barriers and solutions, and for which the participant has adequate readiness and confidence to achieve (i.e., 8+ on a scale from 1 (not ready / not confident) to 10 (ready / confident)). The health coach reviews the final action plan and any anticipated barriers with the participant. Following the session, a summary of the discussion is provided to the participant in a personalised email from their coach.

Sessions 2–6, 8–10 (telephone)
The seven telephone-delivered sessions occur on a tapered schedule: one call per week for the first three weeks reducing to one call every three weeks for the remaining 23 weeks (approximate timeframe). Each session lasts for a duration of 15 to 30 min. The sessions are designed to check on the participant’s progress (both subjectively and objectively with their Fitbit data as in Fig. 2), address problems with adherence, revise goals as needed, and reinforce goal attainment. Adoption of new strategies, and the progression of goals is encouraged by health coaches when participants report high engagement and success with their current plan.

Session 7 (face-to-face)
Coaches schedule an in-person session to coincide with their attendance at the Baker Institute, Melbourne for their 3-month clinical assessment. In a 30-min session, coaches enquire regarding participants’ overall experiences and their readiness to continue with the intervention, and provide feedback on how their their daily steps and active breaks have tracked over time for each week since the first health coaching session according to their Fitbit. Similar to the telephone sessions, participants’ strategies and goals to sit less and move more are revisited and revised as required. This session is offered via telephone when in-person visits are not possible (e.g., due to the COVID pandemic) or declined.

Extended care (tailored text messaging; 6–12 months; expanded protocol) – OPTIMISE
The 6–12-month intervention phase is designed to support maintained behaviour change (or continued improvement) after the 10-session intensive phase has been completed. This program, which is administered remotely, transitions participants from the face-to-face and telephone delivered health coaching to a tailored
text message service using the web-based semi-automated platform, propelo™ (www.propelo.com.au). Coaching involves 24 weeks of text message contact and one telephone coaching session (midway) with their health coach.

The text message content has been informed from formative discussion with research staff, health coaches, and completed OPTIMISE intervention participants who were recruited before the expanded protocol was initiated. This formative research involved qualitative interviews and user-testing of draft text content. Key findings from this formative work highlighted the need for the text message program to: use supportive, non-judgemental language; continue to leverage off the rapport established between the health coach and participant during the intensive phase; and, ensure the texts are tailored to the

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**Fig. 2** Monitoring participant’s Fitbit adherence and goal and strategy attainment in real-time with the Fitabase data management platform. Example participant Fitbit data depicted. Panel A depicts typical daily step count data across selected dates. Panel B depicts hourly break down of step accrualment across selected dates representative of 24 h (00:00–23:59 pm). Traffic light system is depicted whereby large red dots denote high levels of steps, and small green dots indicate low level of steps in given hour.
participant’s Fitbit data. The texts target three key behaviour change strategies in three different types of text messages (see Table 1): prompt actions in real-time (via ‘Sit less prompts’ and ‘Move More prompts’); promote ongoing self-monitoring of behaviour (via ‘Check-ins’); and, monitor and reward goal attainment (via ‘Check-ins’).

During the final OPTIMISE telephone coaching sessions (#8), the health coach notifies participants that they will be receiving text messages over the next six months. Following the session, the coach completes a tailored survey translating the participant’s coaching goals into messaging-friendly “danger zones” (periods of the day or activities when prolonged sitting commonly occurs), strategies to sit less and move more, and goals for steps per day and active breaks per day. The appropriate days and times to send each type of message is also captured. Text messages are sent at a minimum frequency of once per week (see Table 1). The text message content is kept under 160 characters and is initially based on information from the tailoring survey, and subsequently, throughout the intervention, based on data from the participant’s Fitbit data accessed weekly through Fitabase. Either one or two check-in texts are sent monthly (on Mondays), based on whether the participant has met (yes/no/almost) their step goal and their active break goal in the previous week (Monday-Sunday) or their goal attainment could not be verified because the participant did not wear the Fitbit in the week prior. The telephone session with the coach midway through the text message program, involves a review of progress, and retailoring of the goals, danger zones, strategies, message days and times as needed.

Control – delayed intervention
To minimise attrition prior to receiving their delayed intervention (at 12 months), the control participants receive contact in the form of a thank-you letter commencing two weeks after the baseline assessment then, monthly emails containing diabetes fact sheets, along with a follow-up phone call (verifying they received the fact sheet and enquiring whether they have any questions). The fact sheets are published by the NDSS, and provide a non-tailored diabetes-management advice. The fact sheets do not cover sedentary behaviour. Participants may seek other lifestyle interventions to manage their diabetes during this period. Following the completion of the 12 month assessment, control participants are provided with a modified version of the intervention (12–18 months). In the original protocol, delayed intervention (6–9 months) participants were provided with a sit-stand workstation and written education materials only. In the expanded protocol this is referred to as OPTIMISED (12–18 months). As with OPTIMISE, OPTIMISED

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Overview of text messages for the OPTIMISE-extended phase of intervention (6–12 months)</th>
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</thead>
<tbody>
<tr>
<td>Purpose of text</td>
<td>Frequency of texts</td>
</tr>
<tr>
<td>Sit less prompt</td>
<td>Fortnightly, alternate with Move More prompts (n=13 over 26 wks)</td>
</tr>
<tr>
<td>Move more prompt</td>
<td>Fortnightly, alternate with Sit Less prompts (n=13 over 26 wks)</td>
</tr>
<tr>
<td>Check-ins</td>
<td>Monthly (Either 1 text to promote Fitbit use (n=5 over 26 wks) or 2 texts to check goal attainment (n=10 over 26 wks))</td>
</tr>
</tbody>
</table>
includes environmental support via a sit-stand workstation, provision of a Fitbit, and health behaviour change coaching (one delivered by online video teleconferencing and two delivered by telephone). However, the behaviour change health coaching and educational materials are modified to be more suitable for scale-up and external delivery, based on consultation and collaboration with end users and stakeholders. The intervention adaptation process, and the resultant OPTIMISED intervention protocol, will be reported elsewhere.

Primary outcomes
The primary outcomes are overall daily sitting time, and glycosylated haemoglobin (HbA1c) at 6 months, which were originally chosen in order to evaluate the intensive phase of the intervention (OPTIMISE). With the addition of the expanded protocol, cognitive function measures: visual learning and new memory (Paired Associates Learning Total Errors [adjusted]) were added as a primary outcome at 12 months.

Secondary and exploratory outcomes
Secondary outcomes include: sitting time accumulation patterns (sitting time in prolonged bouts \([\geq 30\text{ min bouts}]\), prolonged bouts at work, usual bout duration, alpha \([\text{unitless measure characterising the frequency distribution of sedentary bout durations}]\); sitting time at work; physical activity (active breaks from sitting, time spent standing, stepping, light-intensity physical activity, moderate-to-vigorous intensity physical activity) overall and during work; sleep (total sleep time, sleep efficiency, sleep onset latency, wakefulness after sleep onset); anthropometry (weight, waist, and hip circumference); body composition (fat mass, visceral fat mass, lean mass); fasting and postprandial glucose metabolism assessed as incremental area under the curve \([\text{iAUC}]\) for glucose and insulin during a 2 h 75 g oral glucose tolerance test \([\text{OGTT}]\); fasting lipid levels \([\text{LDL, HDL, total cholesterol, cholesterol ratio, triglycerides}]\); blood pressure \([\text{systolic and diastolic pressure}]\); vascular function \([\text{flow-mediated dilation and shear rate}]\); inflammatory markers \([\text{high-sensitivity c-reactive protein [hs-CRP], interleukin [IL]-6, IL-1\beta, tumour necrosis factor – alpha [TNF-\alpha], adiponectin, and leptin}]\); neurotrophic factors \([\text{brain-derived neurotrophic factor [BDNF], insulin-like growth factor 1 [IGF-1]}]\); and, additional cognitive function domains including reaction time, visual matching ability and visual recognition memory, reaction time, and working memory. Some of the survey measures are considered as outcomes, including the measures of anxiety and depression, musculoskeletal health, fatigue, workplace performance and satisfaction, and motivation. Outcomes regarding longer term trends in physical activity and sleeping are extracted from the Fitbit worn by intervention participants only.

Data collection
Data collection occurs at baseline, 3, 6, 12, 15 and 18 months via: in-person clinical assessments; cognitive testing; device-based monitoring; and online questionnaires administered through REDCap; and, process data collected in REDCap and by the health coach in REDCap health-coaching forms. Table 2 shows the timepoints at which each component of the data-collection occurs under the original, expanded, and COVID-adapted protocols. Table 3 and Additional file 9 provide extensive details of the objective and questionnaire measures, as well as their intended purpose in the trial (e.g., primary outcome, secondary outcome, process outcome). The data collection procedures used for each of these components are indicated below.

Device-based measurement of physical activity, sedentary behavior and sleep
Device-based measures of physical activity, sedentary behavior, sedentary behavior accumulation and sleep are collected using the activPAL4 activity monitor \([\text{PAL Technologies Limited, Glasgow, UK; default settings}]\) worn on the thigh and the Actigraph GT3X+ \([\text{Actigraph, Pensacola, FL, USA}]\) worn on the wrist. Both devices are intended to be worn 24h per day for 10days. Eleven days before their clinic visit, the activPAL4 — previously initialised and waterproofed with a nitrile sleeve — and the GT3X+ monitor and wrist band are sent to participants along with instructions and materials for affixing and wearing both devices \([\text{transparent polyurethane acrylate adhesive patches and wrist band, respectively}]\). It has been previously shown that participants attaching their activPAL devices is feasible, acceptable, and results in adequate placement on the anterior midline of the thigh \([41]\). A sleep diary is provided to participants for 10 consecutive days to define sleeping and waking periods. Incomplete records for sleep and wake times are inferred from using one or more published methods \([\text{visual estimation; automated estimation; average values, for example with, Edwardson et al. [42]; Winkler et al. [43]; LaCroix et al. [44] respectively}]\) and checked against movement visually.

The primary outcome of total daily sitting time \([\text{sitting or lying while awake and wearing the device, h/16 h day}]\) will be derived from the activPAL4 data, as will secondary measures of physical activity, standing time, and sedentary behaviour accumulation. The activPAL4 uses triaxial accelerometry \([\text{30Hz}]\) and activPAL proprietary algorithms \([\text{here, VANE}]\) to measure sitting/lying,
standing, and stepping, stepping cadence, as well as transitions between sitting/lying and upright posture with high accuracy, reliability and excellent responsiveness to change for sedentary reduction interventions [45–48]. Further measures, with less published data on validity, are available using the CREA algorithm [49]. Relative energy expenditure will be estimated as metabolic equivalents (MET) from cadence [50] or acceleration [51] with a similar level of accuracy to most accelerometers. 

Consistent with standard procedures for the field [42], sleep time and device non-wear time (based on the daily log and device non-movement) will be excluded from measures of physical activity and sedentary behavior, as will days with insufficient wear. Sufficient-wear criteria for waking days will be 10h hours wear while awake, with evidence of movement (≥500 steps/day and not ≥95% of the day in any one activity). The activPAL data (activPAL VANE algorithm primarily) are processed in SAS (9.4 or
<table>
<thead>
<tr>
<th>Component</th>
<th>Key constructs</th>
<th>Measures</th>
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<tbody>
<tr>
<td><strong>Clinical and device-based measures collected in the in-person visit clinical assessments</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Component</strong></td>
<td><strong>Key constructs</strong></td>
<td><strong>Primary / secondary outcomes</strong></td>
</tr>
<tr>
<td>Fasting blood draws</td>
<td>Glycaemic control</td>
<td>Glycosylated haemoglobin (HbA1c %, HbA1c mmol/mol)*</td>
</tr>
<tr>
<td></td>
<td>Fasting glucose metabolism</td>
<td>Glucose and Insulin</td>
</tr>
<tr>
<td></td>
<td>Fasting lipid metabolism</td>
<td>LDL, HDL, Total cholesterol, Triglycerides</td>
</tr>
<tr>
<td></td>
<td>Inflammatory markers</td>
<td>Hs-CRP, TNF-α, IL-6, IL-1β, Adiponectin, Leptin</td>
</tr>
<tr>
<td></td>
<td>Neurotrophic factors</td>
<td>BDNF, IGF-1</td>
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<td></td>
<td>Genetic risk factors</td>
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<tr>
<td><strong>2 h Oral Glucose Tolerance Test</strong></td>
<td>Postprandial metabolism of glucose &amp; insulin</td>
<td>iAUC glucose, iAUC insulin, 2 h post-prandial glucose, 2 h post-prandial insulin</td>
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<tr>
<td><strong>Anthropometric</strong></td>
<td>Body weight &amp; body composition</td>
<td>Weight, waist circumference, DXA assessed total and regional fat mass, lean mass, total body fat percentage, DXA software estimated visceral adipose tissue mass</td>
</tr>
<tr>
<td><strong>Vascular</strong></td>
<td>Blood pressure &amp; heart rate</td>
<td>Resting systolic blood pressure, diastolic blood pressure, mean arterial pressure</td>
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<tr>
<td></td>
<td>Flow Mediated Dilation</td>
<td>Post-deflation peak vessel diameter compared to resting diameter (FMD%)</td>
</tr>
<tr>
<td><strong>Cambridge Neuropsychological Test Automated Battery (CANTAB)</strong></td>
<td>Visual learning and new memory</td>
<td>Paired Associates Learning total errors (adjusted)² (PAL TEA), PAL total errors 12 shapes (adjusted)</td>
</tr>
<tr>
<td></td>
<td>Reaction Time</td>
<td>Reaction Time (RTI) simple median reaction time, RTI simple median movement time &amp; RTI median 5-choice reaction time, RTI median 5-choice movement time</td>
</tr>
<tr>
<td></td>
<td>Visual matching ability and visual recognition memory</td>
<td>Delayed Matching to Sample (DMS) percent correct, DMS median correct latency</td>
</tr>
<tr>
<td></td>
<td>Working memory</td>
<td>Spatial Working Memory (SWM) between errors, SWM between errors (12 boxes), SWM strategy (6–12 boxes)</td>
</tr>
<tr>
<td><strong>Cognitive function</strong></td>
<td>Global cognition</td>
<td></td>
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</table>
### Table 3 (continued)

<table>
<thead>
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<th>Key constructs</th>
<th>Measures</th>
<th>Primary / secondary outcomes</th>
<th>Other measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device-based monitoring (thigh-worn activPAL)</td>
<td>Sedentary behaviour</td>
<td>Overall sitting time, Overall prolonged sitting time (≥30 min), Work sitting time, Work prolonged sitting time</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sedentary time accumulation</td>
<td>Usual bout duration, Alpha (overall and work)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Active breaks</td>
<td>Active breaks (n per day overall and work)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Physical activity</td>
<td>Standing, Stepping, LPA, MVPA (all overall and during work)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Sleep</td>
<td>Total sleep time, Sleep efficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep</td>
<td>Total sleep time, Sleep efficiency</td>
<td>Sleep onset latency, Wakefulness after sleep onset</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sleep</td>
<td>Total sleep time, Sleep efficiency</td>
<td>Sleep onset latency, Wakefulness after sleep onset</td>
<td></td>
</tr>
</tbody>
</table>

**Device-based monitoring (wrist-worn Actigraph GT3X+)**

<table>
<thead>
<tr>
<th>Component</th>
<th>Key constructs</th>
<th>Measures</th>
<th>Primary / secondary outcomes</th>
<th>Other measures</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sleep</td>
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</tbody>
</table>

**Abbreviations:** ApoE4 Apolipoprotein E4, BDNF brain-derived neurotrophic factor, BMI body mass index, CANTAB Cambridge Neuropsychological Test Automated Battery, DXA Dual X-ray absorptiometry, FMD flow-mediated dilation, HbA1c Glycosylated Haemoglobin, HDL High density lipoprotein cholesterol, Hs-CRP High-specificity C-Reactive protein, iAUC incremental area under the curve, IGF-1 insulin like growth factor 1, IL-1B interleukin-1 beta, IL-6 interleukin-6, LDL Low Density Lipoprotein Cholesterol, LPA light intensity physical activity, MVPA moderate-vigorous intensity physical activity, TNF-α Tumour necrosis factor alpha

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a Primary outcomes for original OPTIMISE protocol concerning diabetes (primary endpoint = 6 months)
b Primary outcome for expanded protocol concerning dementia (primary endpoint = 12 months)
higher) using a bespoke program adapted from previous studies [52]. Measures are extracted overall and for specific timeframes of interest identified from the log — work and non-work days, work and non-work times, and time at the workplace — and as detailed time-series data (daily; hourly).

The wrist-worn Actigraph GT3X+ activity monitor is used to estimate sleep duration (i.e., total sleep time) and sleep quality metrics (i.e., sleep efficiency, wakefulness after sleep onset, sleep onset latency) and also enables harmonisation of data to other studies that have used wrist-worn devices [53, 54]. Actigraph GT3X+ data are sampled at 30 hz. Behaviour classification from the raw wrist-worn accelerometer data is performed in GGIR, an open source R package [55]. This package implements methods providing valid and reliable estimates sleep duration and quality [56] as well as physical activity [57, 58] from wrist-worn devices. The 24-h wrist monitor data will be separated into sleep periods (for measuring sleep quality and duration) versus waking periods (for other measures) based on sleep and wake times collected in the online-administered daily logs. Sleep quality and duration measures exclude sleep periods during which the device is not worn, which will be identified via the Choi algorithm [59].

**Clinical assessment**

Clinic visits occur at every data collection timepoint, with the exception being at 15 months. Prior to each visit, participants are reminded to abstain from engaging in any moderate- to vigorous-intensity physical activity, from consuming caffeine and alcohol in the 24 h prior to the assessment, to fast for at least 8 h, and to take their medications for the day of the visit at lunchtime during the visit rather than in the morning. For each clinic visit, participants report to the Baker Institute Clinic at 8 am. Over a 5-h period, participants have their body weight, body composition, blood pressure and vascular function assessed, a fasting blood collection, and undergo a 2 h oral glucose tolerance test (OGTT) during which they complete their questionnaires. Upon completion of the OGTT, participants receive lunch (e.g., sandwich/coffee) followed by cognitive assessments. Those participants whose assessment occurs during COVID-19 related social isolation mandates are emailed the questionnaires and referred to off-site pathology for glycosylated haemoglobin (HbA1c) testing, all other measures are omitted.

Clinic measures and their procedures are described below.

**Cardiometabolic outcomes**

A peripheral intravenous catheter is inserted near the antecubital fossa and a fasting blood sample is taken to measure glucose, serum insulin, HbA1c, high-sensitivity C-reactive protein (hs-CRP), full blood examination (FBE), cholesterol, and triglycerides. Thereafter, the participant is guided through a standard 75-g 2 h OGTT [60], with plasma glucose and serum insulin collected at half-hourly intervals. An additional volume of blood is collected for verification of results if required. Further methodological information is available in Table 4.

**Inflammatory and neurotrophic factors**

Markers of inflammation (e.g., hs-CRP, TNF-α, IL-6, IL-1β, adiponectin, and leptin) and neurotrophic factors (BDNF, IGF-1) will be ascertained from serum/plasma samples collected at all clinical assessments except the 3-month assessment. Samples will be analysed using multiplex microsphere-based immunoassays (MAGPIX, Merck Millipore) and traditional ELISA methods (R&D Quantikine) at the Sunshine Coast Health Institute. Apolipoprotein E 4 (ApoE-4), a commonly assessed genetic risk marker for cognitive decline is assessed at baseline only from DNA isolated from blood collected into PAXgene® tubes using QIAGEN DNA extraction kits. Custom-designed primers will be used for PCR amplification of the ApoE gene (Taqman qPCR, Thermofisher Scientific). Refer to Table 4 for further detail on inflammatory and neurotrophic factor methodologies.

**Cognitive function**

Global cognitive function is first screened with the Addenbrooke Cognitive Examination-Revised (ACE-R) and then assessed using the Cambridge Neuropsychological Test Automated Battery (CANTAB) [61]. The ACE-R is administered by the research staff at baseline only, as it provides a global measure of cognition. ACE-R evaluates six cognitive domains (orientation, attention, memory, verbal fluency, language, and visuospatial ability) and includes an inbuilt Mini Mental State Exam [62].

Following the ACE-R test, CANTAB is completed by the participant at baseline, and then tested additionally at the 6, 12 and 18 month assessments. Specific CANTAB tests (and the domain they measure) are: Paired Associates Learning (visual memory and new learning); Reaction Time (motor and mental response speeds, as well as measures of movement time, reaction time, response accuracy and impulsivity); Delayed Matching to Sample (visual matching ability and short-term visual recognition memory); and, Spatial Working Memory (strategy and working memory). The Motor Screening Task is included as an introduction to the CANTAB assessments. The key primary outcome is the total number of errors on the Paired Associates Learning task adjusted (PAL TEA) shown in Fig. 3.
The outcome is automatically calculated by CANTAB. The PAL TEA score represents the number of times a participant chose the incorrect option during the task. Participants that terminate the task early have their scores adjusted; accounting for the estimated number of errors they would have made on all the problems. This allows for comparison with those who completed the final stage of the task. The CANTAB is an iPad administered cognitive battery and results are downloaded from the official Cambridge Cognition platform.

**Anthropometry: height, weight, waist and hip circumferences and body composition**

Height is obtained using a stadiometer (Seca, Germany) at the baseline clinic visit only, measured in duplicate, with a third measurement taken if the difference between

### Table 4 Brain health, cardiometabolic biomarkers and more comprehensive methodology descriptions

<table>
<thead>
<tr>
<th>Cardiometabolic biomarker</th>
<th>Measurement methodology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Spectrophotometric-hexokinase method using the Abbott Alinity Analyser</td>
</tr>
<tr>
<td>Insulin</td>
<td>Chemiluminescent Microparticle Immunoassay using the Abbott Alinity Analyser</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>Standard enzymatic methods using the Abbott Alinity Analyser</td>
</tr>
<tr>
<td>HDL</td>
<td>Accelerator Selective Detergent using the Abbott Alinity Analyser</td>
</tr>
<tr>
<td>LDL</td>
<td>LDL will be calculated using the Friedewald formula using the Abbott Alinity Analyser</td>
</tr>
<tr>
<td>Hs-CRP</td>
<td>Immunoturbidimetric method using the Abbott Alinity Analyser</td>
</tr>
<tr>
<td>HbA1c</td>
<td>Boronate Affinity HPLC method using the Trinity Premier Hb9210.</td>
</tr>
<tr>
<td>Full blood examination (FBE)</td>
<td>Beckman Coulter DXH800 instrument</td>
</tr>
<tr>
<td>TNF-α, IL-6, IL-18, adiponectin, and leptin, BDNF</td>
<td>MAGPIX multiplex microsphere-based immunoassay (Millipore, Billerica, MA)</td>
</tr>
<tr>
<td>IGF-1</td>
<td>Human IGF-I/IGF-1 Quantikine ELISA (R&amp;D Systems)</td>
</tr>
<tr>
<td>Apolipoprotein E 4 (ApoE-4)</td>
<td>Stored in PAXgene DNA tube, PAXgene Blood DNA kits (QIAGEN) used for DNA isolation, PCR will be performed using custom design primers for the amplification of a segment of the ApoE gene and the 96-well Taqman Gene Expression qPCR Assay (Thermofisher Scientific). ApoE Sequencing (of the PCR product will occur using two single nucleotide polymorphisms (SNPs). Validation of sequencing results will be completed by targeted genotyping via differential amplification of ε2, ε3, or ε4 alleles with custom designed primer pairs.</td>
</tr>
</tbody>
</table>

Serum and plasma analyses

In preparation for serum analyses, samples will be collected in SST tubes and, for plasma analysis, in EDTA tubes. Both samples are rested for thirty minutes in the fridge, prior to centrifuging at 2000 RPM for 15 min at 4 degrees, with the separated plasma and serum aliquoted into 400ul and 750ul volumes and stored at −80 degrees celcius.

**Fig. 3** Paired Associates Learning task in CANTAB [63]. Participants are shown boxes on the screen containing specific patterns which are "opened" in a randomised order. The patterns are then displayed in the middle of the screen (as pictured) one at a time and the participant must locate which box the designated pattern is in. If the participant makes an error, the boxes are revealed in sequence again and the participant retries the task [64]. Paired Associates Learning task adjusted (PAL TEA) is a primary outcome.
the first two measurements is $\geq 0.5\text{ cm}$. Body mass is measured using a platform scale (JAC-929; Nuweigh, Australia) taking measures in duplicate, with the average of two reading recorded at each assessment. BMI is calculated using height and weight measurements ($\text{weight} / \text{height}^2$). Waist circumference is obtained using a non-elastic tape measure around the midpoint between the iliac crest and the lowest rib. Hip circumference is measured at the maximum circumference in the horizontal plane, over the buttocks. Both measurements are recorded according to the nearest 0.1 cm, and completed twice unless the first two differ by $\geq 1\text{ cm}$, in which case a third measure is obtained. A whole-body dual energy x-ray absorptiometry (DXA) scan (Lunar iDXA; GE Healthcare, Australia) is used to assess body composition variables, including total and regional fat mass, and lean mass, and total body fat percentage. Visceral adipose tissue (volume and mass) is estimated by the DXA software using the android region of the body. Where participants' body size exceeds the DXA scan area, a half body scan is performed, which has previously been shown to provide valid estimate of body composition [65]. Where possible, the same research staff member will perform each participant's follow-up scan.

**Blood pressure**

Blood pressure is measured via a digital blood pressure monitor (OMRON HEM-907; Omron Healthcare, Japan) placed on the non-dominant arm. Participants are requested to lie down in a dimly lit, temperature controlled (approximately 22–24 C) room. After 10 min of rest, the monitor takes three measurements with an interval of 2 minutes between each measurement. The monitor measures systolic pressure, diastolic pressure, and heart rate and determines the average of the three measurements separately. The three measurements, as well as the average values, are recorded.

**Arterial function**

Arterial function is assessed by flow-mediated dilation (FMD). Participants lie in a supine position in a dimly lit temperature controlled room for at least 20 min before the baseline 'steady state' recording of FMD is obtained. Recording is made on the brachial artery of the dominant arm (opposite to blood pressure) using a high-resolution ultrasound machine (Terason t3200, Teratech, Burlington, MA). A rapid inflatable cuff (SC-12-D, D.E. Hokanson Inc., Bellevue, WA) is placed distally to the antecubital fossa and the ultrasound probe applied to the brachial artery. After an optimal image of the brachial artery has been established, a 1 min recording of continuous resting vessel diameter and blood velocity (shear rate) is collected. The cuff is then inflated to $> 200\text{ mmHg}$ for 5 min. Thereafter, the cuff is released to induce reactive hyperemia. An additional 3 min of ultrasound recording is completed to determine the post-deflation peak vessel diameter, which is compared to resting vessel diameter (FMD%).

**Questionnaire measures**

Surveys are administered either during the clinic visit, or emailed to the participants for self-completion. All surveys, unless specified otherwise, are combined together into one survey, referred to hereon as the OPTIMISE survey. Contingent on COVID-19 and associated social distancing mandates, all surveys are administered electronically. Information pertaining to questionnaire source, rationale for inclusion, reliability and validity is described below and summarised in Additional file 9.

**Socio-demographic characteristics**

Age and gender are ascertained in the eligibility survey. Sociodemographic characteristics (ethnicity, household type, education, occupation) are obtained at the baseline visit, with question formats based upon previous studies such as the Australian Diabetes, Obesity and Lifestyle (AusDiab) study [66]. Changes in occupation are recorded in follow-up assessments.

**Health history checklist**

A health history checklist recording pre-existing health conditions is recorded by research staff with participants at baseline, and updated throughout the trial in the instance it changes. The checklist includes questions pertaining to any history of angina, heart attack, heart bypass operation, stroke, angioplasty for peripheral vascular disease, kidney damage from diabetes, eye or retinal damage from diabetes, nerve damage from diabetes, numbness burning or tingling in feet, foot ulcer, and lower limb amputation.

**Self-reported physical activity, sitting time, and sleep**

The Active Australia questionnaire is used to measure the number of minutes per week engaged in walking, vigorous gardening, moderate activity, vigorous activity (time multiplied by two), and strength training, with amounts totalled to determine MVPA [67]. The IPAQ questionnaire (two-items) is used to measure overall sitting time obtained in hours and minutes across week days and weekends. Sitting time is contextualised as part of work, travel, recreation, on a screen device, online chores (e.g. emails), or ‘other’ sitting that occurs during waking hours [68]. Sitting time and activity are also assessed using the Sedentary, Transport and Activity Questionnaire (STAQ) [69], which assesses time spent in transport, whether driving, on public transport, walking, and cycling. STAQ
has acceptable reliability and validity [69]. Sitting and activity are further quantified using the Occupational Sitting and Physical Activity Questionnaire (OSPAQ) [70]. Here, participants are asked to divide their work day into percentages spent sitting, standing, stepping, and performing heavy labour tasks. OSPAQ has demonstrated acceptable validity and reliability [70, 71]. Additional questions asked include the percentage of the work day that is occupied by prolonged sitting (sitting bouts equal to or greater than 30 min) is also obtained [72], as well as the proportion of the workday spent sitting in common occupational tasks [73]. Participants are asked to identify their desired levels of sitting, standing, and stepping during work and home hours [74]. A 15-item checklist is used to assess participants’ current use of sit less and move more strategies (at home and at work) and a 6-item questionnaire assesses barriers to sitting less and moving more [73]. Knowledge (5-items) and perceived organisational norms (4-items) about sitting, activity, and health are assessed using a questionnaire adapted from a previous trial [75]. Participant’s self-regulation strategies for sitting less and moving more are both assessed with 9-item questionnaires, which are adapted from previous trials [76]. Participants are asked to evaluate how supportive their peers are of reducing sedentary behaviour, as well as engaging in physical activity [77, 78]. Finally, participants are assessed for their perceived changes across 16 domains of sitting in the last 6 months (assessed at 6, 12 and 18 months only). This measure has been adapted from previous research for this trial [79].

Sleep diary
Each morning over a 10-day monitoring period (coinciding with the wear of the activity monitor devices), participants are emailed links to a REDCap administered online daily log. Participants can also request to use a handwritten copy of the diary. Using a modified version of the Consensus Sleep Diary [80], the log enquires about their wake (and out of bed) times that morning, their sleep times and sleep quality the night before (into bed, lights out, time to fall asleep, number and duration of awakenings), and over the previous day, their work hours and work location (workplace / home / other), whether each device was worn that day (yes/no) and the start and end times of any removal greater than 10 min. The consensus sleep diary is a validated measure of sleep [81].

Anxiety and depression
The Hospital Anxiety and Depression Scale (HADS) [82] is used to measure anxiety and depression. It is a valid and widely accepted measure for determining level of anxiety and depression and can reliably differentiate between the two [83]. The questionnaire consists of 14 items: seven for anxiety (e.g. “I feel tense or wound up”), and seven for depression (e.g. “I feel cheerful”).

Managing diabetes
The Problem Areas in Diabetes (PAID) [84] scale assesses perceptions of the intervention and its influence on subjective diabetes management. The measure has demonstrated high reliability [85] and sensitivity to change over time [84], and has demonstrated use for screening depression and emotional problems in people with diabetes [86]. The 5-point scale asks participants to rank aspects of their diabetes management from “Not a problem” to “Serious problem”. Questions pertain to feelings about diabetes treatment and treatment goals, diabetes and social situations, diabetes and adverse events, burden and acceptance of diabetes, and coping with diabetes complications.

Fatigue
Fatigue is evaluated with a Fatigue Symptom Inventory (FSI) [87]. The inventory questions the participant on their current and previous level of fatigue in the last week. It examines how their fatigue interferes with activities of daily living, cognition, relationships, and mood. Participants are asked to rate the level of fatigue on a 0 (no fatigue) to 10 (extreme fatigue) scale. The measure has demonstrated validity with other fatigue symptom measures [87, 88].

Musculoskeletal pain and health
Musculoskeletal pain and health is measured using the 27-item modified Nordic Musculoskeletal Questionnaire, which surveys both the last 3 months and the last 7 days [89]. Participants indicate the body locations they have experienced ‘trouble’ in muscles or joints. Pain is ranked with an adapted 0–10 scale [90], where 0 indicates ‘no pain’, and 10 indicates the ‘worst pain imaginable’. This measure has been demonstrated to be repeatable and sensitive to change [91].

Work
Participants are asked to estimate their hours and days working, and how many leave days they have had in the preceding 3 months due to illness. Perceived workload and caring responsibility are assessed with a valid [92] two-item questionnaire based on the Borg workload scale [93], and NASA Task Load Index [94]. Self-reported work satisfaction [95] and work performance [96] are also assessed via 7-point scales. Participants are surveyed for how they feel during work with the ultra-short measure for work engagement (UWES-3) [97] featuring 3-items with a 7 point scale, including energy levels, enthusiasm,
and being immersed in their work. The Work Limitations Questionnaire (WLQ) [98] is used to examine the frequency of difficulty that the participant has with performing specific work-related tasks. The WLQ has demonstrated validity and reliability and is correlated with arthritis pain, as well as functional limitations and work productivity [98].

Workplace environment
An audit of the participant’s work environment is conducted at baseline only and made according to the Checklist of Health Promotion and Environments at Worksites (CHEW) [99] which was successfully modified for sedentary behaviour interventions in BeUpstanding [100]. Information is captured on layout, the nearby physical environment (e.g. stairs, centrally located printers and amenities), and workplace policy (such as flexible work hours). The 26-item questionnaire also includes questions pertaining to whether the workplace provides sit-stand desks, and whether a wearable tracker has been previously provided by employers.

Medication and allied health appointments
A record of the participant’s medication, including dosage, frequency is created at the baseline clinical assessment. Any changes to their medication is noted at each subsequent assessment. Similarly, any appointments with an allied health professional in the preceding months between clinical visits are recorded and updated at each assessment. Both records inform potential confounding effects of medication and allied health treatment on the primary and secondary analyses.

Personal wearables questionnaire
Participants use of wearable activity trackers and/or apps in the preceding months is recorded at each visit. Questions about type of wearable and app have been adapted from previous research [101], with the inclusion of additional questions pertaining to how long they have been using the device for, what feature they use (e.g., step counts, exercise intensity), how often they follow associated prompts, and whether these are followed at work, home, or both. Similar questions have been used in previous workplace sedentary behaviour interventions [101] and are important for evaluating prior exposure to health-behaviour trackers.

Dietary intake
Dietary intake is measured using the University of Newcastle’s Australian Eating Survey (AES), a Food Frequency Questionnaire which examines eating habits over the previous 3–6 months [102]. It is a semi-quantitative questionnaire of 120 items. The questionnaire has comprehensive validity and reliability [103], requires less time to complete compared to a 24-h dietary recall, and is representative of longer term changes in dietary intake. Completion of the questionnaire results in a report detailing total daily energy intake, the contribution of healthy nutrient-rich and unhealthy nutrient-poor food choice to diet, the Australian Recommended Food Score (ARFS) a diet quality score indicative of the participant’s alignment to Australian dietary recommendations, macronutrient intake, micronutrient intake and fibre intake. The results are considered as confounding variables on primary and secondary analyses.

Quality of life
Quality of life is measured using the Australian Quality of Life Survey (AQoL-8D) consisting of eight dimensions (Independent Living, Happiness, Mental Health, Coping, Relationships, Self Worth, Pain, Senses) totaling 35 items [104]. The questionnaire is validated and has high test-retest reliability [105].

Motivation for physical activity and motivation to break up sedentary behaviour
Motivation for physical activity and motivation to break up sedentary behaviour are assessed using two separate modified versions of the validated Behavioural Regulation Exercise Questionnaire (BREQ-3) [106] based on self-determination theory [107]. The original prompt of “Why do you engage in exercise?” has been modified for the two questionnaires separately as “Why do you engage or not engage in physical activity?” and “Why do you break up sitting with standing up and/or moving more versus continued sitting?” respectively. These two questionnaires contain 24 items each with a five-point Likert scale. There are six subscales that represent the average scores for 4 items: amotivation (lack of intention), four subscales reflecting degrees of extrinsic motivation - external regulation, introduced regulation, identified regulation, integrated regulation - and intrinsic regulation. This is the first known study to measure motivation to break up sitting time using a modified version of the BREQ-3 questionnaire.

Menopause status questionnaire
The menopause status questionnaire asks questions to assist in classifying menopause status according to the Stages of Reproductive Aging Workshop (STRAW±10) criteria [108]. It is administered only to those participants identifying as female. Participants answer questions pertaining to criteria that fall outside of the STRAW±10
including polycystic ovarian syndrome, premature ovarian failure, hypothalamic amenorrhea, oestrogenic malignancy, or endometriosis. To determine menopause status, participants are asked when (if at all) they had their first menstrual period, and whether they have either temporarily stopped, or finished having their period. Menstrual cycle history, use of hormonal contraceptive or hormonal therapy, and associated symptoms (according to Greene Clinimetric scale) [109] are recorded.

**Experience in the OPTIMISE your health intervention**  
At the 6, and 12 month assessments for the intervention group, and at the 18 month assessment for the delayed intervention group, questions are included pertaining to the participants’ experience in the intervention. These questions are primarily adapted from previous research [110] and related to overall experience, as well as experience with the specific components of the intervention. Participants are asked about how the intervention has led to changes in their activities of daily living, and whether the trial changed these activities on a scale of a lot, a little, or no change. The components of the trial are ranked from most important to least important according to their perceived utility to assist with making changes in the domains of sitting less and moving more. Finally, participants are asked about their goal setting, and whether it was realistic and achievable and supported by the research team, as well as the applicability of the intervention to people without diabetes in order to inform the generalisability of the intervention messaging.

**COVID-19 impact questionnaires**  
A questionnaire was originally added to assess the immediate impact of the pandemic and restrictions (Additional file 8). The questionnaire records any changes that the participant incurred with respect to workload, work environment, caring responsibilities, sitting and standing at their workstation, joint and muscle discomfort, motivations to sit less and move more, and physical activity participation changes due to the pandemic and restrictions. Following the temporary ending of restrictions and return of the trial in October 2020, this questionnaire was replaced with a five-item questionnaire. The new questionnaire asks on a ten point scale (not at all – very much) how the pandemic impacts self-management of diabetes, sitting at desired levels, moving at desired levels, and participation in the trial. Finally, participants are asked how the pandemic has changed their work commute.

**Adverse events**  
Any adverse events encountered during the trial are recorded by the research staff when they arise. Adverse health events may lead to a pause in participation or withdrawal from the study. Information collected includes the type of adverse event, the date of onset and resolution (if applicable), the maximum intensity of the adverse event (mild, moderate, severe), action taken, the adjusted medication due to event, the likelihood of relationship to the trial (scale of 1–4; 1 indicating unrelated; 4 indicating definitely related), and whether the event has resolved. Adverse events are reported to Baker Governance and Alfred Ethics Committee (Additional file 10). The participant that reports the adverse event is followed up with a phone call in order to monitor their health and participation in the trial.

**Process evaluation**  
A process evaluation is undertaken for the intervention and its components by assessing direct implementation indicators and surveying participants at the end of the intensive (6months) and extended phase (12months) timepoints for the intervention group and at 18 months for the delayed intervention group. Elements of context (e.g. workplace support), implementation (e.g., number and duration of health coaching sessions), and mechanisms of impact (including potential mediators) are explored in accordance with the Medical Research Council process evaluation framework [111]. Process evaluation for the intervention components is summarised in Table 5.

**Economic evaluation**  
Incremental cost-effectiveness analysis is to be undertaken to determine whether the intervention represents “value for money” compared to the “usual care” control. The economic evaluation is conducted from a limited societal perspective, using detailed pathway analysis to specify all relevant intervention activities and costs. A detailed accounting of resource use required to deliver the two arms in the trial is undertaken to allow accurate costing of the interventions. The limited societal perspective incorporates cost impacts on government as the provider of healthcare services, healthcare costs to individuals and costs to workplace organisations. The intervention is costed assuming it is in ‘steady state’ (i.e. excluding research-related costs).

Additionally, a within-trial economic evaluation is to be undertaken as a cost-consequence analysis, comparing the costs of the intervention with the primary outcome measures (e.g. cost per change in HbA1c) at 6 months and 12 months timepoints. A modelled economic evaluation is to be undertaken, extrapolating intervention costs and effects and extending the target population, time horizon and decision context. The model will be extrapolated to lifetime to incorporate
<table>
<thead>
<tr>
<th>Component</th>
<th>Data collected</th>
<th>Collected</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Health coaching: participation and selections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Danger zones for sitting</td>
<td>Sessions 1 &amp; 7</td>
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<tr>
<td></td>
<td>Strategies to sit less at work selected by participant (select any number of 12 listed + 2 'other')</td>
<td>Sessions 1–10</td>
</tr>
<tr>
<td></td>
<td>Strategies to sit move more at work selected by participant (select any number 17 listed + 2 'other')</td>
<td>Sessions 1–10</td>
</tr>
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<td>Strategies to sit less across the day selected by participant (select any number 12 listed + 2 'other')</td>
<td>Sessions 1–10</td>
</tr>
<tr>
<td></td>
<td>Strategies to move across the day selected / continued (select any number 8 listed + 2 'other')</td>
<td>Sessions 1–10</td>
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<tr>
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<td>Goal setting - smart goals (sit less across the day, sit less at work, move more at work, move more across the day)</td>
<td>Sessions 1–10</td>
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<td>Stand more at desk goal</td>
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<td>Active breaks goal (encouraged 1 break per hour)</td>
<td>Sessions 1–10</td>
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<td>Daily steps goal</td>
<td>Sessions 1–10</td>
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<td>Readiness level (1–10) to change sitting and moving habits</td>
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<td>Anticipated barriers to goal achievement</td>
<td>Sessions 1–10</td>
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<td>General review of strategies / goals (open text) including barriers, ease/difficulty &amp; modifications</td>
<td>Sessions 2–10</td>
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<td>Number of coaching sessions completed (0–2 face to face; 0–8 telephone)</td>
<td>Sessions 1–10</td>
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<td><strong>OPTIMISE-extended health coaching: participation and selections</strong></td>
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<td>Two danger zones for sitting (1 &amp; 2) selected by coach from 3 listed + other 4</td>
<td>Tailoring session 1 &amp; 2</td>
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<td>One strategy to sit less per danger zone selected by coach from 32 listed + other 4</td>
<td>Tailoring session 1 &amp; 2</td>
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<td>Two strategies to move more (1 &amp; 2) selected by coach from 17 listed and other 4</td>
<td>Tailoring session 1 &amp; 2</td>
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<td>Active breaks goal set by participant (n active breaks/ day, 1–24)</td>
<td>Session 10 &amp; Tailoring 2</td>
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<td></td>
<td>Daily steps goal set by participant (n steps / day, 5000–20,000)</td>
<td>Session 10 &amp; Tailoring 2</td>
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<td>Number of texts sent (total, by week, by type), number of text messages replied to by participants (total, by week), content of participant replies.</td>
<td>propelo</td>
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<tr>
<td><strong>Fitbit (Fitabase)</strong></td>
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<td>Continuous from Session 1 to end of study</td>
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<td>Usage (wear days, non-wear days)</td>
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<td>Physical activity / sedentary behaviour (step counts, estimated energy expenditure, time spent in LPA, MPA, VPA, inactive behaviour), physical activity events autodetected &amp; logged (e.g., 'weights', 'walk')</td>
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<td>Heart rate</td>
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<td>Sleep &amp; sleep quality (Total sleep time duration, duration of each sleep stage, sleep onset latency, sleep efficiency, number and duration of wakes after sleep onset, restless- ness count and durations)</td>
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<td><strong>Intervention fidelity</strong></td>
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<td>Health coaching participation (n sessions completed)</td>
<td>Sessions 1–10</td>
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<td>Extended care participation (n text messages received)</td>
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<td>Fitbit usage (% of days in intervention wore Fitbit)</td>
<td>Fitbit</td>
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<td>Sit-stand workstation in standing position (not used / some days / most days / every day)</td>
<td>OPTIMISE survey 6 M &amp; 12 M</td>
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<td><strong>COVID-19</strong></td>
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<td>Impact of COVID-19 pandemic on ability to participate in OPTIMISE program (0–10), 1 item</td>
<td>OPTIMISE survey 6 M, 12 M &amp; 18 M</td>
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benefits accruing to both T2D and dementia prevention. As 5 years is insufficient to observe outcomes of dementia in a prevention study, the intermediate outcomes of the trial (cognitive function, neurotrophic factors and inflammatory markers) will be incorporated into final outcomes for economic evaluation, e.g., dementia diagnosis, time to dementia.

Incremental health benefits, reported as quality-adjusted life years (QALYs) saved, and incremental healthcare cost offsets attributable to T2D prevention and dementia are reported. The commonly accepted cost-effectiveness threshold of AUD$50,000 per QALY saved will be used to determine cost-effectiveness over the lifetime. Utility is calculated from the Assessment of Quality of Life AQOL-8D using the Australian algorithm [112] and multiplied using the area under the curve method by the time in the trial to derive the QALYs.

Finally, an incremental cost-effectiveness ratio will be determined by calculating the difference in cost between the intervention and usual care, divided by the difference in QALYs between intervention and usual care.

Statistics

Sample size

With an estimated 20% attrition based on our previous intervention trials, 2-tailed significance of 2.5% (correcting for two primary outcomes of the original OPTIMISE protocol), 125 participants per group (250 total) are required for 80% power to detect minimum differences of interest in HbA1c and sitting of 0.5% and 0.5 h/16 h-day, assuming standard deviations (SD) of 1.6 and 1.3 and a pre-post correlation (r) of 0.7 and 0.6 respectively. A 0.5% HbA1c decrease is clinically meaningful corresponding to an approximate 10% reduction in diabetes-related mortality [7]. Assumptions concerning attrition, SD and r for primary and most secondary outcomes were based on Living Well with Diabetes [77], AusDiab [66] and Stand Up Victoria [76] studies. Recruitment projections indicate that a sample of 250 participants is feasible within the allocated timeframe. Recruitment will stop when the trial reaches either the required sample size or the maximum number of participants who can be recruited in the trial’s allotted recruitment timeframe, while complying with the unforeseeable restrictions and conditions related to the COVID-19 pandemic.

The sample size for the cognitive function outcomes are dictated by the original sample size calculations described above. From a sample size of 250, we anticipate 160 participants (80 in each arm) will complete the 12-month assessment. This sample size of 80 per group provides > 80% power (5% 2-tailed significance) to detect our minimum difference of interest in the primary outcome of visual memory (PAL TEA) at 12 months (1/3 SD, d = 0.33) assuming r = 0.7, based on a previous trial [113]. Changes in cognitive function have been detected in a similar sample with 145 participants participating in a 24-week RCT assessing pharmacotherapy to improve metabolic control. Minimum detectable differences will be recalculated if the actual sample size is lower than projected due to the potential impact of the COVID-19 pandemic.
Statistical analyses
Outcomes are all continuous and expected to be either normal or log-normal, in which case log-transformation will be used. Analyses will be performed in STATA version 15 or higher. Significance is set at \( p < 0.05 \) two-tailed (except for \( p < 0.025 \) when testing co-primary outcomes based on \( \alpha = 0.025 \)). To test the differences between groups in primary and secondary outcomes during (3 months), end of the intervention (OPTIMISE; 6 months) and end of the extended maintenance phase (12 months – OPTIMISE-extended) mixed models statistical analysis will be employed, accounting for repeated measures, adjusting for baseline values, randomisation strata, and potential confounders. Within-group changes for intervention participants occurring during the no health coaching contact phase from 12 to 18 months will be tested and compared to intervention phases. Within-group changes will also be tested in the delayed intervention participants receiving the OPTIMISED intervention after 12 months, at the 18 month timepoint, using paired t-tests (or non-parametric paired tests). Possible confounders will be identified a priori from the literature and narrowed down to a number that can be modelled without overfitting, based on an objective criterion not open to manipulation (backwards elimination: retaining age, sex, and \( p < 0.2 \) association with the outcome). Analyses will follow intention-to-treat principles. Sensitivity to handling missing data will be evaluated by comparing results from the main analyses (evaluable case analysis for mixed models; complete-case analysis for t-tests) with alternative methods that are appropriate for different missing data scenarios (e.g., multiple imputation; selection-covariate adjustment). Descriptive statistics will be used to describe the implementation indicators of the different phases of the intervention.

Discussion
Adults with T2D have been shown to engage in higher levels of sedentary behaviour than those with normal glucose metabolism, and many undertake little or no physical activity. Regularly interrupting prolonged sedentary time has been demonstrated to improve cardiometabolic health [18], and increasing physical activity has the potential to improve glycaemic control [114]. Findings from earlier intervention trials have demonstrated the feasibility of reducing sedentary behaviour [115] and have shown modest changes to markers of cardiometabolic health in non-clinical groups [21]. However, no studies have specifically focused on the combination of “sitting less” and “moving more” in the context of type 2 diabetes management.

The Optimise Your Health trial will take advantage of a large sample that is powered to address multiple research questions. There will be an extensive follow-up process at short, medium, and long term with each timepoint encompassing a wide array of phenotyping. A multicomponent intervention will be deployed based on the extensive insights previously obtained from earlier sedentary behaviour interventions, extending to novel behavioural prompts and strategies to promote sitting less and moving more across different behavioural contexts. A modified version of the Optimise Your Health program (OPTIMISED) that is less resource intensive will be implemented and evaluated for feasibility and acceptability. This, in addition to a cost-effectiveness evaluation, will be critical to guiding future wider scale uptake.

Results from the trial will inform whether a sit less and move more intervention is effective in adults with type 2 diabetes. The findings have the potential to inform more prescriptive guidelines and behavioural strategies of benefit in a clinical management context. Overall this study will contribute extensively to the field of sedentary behavior research, build upon existing evidence and provide new insights on the merits of targeting sitting less and moving more as a therapeutic utility to improve health outcomes.

Abbreviations
ApoE4: Apolipoprotein E4; AqoL: Assessment of Quality of Life; AusDiab: Australian Diabetes, Obesity and Lifestyle study; BCW: Behaviour Change Wheel; BDNF: Brain-derived neurotrophic factor; BMI: Body mass index; CANTAB: Cambridge Neuropsychological Test Automated Battery; COM-B: Capability, opportunity, motivation-behaviour; FBE: Full blood examination; HDL: High-density lipoprotein; hs-CRP: High-sensitivity C-reactive protein; IAUC: Incremental area under curve; IGF-1: Insulin-like growth factor 1; IL-1β: Interleukin 1 beta; IL-6: Interleukin 6; LDL: Low-density lipoprotein; Mvpa: Moderate-to-vigorous physical activity; NDSS: National Diabetes Services Scheme; NHMRC: National Health and Medical Research Council; Ogtt: Oral glucose tolerance test; QALY: Quality adjusted life year; RCT: Randomised controlled trial; TNF-α: Tumour necrosis factor alpha.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s12889-022-13123-x.

Additional file 1. Research funding.
Additional file 2. Participant information and consent form.
Additional file 3. Inclusion and exclusion criteria.
Additional file 4. Intervention handbook.
Additional file 5. Example activity feedback report.
Additional file 6. Intervention strategy list.
Additional file 7. Health coaching script.
Additional file 8. COVID-19 Snapshot Questionnaire.
Additional file 9. Questionnaire measures.
Additional file 10. Adverse events report.
Additional file 11. SPIRIT checklist.
Acknowledgements
We wish to thank the study participants. We would also like to thank the National Diabetes Services Scheme (NDSS) for supporting the recruitment of this trial. We are grateful to Elly Fletcher for work on the original development of the trial, Danielle Ostendorf for development of motivation to break up sedentary behaviour questionnaire and support with REDCap instruments, and Laura E. Pernoud for development of the menopause status questionnaire and supporting text in this protocol. Finally, we would like to thank the project staff for their continued dedication and engagement: Melanie Townsend, Francis Dzaprakzu, Kym Rickards, Ashleigh Homer, and Frances Taylor.

Authors’ contributions
Funding for this research was obtained by DD, NO, EE, SJHB, GNH, RMD, DG, MM, EW, NC, PG, LG, TC, BF, MAS. EW is the trial data analyst and developed the statistical analyses plan. PN, MM, TC, LG developed the economic evaluation plan and text section. MB provided input on the device-based measurement section. RG provided extensive support in writing the text. All authors have contributed to the design of the trial. The first draft of this manuscript was produced by CB and all authors have reviewed, edited and approved the final version.

Funding
This project is funded by the National Health and Medical Research Council (NHMRC) with a project grant acquired by the Baker Heart & Diabetes Institute, The University of Queensland, and Deakin University (APP1139974), and a Boosting Dementia project grant acquired by The University of Southern Queensland, Baker Heart and Diabetes Institute, The University of Queensland, and The University of Sunshine Coast (APP1171759). An additional grant from the Diabetes Australia Research Foundation in 2020, acquired by The University of Queensland, Baker Heart and Diabetes Institute, and The University of Southern Queensland. Healy is funded by an MRFF Emerging Leadership Fellowship (APP1193815). Additional project funding is provided by the Victorian Government’s Operational Infrastructure Support program.

Availability of data and materials
Availability of the data from the OPTIMISE Your Health trial is subject to the approval of a formal application made to chief investigators on the project.

Declarations
Ethics approval and consent to participate
Ethics approval was granted by Alfred Health Human Ethics Committee (Melbourne, Australia), The University of Queensland Institutional Human Research Ethics Committee (Brisbane, Australia), and University of the Sunshine Coast Human Research Ethics Committee (Sunshine Coast, Australia). Trial progress reports are sent to Alfred Health Human Ethics Committee for ethics approval on an annual basis and the acknowledgement is provided to the other ethics committees. All participants provide written consent to participate in the trial.

Consent for publication
Not applicable.

Competing interests
No competing interests to disclose.

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Received: 14 March 2022   Accepted: 16 March 2022

Published online: 10 May 2022

References


Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.
5.3 Summary and implications of the findings

This paper describes the methods and protocol of the OPTIMISE Your Health trial, which was a major feature of the PhD candidature. The trial primarily aims to determine the effectiveness of a multicomponent sedentary behaviour intervention to improve glycaemic control (HbA1c) in desk workers with type 2 diabetes. Numerous secondary outcomes are tested in this study, not limited to cognitive function, vascular health, lipids, body composition, sleep, anthropometry, quality of life, and diabetes distress which in turn will provide further insights into the effect of the intervention on the management of type 2 diabetes. Extensive process evaluation is planned, including identifying the potential mediators responsible for instigating change. Economic evaluation is also planned for each of the phases of the trial, which will identify whether the intervention (intervention, or delayed intervention) constitutes as value for money to the public. An abbreviated version of the intervention is also planned, which is provided to control participants. This version of the intervention will be evaluated for its potential for public uptake, and delivery by health care providers in the community, and therefore translation of the findings. Published findings are expected on an array of outcome measures into the future.

With the onset of the COVID-19 pandemic and immediate suspension and delay of the trial, it became apparent that the trial was unable to be completed during the timeline of the PhD candidature (including reporting the baseline findings as originally proposed). However, this did provide its own unique research opportunity. By pursuing new investigations, it was possible to take advantage of a convenience sample of early participants enrolled in the OPTIMISE trial both before and during the COVID-19 pandemic restrictions in 2020.

In Chapter 6, data from the Fitbit wrist-worn fitness tracker were used as an exploratory outcome measure to examine how physical activity and sedentary behaviours changed during the COVID-19 lockdown restrictions in the OPTIMISE trial.
Chapter 6: The associations of COVID-19 lockdown restrictions with long-term Fitbit-assessed activity levels of working adults with type 2 diabetes: cohort study

6.1 Introduction

Wrist-worn fitness trackers are increasingly being adopted in behaviour change research and the public alike to promote and support health behaviour change. In a research context, providing a Fitbit has demonstrated efficacy with improving health behaviours such as step counts, and is even more potent with the co-provision of face-to-face health consultation (187). This suggests the devices have potential for wider health care adoption. However, up until recently wrist-worn trackers have been unable to collect meaningful and valid physical activity and sedentary behaviour data, nor have they provided reliable ways for this data to be collected.

In the OPTIMISE Your Health trial, participants were provided with a Fitbit tracker for the purpose of increasing their daily steps to a target of 10,000 steps per day, and to break up sitting regularly with prompts from Fitbit’s active break reminder that would remind them to attain at least 250 steps per hour. These behaviours were monitored by the researchers in real-time using the proprietary Fitabase data collection software service, and this data was used to help guide health coaching sessions. Noting the resolution and scale of data collection possible with this software, the research team originally conceived using the Fitbit data as an exploratory outcome measure, and potentially for interpreting intervention adherence longer term in the OPTIMISE Your Health trial, with comparisons to the activPAL thigh worn monitor. However, in less than a year since commencement, the trial was suspended due to the COVID-19 pandemic. The pandemic and associated lockdown restriction countermeasures caused significant life disruption to the OPTIMISE participants, which warranted observation.

The fourth paper of this thesis, presented here in Chapter 6 section 6.2, investigates the longer-term changes in physical activity and sedentary behaviours in participants in the OPTIMSE Your Health study (described in detail in Chapter 5). Participants were community dwelling adults in
Melbourne, Australia with type 2 diabetes. Further summary and implications of the manuscript are presented in section 6.2.

6.2 Manuscript
This manuscript was published in the peer-reviewed Journal of Medical Internet Research Diabetes (JMIR Diabetes) in May 2022. Description and extent of contributions are detailed in Appendix A. Supplementary materials are listed in Appendix E and accessible through https://doi.org/10.2196/36181. This manuscript was published and can be reproduced under the terms of Creative Commons Attribution license 4.0

Citation:
The Associations of COVID-19 Lockdown Restrictions With Longer-Term Activity Levels of Working Adults With Type 2 Diabetes: Cohort Study

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Abstract

Background: Lockdown restrictions reduce COVID-19 community transmission; however, they may pose challenges for noncommunicable disease management. A 112-day hard lockdown in Victoria, Australia (commencing March 23, 2020) coincided with an intervention trial of reducing and breaking up sitting time in desk workers with type 2 diabetes who were using a provided consumer-grade activity tracker (Fitbit).

Objective: This study aims to compare continuously recorded activity levels preceding and during COVID-19 lockdown restrictions among working adults with type 2 diabetes participating in a sitting less and moving more intervention.

Methods: A total of 11 participants (n=8 male; mean age 52.8, SD 5 years) in Melbourne, Australia had Fitbit activity tracked before (mean 122.7, SD 47.9 days) and during (mean 99.7, SD 62.5 days) citywide COVID-19 lockdown restrictions. Regression models compared device (Fitbit Inspire HR)–derived activity (steps; metabolic equivalent tasks [METs]; mean time in sedentary, lightly, fairly, and very active minutes; and usual bout durations) during restrictions to prerestrictions. Changes in activity were statistically significant when estimates (\(\Delta\%\)) did not intercept zero.

Results: Overall, there was a decrease in mean steps (–1584 steps/day; \(\Delta\% –9\%, 95\% \text{CI} –11\% \text{ to} –7\%\)); METs (–83 METs/day; \(\Delta\% –5\%, 95\% \text{CI} –6\% \text{ to} –5\%\)); and lightly active (\(\Delta\% –4\%, 95\% \text{CI} –8\% \text{ to} –1\%\)), fairly active (\(\Delta\% –8\%, 95\% \text{CI} –21\% \text{ to} –15\%\)), and very active (\(\Delta\% –8\%, 95\% \text{CI} –11\% \text{ to} –5\%\)) intensity minutes per day, and increases in mean sedentary minutes per day (51 mins/day; \(\Delta\% 3\%, 95\% \text{CI} 1\% \text{ to} 6\%\)). Only very active (+5.1 mins) and sedentary (+4.3 mins) bout durations changed significantly.

Conclusions: In a convenience sample of adults with type 2 diabetes, COVID-19 lockdown restrictions were associated with decreases in overall activity levels and increases in very active and sedentary bout durations. A Fitbit monitor provided meaningful continuous long-term data in this context.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12618001159246; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12618001159246

(JMIR Diabetes 2022;7(2):e36181) doi: 10.2196/36181
KEYWORDS
COVID-19; Fitbit; activity; sedentary behavior; type 2 diabetes; digital health; pandemic; physical activity; wearable; health technology

Introduction
The COVID-19 pandemic continues to have a lasting impact on the health care system [1,2]; as of December 2021, there have been 270 million confirmed cases since the pandemic began [3]. Type 2 diabetes mellitus is prevalent in patients admitted to hospitals with COVID-19 [4,5], with rates as high as 33.8% [6]. Poorer glycemic control can also be a predictor of COVID-19 mortality [7,8]. Regular physical activity is recognized as a cornerstone of diabetes management and glycemic control [9]. However, there is now evidence that some of the public health measures used to contain the spread of the virus, including restriction of movement via community-level lockdowns, may have impacted physical activity levels [10]. Specifically, there is evidence of pandemic-associated decreases in overall physical activity [11,12] and decreases in activity of different intensities (ie, light, moderate, and vigorous) [13,14], along with an increase in sedentary time [15]. For example, a study using hip-worn accelerometers found that sedentary behavior time and prolonged sedentary bouts increased and total daily steps decreased during lockdowns [16]. Collectively, these findings suggest that COVID-19 lockdown restrictions are likely to adversely impact a set of lifestyle behaviors important to the management of type 2 diabetes; however, the relevant evidence has some limitations. Most of these studies have used self-report measures of activity [17-19] with many involving cross-sectional designs [15,20] or using retrospective data collection [12,21]—design types that are prone to recall and reporting biases. In those studies where devices were used (eg, body-worn accelerometers), short time frames (7-8 days) were observed [16,22], which limits the opportunity to understand long-term trends. Aside from a few studies [23-26], most investigations have featured short or singular time frames of observation and, importantly, have not measured activity behaviors both immediately before and at the point of a COVID-19 outbreak. Furthermore, despite being recognized as a population at greater risk of the health impacts of COVID-19, no studies have featured short or singular time frames of observation and, importantly, have not measured activity behaviors both immediately before and at the point of a COVID-19 outbreak. Furthermore, despite being recognized as a population at greater risk of the health impacts of COVID-19, no studies have assessed physical activity with continuously worn devices prior to and during COVID-19 in people with type 2 diabetes.

Prolonged and restrictive lockdown conditions imposed on residents living in Melbourne, Australia coincided with the conduct of a clinical trial in working adults with type 2 diabetes (ANZCTR12618001159246), targeting both reductions in sedentary time and increases in physical activity. With one of the intervention components requiring participants to use a wrist-worn activity tracker throughout, this presented an opportunity to ascertain the impact of lockdown on these trial participants.

This exploratory study uses data from a wrist-worn consumer device (Fitbit) to describe and compare activity levels of working adults with type 2 diabetes participating in a behavior change intervention trial prior to and during a prolonged citywide lockdown due to COVID-19.

Methods
Participants and Setting
Participants were from the intervention arm of the OPTIMISE Your Health trial [27]. This trial, which began in 2019, aims to both reduce sedentary behavior (sit less) and increase movement (move more) in desk workers with type 2 diabetes aged 35 to 65 years [28]. Eligibility is based on having been diagnosed with type 2 diabetes (confirmed with recent hemoglobin A\(_1c\) [HbA\(_1c\)] test), not being on insulin therapy, working in a desk-based occupation (0.8-1 full-time equivalent), high sedentary time (>50% of waking hours), not meeting physical activity guidelines (ie, doing <150 min of moderate-vigorous physical activity/week and <2 strength sessions/week), and living within a 40 kilometer radius of the Baker Heart and Diabetes Institute (Melbourne, Australia). Participants were randomized following baseline assessments into control or intervention arms. Those in the intervention arm received a height-adjustable desk, a Fitbit Inspire HR wrist-worn fitness tracker, and behavior change health coaching support, as described in detail elsewhere [27]. In brief, the health coaching involved participants setting incremental goals to reduce sitting and increase physical activity, which was facilitated by behavioral strategies that encouraged self-management (eg, standing up after a work task or taking a light walk after finishing a meal). A convenience sample of 11 intervention-arm participants who wore the Fitbit both prior to and during the lockdown restriction periods were included in this study. Participants were recruited sequentially into the broader trial, hence Fitbit observation windows differed for each participant.

Ethical Considerations
Protocols and ethics were approved by the Alfred Health Ethics Committee (#359/18), and all participants provided written informed consent.

Data Collection
The baseline assessment included demographic questions, anthropometric measures (height, weight), and a fasting blood glucose examination. Two weeks following baseline assessment, participants were provided with their Fitbit Inspire HR device, which they were encouraged to wear as often as possible to promote and maintain physical activity behaviors. Participants were not required to wear the Fitbit while sleeping; therefore, sleep was not investigated. Participants consented to give access to their Fitbit activity (recorded on the study account) via Fitabase (Small Steps Labs LLC), a third party web-based data management platform. Each participant was set up with a unique Fitabase study account linked to their Fitbit device and associated smartphone app. All data synchronized from the wearable device to the Fitbit app was uploaded to Fitabase automatically where it could then be exported into date- and time-stamped minute intervals for the time period from August.
COVID-19 Lockdown in Melbourne, Australia

The first COVID-19 lockdown restrictions in Melbourne, Australia commenced on March 23, 2020, and were eased intermittently, then reinstated, and not lifted until October 18, 2020. During this time, Australia was ranked as having one of the strictest pandemic mitigation strategies in the world, reaching a high of 80 in a 1 to 100 stringency scale in March 2020 [29]. Of all Australian cities, Melbourne had the strictest lockdown during this time due to high rates of transmission and the state government’s intention for complete elimination of community transmission of the virus. Varying restrictions were imposed in Melbourne throughout the period of observation; these are described in greater detail in Multimedia Appendix 1. The lockdown restrictions led to the OPTIMISE Your Health trial being placed on temporary hold. This entailed the suspension of recruitment and clinical assessment visits. Following this, participants were sent a survey via email with a series of questionnaires enquiring about any changes incurred due to the pandemic. The questions pertained to changes in work hours; work location; sitting, standing, and activity behaviors at work; workload; care load; physical activity and exercise; sedentary behavior; motivation; work environment; and musculoskeletal health. Enrolled participants who were involved in the trial during the lockdown period were encouraged to complete their participation to the end of the original trial date (6 months).

Fitbit-Derived Activity Metrics

The Fitbit Inspire HR is a wrist-worn, triaxial accelerometer. The device also uses photoplethysmography, which measures heart rate with infrared light through the skin. The device is powered by a lithium polymer battery with an average battery life of 5 days depending on use. A proprietary algorithm converts the raw acceleration signal from the tracker into step counts and activity intensity. Each minute interval is categorized as sedentary (<1.5 metabolic equivalent tasks [METs] according to Fitbit), lightly active (1.5-3 METs), fairly active (3-6 METs), or very active (>6 METs or ≥145 steps/min in at least 10 min bouts) according to Fitbit’s determination of METs [30]. Data were collected continuously by the wrist-worn tracker for 30 days, at which point the device must be synchronized via Bluetooth with a smartphone and the Fitbit app. For the OPTIMISE Your Health trial, the provision of the Fitbit allowed participants to monitor their activity behaviors on the device and the smartphone app. Participants were encouraged to self-select daily stepping goals and activity break reminders (up to 14 per day) that prompted them to achieve 250 steps in each hour of the day.

A recent validation study determined that the Fitbit Charge 2, an older model, demonstrated high correlation (intraclass correlation coefficient >0.89) with an established research-grade accelerometer (Actigraph GT1X) in free-living observations [31]. In that study, correlations between the Fitbit Flex and GT3X+ data were high for sedentary time (r=0.9) but weaker and overestimated for moderate-vigorous intensity physical activity (r=0.65-0.76) [32]. A systematic review in 2016 featuring analysis of 13 studies examining the accuracy of Fitbit in free-living conditions determined that the Fitbit had a tendency to overestimate steps (700-1800 steps/day) compared to research-grade devices [33]. There is currently no validation study published for the Fitbit Inspire HR used in this trial.

Statistical Analyses

For each study participant, the following data was downloaded via Fitabase for the entire wear period: daily steps, METs, heart rates, and estimated daily sleeping time (if available). Steps, METs, and heart rate data are available in 1-minute resolutions, and the associated time stamps are available for all variables. Prior to analyses, all data where the time stamps matched at least one of these criteria were removed: corresponded to time intervals detected as sleeping time by Fitbit, was between midnight and 5 AM daily, and time stamped with a heart rate reported as 0. The first two criteria were used to remove segments that correspond to sleeping time, and the third was used to remove segments when the Fitbit was not worn. This defined the daily waking period. The remaining data were analyzed with models fitted for each participant, separately for METs per minute, the intensity minute categories (sedentary, lightly active, fairly active, very active intensity mins), and step counts. For METs-based analysis, data were analyzed at 1-minute resolution with the logarithm of each day determined as a METs per day–dependent variable. For the intensity-based analyses, the log average number of minutes spent in each intensity category was used as the dependent variable. For steps-based analysis, the logarithm of the daily number of steps was used as the dependent variable. These dependent variables were log transformed to improve the normality of residuals in the model and to ensure nonnegative predicted values following back transformation. The usual bout duration, also known as the weighted median statistic (w50 or x50), was calculated for all activity intensities according to a previously devised method [34]. This entailed all bouts being ordered according to bout duration (mins) and normalized as a proportion of total time spent in each activity intensity type. Participants accumulated half of all their activity time in bouts longer than their usual bout duration.

We used fixed-effect meta-analysis to combine the regression coefficient with lockdown effects into a pooled result for all participants. The METs per minute and intensity minutes models were fitted using generalized least squares regression with autoregressive error structure to handle within-individual autocorrelation. Step counts were fitted with negative binomial regression methods. For all models, the main independent variable was the lockdown time indicator. This indicator included two states: before lockdown (before March 23) or during lockdown (on or after March 23). Independent variables were also added to adjust for differences in Fitbit wear habits that may have occurred following lockdown restrictions: these were calculated as sin(2πt/24) and cos(2πt/24), where t was the time stamp in a 24-hour continuous time format, and the interaction between lockdown time indicator and sin and cosine terms was modeled. To determine the average absolute change following restrictions, steps and METs were transformed from hour and minute intervals to per day for ease of interpretation.
For all analyses, the main parameter of interest was the antilog of the regression coefficient associated with the lockdown variable; this was interpreted as relative rates, with the prelockdown period considered the reference. Relative rates were then transformed into percentages (Δ%). A statistically significant difference between the lockdown period and the prelockdown period was determined when Δ% did not intercept zero.

A postpower calculation was performed using the R Package “PASSED” version 1.2.1 [35] for daily step count. For this analysis, it was assumed that steps per day followed a negative binomial distribution with the distribution statistic (theta) set at 5. Given a mean daily step count of 10,000 steps prelockdown restrictions and a minimum of 100 days prelockdown and 100 days following lockdown restrictions, there was at least 80% power to detect a 10% or more reduction in step count for 11 participants.

**Results**

**Sample Characteristics and Period of Observation With Fitbit in the COVID-19 Pandemic**

The mean age of the 11 participants was 52.8 (SD 5) years, and the majority were male (n=8, 73%). In line with the trial inclusion criteria, participants were overweight/obese (mean BMI 35.2, SD 5.1 kg/m²), with a mean HbA1c of 7.6% (SD 0.8%) at the commencement of their trial participation. A timeline of stage 2, 3, and 4 COVID-19 lockdown restrictions that entailed stay-at-home orders are summarized with novel case data for the state of Victoria (capital city: Melbourne) in Figure 1. According to questionnaire findings (Multimedia Appendix 2), following the imposed restrictions, participants (n=9) reported a shift toward working from home more, a less desirable workplace environment, and reductions in physical activity and exercise participation. None of the participants reported having a COVID-19 infection or having to self-isolate as a close contact during the period of observation. Timelines of Fitbit data collection were reported for each participant. A total of 2447 wear days were recorded across the 11 participants with a median of 197 (range 167-418) days per participant. All participants had substantial periods of observation prior to (mean 122.7, SD 47.9 days) and during the lockdowns (mean 99.7, SD 62.5 days).

**Comparison of Activity Minutes Identified by the Fitbit During and Prior to Lockdown**

In the overall pooled-analysis of the participants’ activity levels (Table 1), it was determined that both steps (absolute change –1584; Δ% –9%, 95% CI –11% to –7%) and METs per day (absolute change –83; Δ% –6%, 95% CI –6% to –6%) decreased under lockdown restrictions compared with prerestriction levels. Lightly active minutes (absolute change –11 mins; Δ% –4%, 95% CI –8% to –1%) and fairly active minutes (absolute change –3 mins; Δ% –18%, 95% CI –21% to –15%) decreased following the restrictions, and there was a gain to sedentary minutes (absolute change 51 mins; Δ% 3%, 95% CI 1%–6%). Minutes of very active intensity decreased (absolute change –5
mins; Δ% −8%, 95% CI −11% to −5%); however, the usual bout duration of the very active bouts increased (absolute change 5.1 mins; Δ% 25%, 95% CI 4%−49%). Usual sedentary bout duration also increased (absolute change 4.3 mins; Δ% 20%, 95% CI 16%−25%). There were minimal changes to lightly active and fairly active intensity usual bout durations following restrictions, with estimates not reaching statistical significance.

In the individual participant analysis (Multimedia Appendix 3), there was evident heterogeneity in the participants’ responses to lockdown restrictions. Considering the 11 participants individually, 4 increased their mean daily step counts with 2 of these participants also increasing their METs. The increases made to activity levels by these participants were outweighed by the remaining sample that saw a decrease in activity for steps (mean increase 575 steps; mean decrease 2760 steps) and for METs (mean increase 43 METs; mean decrease 144 METs). Discrepancies between changes in step counts and energy expenditure occurred due to differing engagement in activity intensities following the restrictions. Of all participants, 3 increased lightly active intensity minutes, 4 increased fairly active intensity minutes, 5 increased very active intensity minutes, and 5 decreased sedentary minutes per day. The most consistent changes at the individual level were increases to usual sedentary bout durations with 10 participants (9 statistically significant) increasing their volume of time spent in sedentary bouts. Similarly, 7 participants increased usual very active intensity bout durations, although only 2 had statistically significant within-individual changes. The individual responses to the lockdown restrictions are depicted in the Figure 2 heat map visualizations for each participant.

Table 1. Activity conducted during lockdown restrictions compared to activity conducted prior to lockdown restrictions.

<table>
<thead>
<tr>
<th></th>
<th>Overall pooled estimates</th>
<th>Prior to lockdown restrictions, mean (SD)</th>
<th>During lockdown restrictions, mean (SD)</th>
<th>Difference</th>
<th>Δ% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall activity per day</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Steps (n/day)</td>
<td></td>
<td>10,623 (4439)</td>
<td>9039 (3351)</td>
<td>−1584</td>
<td>−9 (−11 to −7)</td>
</tr>
<tr>
<td>METs (n/day)</td>
<td></td>
<td>1940 (264)</td>
<td>1857 (173)</td>
<td>−83</td>
<td>−5 (−6 to −5)</td>
</tr>
<tr>
<td>Lightly active intensity (mins/day)</td>
<td></td>
<td>251 (6)</td>
<td>240 (6)</td>
<td>−11</td>
<td>−4 (−8 to −1)</td>
</tr>
<tr>
<td>Fairly active intensity (mins/day)</td>
<td></td>
<td>16 (0)</td>
<td>13 (1)</td>
<td>−3</td>
<td>−18 (−21 to −15)</td>
</tr>
<tr>
<td>Very active intensity (mins/day)</td>
<td></td>
<td>32 (1)</td>
<td>27 (2)</td>
<td>−5</td>
<td>−8 (−11 to −5)</td>
</tr>
<tr>
<td>Sedentary (mins/day)</td>
<td></td>
<td>1064 (25)</td>
<td>1115 (36)</td>
<td>51</td>
<td>3 (1 to 6)</td>
</tr>
<tr>
<td><strong>Usual bout duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lightly active intensity (mins)</td>
<td></td>
<td>4.4 (0.5)</td>
<td>4.5 (0.9)</td>
<td>0.1</td>
<td>1 (−4 to 7)</td>
</tr>
<tr>
<td>Fairly active intensity (mins)</td>
<td></td>
<td>2.7 (0.6)</td>
<td>2.5 (0.7)</td>
<td>−0.2</td>
<td>−7 (−19 to 6)</td>
</tr>
<tr>
<td>Very active intensity (mins)</td>
<td></td>
<td>15.7 (20.2)</td>
<td>20.8 (25.7)</td>
<td>5.1</td>
<td>25 (4 to 49)</td>
</tr>
<tr>
<td>Sedentary (mins)</td>
<td></td>
<td>20.2 (6)</td>
<td>24.5 (7.6)</td>
<td>4.3</td>
<td>20 (16 to 25)</td>
</tr>
</tbody>
</table>

Δ%: change in activity following pandemic lockdown restrictions.
MET: metabolic equivalent task.
Usual bout duration describes the median weighted bout length; participants accumulate half of all their activity time in bouts longer than the estimate.
Discussion

Principal Findings

Participants with type 2 diabetes involved in an intervention targeting sitting less and moving more wore a consumer-grade activity-monitoring device (Fitbit Inspire HR) that identified overall decreases in active time and increases in sedentary time following COVID-19 lockdown restrictions. These changes were characterized by a decrease in time spent in lightly active, fairly active, and very active physical activity intensities, and an increase to time spent sedentary. Combined, these behavioral changes would be expected to have adverse implications for glycemic control and diabetes management.

Findings from this study corroborate current evidence on changes to physical activity associated with the COVID-19 pandemic [10] and confirm findings published online by Fitbit in early 2020 [37]. They also align with observations that those who are overweight or obese were also likely to have their physical activity levels adversely affected by the pandemic [23]. In Spain, a study of 72 patients with diabetes self-reported a significant decline in their weekly walking time during lockdown restrictions [38]. Examining data from a cohort similar
to those in our study, a recent study [39] featuring people with type 2 diabetes living in Melbourne, Australia found that self-reported total physical activity did not change, but incidental walking decreased. For this study, less incidental activity could have contributed to the observed prolonging of sedentary bouts. This could be due to a number of reasons such as minimizing movement to reduce chance of transmission in the community [40], anxiety leaving the house [41], a reduction in physically active commuting [42], and widespread changes to permitted activities in the neighborhood environment [43]. It has previously been reported that fitness-oriented walking was surmised to have increased due to it being designated as one of the permissible reasons to leave home during restrictions [39]. More purposeful fitness-based walking may have explained the slight increase in very active intensity bout duration found in our Fitbit analysis. However, the modest increases to average time spent in very active intensity bouts were not sufficient to counter the overall decline in total activity in the pooled analyses.

Comparison With Prior Work and Implications for Future Research

In the context of a continuing pandemic that may involve future restrictions, we have identified the need to proactively address sedentary behavior reduction and the promotion of increased physical activity (even light-intensity physical activity) in people with type 2 diabetes [44]. The overall decline in step counts observed in this study have potential implications for health outcomes. Based on previous observational research findings, a reduction of 500 steps per day in inactive people is associated with an approximate 2% to 9% increased risk of cardiovascular morbidity and all-cause mortality, and is associated with a 5% increase in all-cause mortality risk when measured by wrist-worn devices [45]. These extrapolations are important for people with type 2 diabetes who are already at heightened risk of cardiovascular disease and morbidity [46]. Conversely, maintaining physical activity levels is associated with a lower susceptibility to viral infections such as COVID-19 [47], improved vaccine efficacy [48], and reduced odds of hospitalization with severe COVID-19 outcomes [49]. Therefore, during public health crises like a pandemic, physical activity levels should be monitored to inform policy that strikes a balance between disease mitigation and the maintenance of physical activity participation in the community [50].

Here, we used a Fitbit device to evaluate the effects of COVID-19 restrictions, with the overall findings indicating a decline in activity levels largely corroborated by other recent evidence. It should, however, be acknowledged that some people within this analysis succeeded in either increasing their activity or decreasing sedentary time despite the lockdown restrictions. For example, the heat map visualizations in Figure 2 illustrate that both ID6 and ID11 increased their very active intensity bout lengths when they engaged in them, while ID10 spent less time in unbroken sedentary bouts that contributed to the preservation of their activity levels. For ID7, there was a significant increase in time spent in lightly active intensities and an increase in lightly active bout durations following the restrictions. While the findings overall indicate a negative impact of the lockdown restrictions, understanding how some participants maintained or improved their activity levels may inform intervention approaches and recommendations for subsequent lockdown restrictions and preventative measures.

Beyond the pandemic, there is potential for consumer-grade devices to be used for measurement in research studies [51], especially considering their ubiquity in society and constant technological advancement. Importantly, these devices can capture physical activity data over longer periods of time than those achieved by traditional research-grade activity monitors that typically measure 7 to 14 days of data. However, consumer-grade devices need to be validated against measures derived from traditional research-grade monitors, and comparisons made between short-term and longer-term periods of physical activity measurement. There is the potential for consumer-grade devices to be used in determining physical activity adherence and the effects of interventions (eg, following physical activity or dietary intervention) or to investigate longer periods of activity and the relevance to long-term factors of diabetes management such as glycated hemoglobin, adiposity, or diabetes complications. Consumer-grade continuous measurement devices have already been used to prompt behavior change and improve glycemic control [52], and there may be added benefit through combining their use with continuous glucose monitors.

Strengths and Limitations

This is one of only a few studies [23,53] that has used a continuous objective measure of physical activity to determine activity levels prior to and during the COVID-19 pandemic lockdown restrictions and the first to use this methodology in a sample of patients with type 2 diabetes. Using a Fitbit wrist-worn activity tracker, over 2000 wear days were recorded measuring physical activity continuously via accelerometry and heart rate, collected at 1-minute intervals. A wrist-worn device permitted enhanced capturing of physical activity levels when compared to a smartphone app, especially when confined to the home setting. With regression modeling, we were able to investigate the prospective associations of lockdown restrictions on activity levels.

Although we used an advanced method of analysis with high-resolution data with hundreds of wear days per person, we were limited by a small sample size, thus the findings are exploratory. Further participant recruitment was not feasible with pandemic restrictions, and it was necessary to restrict the selection of participants to a period in which they were exposed to comparable lockdown measures. Therefore an a priori power analysis to estimate necessary sample size was not pragmatic. The findings may have limited generalizability to the broader population of adults with type 2 diabetes. For instance, our participants were involved in an intervention trial in which they received coaching and tools to increase activity and reduce sedentary behavior, which became suspended because of restrictions. As the control group was not provided a Fitbit, the influence of the intervention could not be differentiated. One possibility is that the intervention could have provided protection from even further declines in activity level. Nevertheless, the observation that most of these intervention participants did not manage to keep their current activity levels may illustrate the...
substantial impact of the lockdown restrictions. All participants had type 2 diabetes, and while having relatively good management, evidenced by their levels of glycemic control, they had low baseline levels of physical activity that may have predisposed them to have greater changes induced by the restrictions. Another consideration is that, compared to other cities and countries, Melbourne and Australia had stringent lockdown restrictions. This means that these findings may not apply to other jurisdictions with less severe restrictions. Finally, the Fitbit is uniquely able to characterize longer-term physical activity; however, the model (Inspire HR) that we used does not have a validation study supporting it. Future studies are now required to corroborate these findings with research-grade measures and to better understand the potential for Fitbit to characterize physical activity over long observation periods.

Conclusions
For participants with type 2 diabetes enrolled in an intervention trial to reduce sitting time and increase daily physical activity, the COVID-19 pandemic and subsequent lockdown restrictions led to a decrease in steps; METs; and lightly active, fairly active, and very active physical activity intensities, and an increase in time spent in very active and sedentary bout durations overall; however, there was wide individual variation. Data from the wrist-worn Fitbit consumer device provided interpretable long-term activity data to be able to examine these activity patterns. Further corroboration using concurrent data from research-grade measures is required.

Acknowledgments
We acknowledge and thank all OPTIMISE Your Health study project staff for collecting data and ensuring continued progress of the study. We would like to thank the project staff and trial participants for continuing with the study during a global pandemic. Results from this study are from a trial currently in progress. The trial (OPTIMISE Your Health) was funded by the National Health and Medical Research Centre with a project grant acquired by the Baker Heart and Diabetes Institute, The University of Queensland, and Deakin University (APP1139974), and a boosting dementia project grant acquired by the Baker Heart and Diabetes Institute, The University of Queensland, and The University of Sunshine Coast (APP1171759). An additional grant was also acquired with the Diabetes Australia Research Foundation in 2020.

Authors’ Contributions
CJB conducted the analysis, wrote the manuscript, recruited participants, and devised the original study design. AS devised the statistical modeling and advised on the writing of the statistical analyses section. RG and KR recruited participants and advised on the writing and editing of the manuscript. AC, GNH, NO, and DWD were involved in the conception of the study design, advised on the analyses, and edited the manuscript.

Conflicts of Interest
None declared.

Multimedia Appendix 1
[DOCX File, 19 KB-Multimedia Appendix 1]

Multimedia Appendix 2
Self-reported changes in work, physical activity, sedentary behaviour, motivation, and musculoskeletal discomfort following COVID-19 pandemic lockdown restrictions.
[DOCX File, 136 KB-Multimedia Appendix 2]

Multimedia Appendix 3
Linear regression activity comparisons prior to lockdown restrictions and during for each participant.
[DOCX File, 35 KB-Multimedia Appendix 3]

References


Abbreviations

HbA1c: hemoglobin A1c
MET: metabolic equivalent task
6.3 Summary and implications of the findings

The COVID-19 pandemic placed considerable impact and disruption to the population of Victoria, Australia and the OPTIMISE trial, which was originally conceived to contribute more content to this thesis. Beyond the interruption and temporary suspension of the trial, the pandemic itself led to significant lifestyle changes. In this investigation, a major contributor to these changes were the government-mandated restrictions which led to more participants working from home. These mandates were successful in reducing community transmission of the virus, however simultaneously had implications for modifiable lifestyle factors such as physical activity and sedentary behaviour. Not only was the intervention trial suspended temporarily, but as it resumed with reducing community transmission, lifestyle circumstances had already changed, leading to adaptations to the OPTIMISE trial (Chapter 5), not limited to more remotely conducted assessments and health coaching delivery. The pandemic and restrictions may have unique implications for this trial as it focuses specifically on the behavioural goals of sitting less and moving more. This investigation with Fitbits allowed us to better understand some of these long-term changes induced by the pandemic. Following the onset of restrictions on March 23rd, 2020, participants were more likely to decrease their step counts, decrease activity levels (and energy expenditure), decrease active intensity behaviours (Fitbit derived activity intensities: lightly active, fairly active, and very active minutes), and increase time spent in usual sedentary behaviour bouts, suggesting more prolonged sedentary behaviour episodes throughout the day. Whilst very active minutes declined following restrictions, the usual bout length of these activities increased, which may have suggested a shift from incidental activity to more purposeful exercise following restrictions. This may have been because one of the permissible reasons to leave the house was for exercise in the community.

With both the OPTIMISE trial and the COVID-19 pandemic continuing for the foreseeable future, these findings may have direct implications on the progress of the intervention described in Chapter 5. Increased sedentary time, and decreased incidental activity, and an overall decline in activity levels likely will correspond to lower intervention adherence and worsened glycaemic control and cardiometabolic health, which are relevant to people at risk.
and with type 2 diabetes. Whilst not studied directly in this thesis, sedentary and activity bout length are known to have distinct implications for cardiometabolic health, even in some instances when adjusting for total sedentary time (188).

The pandemic restrictions have likely become a new barrier to sedentary behaviour reduction and sedentary behaviour countermeasures. With the possibility of future pandemic restrictions, governments should take heed of public health initiatives and their holistic effect on health, beyond infectious disease transmission reduction. Surveillance of physical activity and sedentary behaviour could be used to inform this policy, aiming to strike a balance between disease mitigation and the maintenance of healthy lifestyle behaviours in the community. This is especially relevant when physical activity is an effective countermeasure against viral infections, and for type 2 diabetes glycaemic control is correlated with severity of outcome with COVID-19.

Future research should explore the potential for wrist-worn consumer grade devices to measure longer-term activity levels. These trackers could be used to enhance lifestyle behaviour change in clinical settings, and to examine longer-term engagement with physical activity and sedentary behaviour mitigation and the associations with disease related outcomes. The data from wrist-worn trackers, which are ubiquitous in society, could also be harnessed by governments to provide dynamic insights into physical activity and sedentary behaviour levels in the population and ultimately informing public health policy (189).
Chapter 7: Discussion

This chapter synthesises the findings from the four studies presented in this thesis, expands on their collective relevance to the field, and elaborates on their strengths, limitations, and clinical and public health implications. The chapter concludes with identification of directions for future research.

7.1 Overview of the key findings and relevance to available evidence

Key contributions of the research presented in this thesis to the literature include:

1) The examination of a daily activity time-use composition found that higher stepping time and lower sitting time in a 24hr day is most beneficial for glycaemic control (Chapter 3). Findings also suggested that, for some risk markers, high volumes of standing can compensate for lower stepping time (Chapter 4).

2) Curvilinear relationships were identified, where higher daily sitting time was associated with adverse glycaemic control and related cardiometabolic risk levels and to a greater degree than the beneficial associations estimated for compositions higher in stepping time (Chapters 3 and 4). Further, balancing sedentary time with standing or stepping had a progressively beneficial relationship up until a certain level, suggesting that there may be a potential upper limit of benefit for sedentary behaviour reduction interventions (Chapter 4).

3) Differential relationships by level of glycaemic control and diabetes status were identified, where modifications to sitting, standing, and stepping time-use may play a greater role in cardiometabolic health and glycaemic control in people at risk of, and with type 2 diabetes (Chapters 3 and 4).

4) An account was provided of an intervention and associated evaluation protocol to support working adults with type 2 diabetes to sit less and move more (Chapter 5).

5) Evidence was reported from the use of a Fitbit tracker to observe longer-term daily activity patterns both pre- and post- restrictions imposed due to the COVID-19 pandemic in desk workers with type 2 diabetes. It was found that, on average, sedentary levels increased and physical activity levels decreased; however, there was considerable
individual variability (Chapter 6).

7.1.1 Role of posture and movement within daily activity time use compositions

An important contribution of this thesis was the ability (through the activPAL data collection) to examine the potential role of standing in a time-use composition. The majority of CoDA studies to date have used hip, waist or wrist-worn accelerometer data (141), which can misclassify standing as either light intensity or sedentary time (141,190). Correspondingly, the role of this common daily behaviour (with estimates suggesting that standing can occupy 31% of an adults waking day (118)) has been relatively unclear. Only a few CoDA studies examining cardiometabolic health have used standing in their composition of exposures (142,143,191). So far, the results of these studies suggest that standing time has mixed associations with cardiometabolic risk markers and glycaemic control. Findings from this thesis suggest that time-use compositions higher in standing, in lieu of sitting time were inversely associated with FPG or waist circumference especially in people at risk of or with type 2 diabetes compared to people with normal glucose metabolism (Chapter 3 and 4). Otherwise, glycaemic control outcomes were most strongly associated with compositions lower in sitting time and higher in stepping time. A key example of this was the strong inverse associations of 2hPLG with stepping time and HbA1c especially in people at risk of or with type 2 diabetes compared to people with normal glucose metabolism. Collectively, and in line with previous evidence (118,138), these findings suggest that different compositions of time may distinctly impact risk markers.

Time-use favouring upright and active behaviours that displace sedentary behaviours have consistently been associated with beneficial glycaemic control and cardiometabolic health (118), decreased risk of type 2 diabetes (9), cardiovascular and all-cause mortality (192). In line with this, findings in this thesis suggests daily activity time-use compositions higher in stepping and lower in sitting time-use are beneficial to glycaemic control and cardiometabolic health; however, where higher stepping levels are not achieved, time-use can be compensated by higher standing levels, albeit at greater volumes. It should be noted that higher stepping time in lieu of standing time was not shown to be more beneficial in association than higher stepping
time in lieu of sitting time, suggesting that reducing sedentary time use for upright and ambulatory behaviours is most important for behavioural interventions.

Importantly, beneficial associations were apparent when sitting time was hypothetically replaced by combinations of both standing and stepping time. These findings suggest that modifications to multiple behaviours in the daily time-use composition may be most desirable. Previous observational studies have typically investigated the association of one behaviour varying with another, or with the remaining behaviours made lower relative to the sample’s mean composition (140,143). One prospective study that examined compositional changes in sitting, standing and stepping found beneficial associations with cardiometabolic risk markers when both standing and stepping were increased in combination relative to sitting time (177). This study, which recruited adult desk workers without metabolic impairment, found only small improvements to a clustered cardiometabolic risk score when compositions shifted to less sitting and more standing. The findings in this thesis corroborate these findings, suggesting that higher standing time-use is beneficial, and higher standing and stepping time-use is even more beneficial to cardiometabolic health and glycaemic control. Only one study has experimentally induced combined modifications to ambulatory behaviours (i.e. increasing both standing and stepping time), in lieu of sedentary time (193), and this study found similar beneficial associations with cardiometabolic health. Future experimental designs could test an array of time-use compositions (compositions higher in standing or compositions higher in stepping replacing sedentary time) and compare between them their association with glycaemic control and cardiometabolic risk. This may give more robust insights and corroborate the research in this thesis as to optimal time-use combinations and their differential effects on cardiometabolic risk and glycaemic control.

7.1.2 Identification of curvilinear relationships

Another finding observed within the observational studies of this thesis was that the ratios of time spent sitting to standing or sitting to stepping were curvilinear. This may suggest that higher daily sitting time negatively impacts glycaemic control and cardiometabolic health to a greater extent than what may be achieved by stepping and standing to improve it. Similar
asymmetric relationships have been observed in previous studies that have used CoDA (138,142,194,195), it is however difficult to discern whether this truly reflects the relationship with cardiometabolic and glycaemic control physiology, or whether this is a unique feature of this particular statistical approach. Whilst there are questions about whether isotemporal substitution methods appropriately handle time-use data (139), the estimations will always be linear by comparison (196). Mechanistic and intervention studies, that specifically investigate dose of sedentary behaviour reduction (whether through standing, stepping, or combinations) are needed to confirm whether these curvilinear relationships are true.

The relationship of sedentary behaviour reduction with cardiometabolic risk was observed to have a threshold or upper limit for the beneficial associations. Similar curvilinear relationships with diminishing returns have been observed in other research designs concerning disease and mortality risk. For example, higher step counts have been associated with a progressively decreasing associations with all-cause mortality, with the threshold of diminishing returns occurring with less steps in the older group (≥60 years of age) than the younger group (6,000 – 8000 steps vs. 8,000 – 10,000 steps) (197). In a multinational meta-analysis, sedentary behaviour was associated with progressively higher risk for all-cause mortality after 9 hours/day, and LPA at 300 mins/day (101). One other paper has considered modelling MVPA to SB in isometric log ratio, and non-linear associations were also observed for all-cause mortality (192). In this investigation, approximately 2.5 minutes of MVPA per hour of sedentary behaviour was associated with reduced mortality risk, and further compositional increases to MVPA/SB were associated with diminishing beneficial risk ratios. New research is examining optimal time use days (24 hours) associated with best health outcomes within a population, colloquially referring to them as ‘goldilocks days’ (198). The findings from this research suggest that optimal day composition balances differ by the respective health outcome being investigated. Collectively the evidence in this thesis suggests that daily time-use compositions, with the reduction of sedentary behaviour as a primary objective, may have an optimal time-use balance depending on the cardiometabolic and glycaemic control outcome of interest. For Considering clustered cardiometabolic risk (CMR) as an example: 7 hours sitting, 5.2 hours standing, and 3.9 hours stepping may be an optimal balance of waking time-use (estimates
using the findings from isometric log-ratios spline models in Chapter 4). These composition estimates can be used to inform time-use guidelines and intervention behavioural targets.

7.1.3 Differential relationships by level of glycaemic control and diabetes status

Within this thesis, the analysis of two separate cohorts from two countries showed that the associations of sitting, standing, and stepping with glycaemic control and related cardiometabolic risk markers were stronger in people at risk of diabetes, and even stronger in people with type 2 diabetes. This suggests that people with type 2 diabetes may be more likely to stimulate beneficial health outcomes when altering their daily composition of activities to reduce sitting and increase standing and stepping behaviours. People with type 2 diabetes have greater variability in their glycaemic control levels, and the reduction of sedentary behaviour may be an important ongoing management strategy for this, where it would otherwise be less of an important countermeasure to people with less impaired metabolism. As noted in Chapters 3 and 4, these findings are in line with the experimental trial evidence, which found that the metabolic response to prolonged sitting was more detrimental in those with existing metabolic impairment (185,199). Participants involved in these experimental trials are typically provided an intensive glucose challenge meal / drink, advised to sit for prolonged and non-representative time periods (e.g. 8 hours), and advised to perform sedentary behaviour breaks that are seldom performed in the population (200). Despite differences with the free-living setting, it is encouraging that the experimental work is corroborated by free-living epidemiological investigations detailed in this thesis. Additionally, the findings suggest that people with metabolic impairment may have greater efficacy when aiming to improve their metabolism with sedentary behaviour reduction interventions. This pronounced association in those with metabolic impairment may explain the modest or null findings for glycaemic control in sedentary behaviour interventions that have predominately involved people with normal glucose metabolism (201). More randomized controlled sedentary behaviour intervention trials with wider variance of metabolic impairment and diabetes durations among participants would be required to further elucidate these relationships.
7.1.4 Development of an intervention protocol

The aforementioned findings support the objectives of the OPTIMISE Your Health trial (as described in Chapter 5) targeting the behaviours of sitting less and moving more in people living with type 2 diabetes. The findings from the prospective OPTIMISE Your Health trial have the potential to inform clinical guidelines on sedentary behaviour reduction initiatives for type 2 diabetes management. As identified in Chapter 1, few studies have attempted to investigate the role of sedentary behaviour reduction in people with type 2 diabetes and monitored the effect on long term markers of disease including glycated haemoglobin and cognitive function. The OPTIMISE intervention is unique as it employs multiple components, with extensive follow-up. A modified version of the trial (OPTIMISED) will be implemented and evaluated for feasibility and acceptability, with the intention of translating the findings to health care practice.

7.1.5 Observation of long-term activity patterns pre- and post-COVID-19

The OPTIMISE Your Health intervention was significantly impacted by the COVID-19 based lockdown restrictions in Melbourne, Australia. During this period, participants with type 2 diabetes on average saw overall decreases in active time and increases in sedentary time following COVID-19 lockdown restrictions. The changes were characterised by a decrease in time spent in lightly active, fairly active, and very active physical activity intensities, and an increase in time spent sedentary. More time was spent in prolonged unbroken sedentary bouts and prolonged ‘very active’ (Fitbit derived vigorous-intensity physical activities) intensity bouts. More time spent in very active bouts may have been a feature of fitness-based walking being one of the permissible reasons to leave the house during restrictions, however more time spent in these activities was not sufficient to counteract the overall decline in physical activity and increases in sedentary behaviour. Overall, these findings suggest that the pandemic and its associated restrictions present an additional barrier to behaviour change and adherence to the sedentary behaviour reduction. Physical activity changes induced by the pandemic are well substantiated in the literature (202), however impacts on sedentary behaviours and temporal patterns of activity (e.g. longer bouts of activity / SB) are less understood. Only one other study
has investigated people with type 2 diabetes with objective measures prospectively before and during the COVID-19 pandemic, and it found similar findings with reductions in overall physical activity (203).

While the findings overall indicated a negative impact of the lockdown restrictions on sedentary behaviour and physical activity, there was inter-individual variability with some participants observed to have increased their physical activity and reduced their sedentary behaviour despite the restrictions. Understanding how some participants maintained or improved their activity levels may inform intervention approaches and recommendations for subsequent lockdown restrictions. The pandemic itself has also promoted the adoption of hybrid work environments, which for some may reduce the opportunity for active commuting to and from work (204). On the other hand, a study in New Zealand reported an improvement in physical activity engagement in inactive participants following COVID-19 pandemic restrictions (205). Changes were attributed to hybrid work adoption, where it was easier to incorporate physical activity and remain motivated in the work from home environment (205). Occupational health initiatives and interventions should consider that the pandemic has the potential to be a double-edged sword, constituting as both a barrier and an opportunity for sedentary and physical activity behaviour change (206).

7.2 Strengths of thesis

7.2.1 Compositional data analysis

A key strength of thesis was the use of the Compositional Data Analysis (CoDA) technique within two separate data sources (Australia and Netherlands). As discussed in Chapters 3 and 4, CoDA allows for the categorisation of all behaviours into a finite day and allows for inter-related and competing behaviours to be tested together in one composition. Importantly, CoDA appropriately adjusts for multiple behaviours in finite time-use and handles the obfuscating effect of multicollinearity on the model (139,196). Compositional data analysis has relevance to the behaviour change field, especially given sleep (207), physical activity (208), standing (209), and sedentary behaviour (118) have their own independent impacts on cardiometabolic risk
and glycaemic control. To date, no studies have tested the interaction of diabetes status on CoDA isometric log coordinates, and thus tested the influence of metabolic impairment on these associations of cardiometabolic health with free-living behaviours conducted in the day. The CoDA techniques developed in this thesis will likely be used as a component of future analyses pertaining to the sedentary behaviour intervention, which primarily aims to modify multiple behaviours such as standing and stepping simultaneously (such as in the OPTIMISE trial detailed in Chapter 5), or MVPA for the improvement of health.

7.2.2 High quality measurement

As previously noted, the accurate measurement of standing was a key strength of this thesis. The activPAL provides the most accurate measurement of sedentary time and breaks in sedentary time in field research and is superior to other hip or waist worn accelerometers when interpreting sedentary time compared with direct observation (210,211). Whilst a less accurate measure of sedentary behaviour, the use of the Fitbit instead enabled examination of long-term continuous activity data. Hundreds of days were observed per participant which may improve the robustness and representativeness of our data to characterise the unprecedented changes caused by the pandemic. The Fitbit also provided continuous heart rate measurement, providing the opportunity to measure intensity of activity that doesn’t have acceleration at the wrist (a requirement of activity detection with wrist-worn Actigraph), and also being able to appropriately detect non-wear time (as no heart rate is recorded when unworn). Using the Fitbit, originally conceived only as a health behaviour change tool within the OPTIMISE trial, prevented any need for retrospective data collection or recall bias from our participants. These factors have been acknowledged as being a limitation for many other COVID-19-induced behaviour change investigations (212).

The included studies in this thesis have some of the most comprehensive and robust measures of cardiometabolic risk and glycaemic control markers. This includes full oral-glucose tolerance tests – a test with excellent sensitivity to assess the level of metabolic impairment via glucose absorption and insulin sensitivity (159) – but rarely used at scale due to its with high time burden for administration. The studies included also had a wide battery of self-report measures
capturing socio-demographics, economic, and occupational factors, as well as a range of other health behaviour such as diet and smoking status. This allowed for confounder adjustment for a range of factors that may influence the associations observed.

7.3 Limitations of thesis

The strengths of this thesis should be considered alongside the limitations, which ultimately inform directions for future research. Limitations are categorised according to design, statistical, as well as measurement and methodological limitations.

7.3.1 Sample, recruitment, and overall design limitations

A key limitation across all of the observational studies described in this thesis was the constraints on the sample size to thoroughly address some research objectives of interest. Examples of this included the sample described in Chapter 3 using the AusDiab study and cohort in 2011 – 2012. Of the participants that attended the third follow-up, 741 wore the activPAL thigh monitor. This cohort was significantly healthier than the broader AusDiab sample, and a low prevalence of people with type 2 diabetes (50 participants with at least one valid activPAL wear day). Participants with diabetes were required to undergo a longer assessment battery compared to the rest of the sample, and thus were more likely to arrive for activPAL monitor allocation after the devices had been exhausted (118). This invariably resulted in a research question that focused on those with some level of metabolic impairment, as opposed to people with type 2 diabetes and those without. Similarly, the OPTIMISE sample described in Chapter 5 was a sub-sample of the cohort containing only those in the intervention group who incurred the first COVID-19 based pandemic restrictions. In this study, only 11 participants were included due to the intention to include participants exposed to homogenous lockdown restriction settings and as well the pre-pandemic conditions to allow for comparison. The post-hoc power analysis found that there was significant power to address the main research questions; however, higher numbers would have provided further insights into the variability of response to the restrictions and the factors that underpinned it. Another limitation of the research in this thesis was the lack of representation of more diverse socio-economic,
and ethnic groups. The AusDiab study became less representative of the Australian population as attrition occurred with each follow-up study. The Maastricht study reported low ethnic diversity, suggesting the findings may only apply to Caucasian and western populations (162). The OPTIMISE study, and the exploratory study depicted in Chapter 6 is comprised of office workers, who may have different education and socio-economic status to the rest of the population. Therefore, there is a potential for selection bias in this thesis, thus potentially precluding the generalisability of our findings to different populations.

7.3.2 Statistical limitations

Another limitation was the use of cross-sectional designs to inform investigations. Within these designs, it is essential to make a clear assumption about the causal pathway, from exposure to outcome. To address this, directed acyclic graphic methods were used to logically evaluate covariates. Within this modelling, confounding factors are identified in accordance with previously devised methods for clinical health epidemiology (213). Despite adjustment, there is still the chance of residual confounding in the relationships tested, that is, a true confounder not included could have been a significant influencer in the causal relationship tested.

The presence of reverse-causality must also be considered with cross-sectional observations. The studies in this thesis employed several statistical approaches, which were used to cater for the single observation timepoint, however reverse causality cannot be discounted from significantly influencing the results. As such, it is important to acknowledge the assumptions made regarding the direction of the associations explored within these investigations. For example, the associations may be revealing that diabetes and clustered cardiometabolic risk may be causing physical activity intolerance, fatigue, or musculoskeletal pain that may itself be causing changes to activity and sedentary behaviour levels.

The stratification of the sample was another apparent limitation in this thesis. This technique, whilst important for the research questions and handling of oversampling, comes with limitations. Stratification necessarily reduces the sample size, resulting in lower precision of estimates and greater potential of error. Stratification may potentially introduce a form of collider bias. Collider bias occurs when an exposure (e.g. sitting), and an outcome (e.g. HbA1c)
influence a third variable, and that variable is controlled for by design – in this case stratification (214). Stratifying by higher diabetes risk in Chapter 3 may have isolated the variation in outcome variable to one group, and thus increasing the chance of type 1 errors with the hypothesis concerning differences by diabetes risk strata.

7.3.3 Measurement tools and analytical limitations

The activity monitoring devices used in this thesis, such as the Fitbit and activPAL, as well as the CoDA methods using activPAL data have their own limitations as well. The Fitbit used in this trial (Inspire HR model) is yet to be validated, although it can be assumed that it has similar accelerometer technology as previous Fitbit devices that have been validated (215). The Fitbit also uses a proprietary algorithm (not open source) to process the signals determined from the device, with methods unknown to independent researchers. This means that the methods used are not easily extrapolated to other areas of research including other wrist-worn activity monitoring.

The activPAL thigh monitor is not without its limitations either. Affixed to the thigh, the device cannot appropriately interpret upper body activities, or stationary exercise without leg cadence such as resistance training exercises. The older activPAL monitors (activPAL3) do not appropriately detect cycling exercises. Using the proprietary algorithm for activity detection, activPAL will categorise minutes featuring <20 steps (0.3hz) as a standing minute (216), potentially misclassifying true activities and energy expenditure. Compositional data analysis techniques that handle the activPAL data do not consider the temporal sequence of how behaviours are performed, and instead capture a running total, having implications for chronic disease management (217). Compositional beta coefficient estimates are logarithmic ratios of time-use, and refer to the balance of time, therefore these estimates may be less interpretable to lay audiences who may be more familiar with step counts, and minutes of time-use. For the CoDA investigations in this thesis, sleep was not always catered for in time-use composition. Intensity was also not considered in time-use compositions, nor bout lengths (e.g., short MVPA bouts, long sedentary behaviour bouts in composition). These were not explored due to simplicity, however the influence of both intensity and bout duration could be explored in
future CoDA investigations. Time-use is a relatively new investigative approach, and whilst demonstrating strong potential for validity and robustness in health behaviour epidemiology, it has only been applied to a small number of studies. More investigations using CoDA approaches are needed to progress the field and ultimately the adoption of time-use guidelines (136).

7.4 Clinical and public health implications of findings

Increasingly, the management of health is being considered holistically (136,218). That is, rather than considering one avenue of intervention, such as exercise participation, multiple behaviours and modifiable lifestyle factors are considered as interrelated factors. This is particularly relevant to sedentary, upright, and active behaviours undertaken during the day, that have their own distinct relationships with health, and also induce physiological changes with dependency on total volume (101) and the sequence that they are performed (105,219). Time use guidelines such as 24hr movement guidelines from Canada (136) fundamentally acknowledge these principles, and understand that the merits of exercise or light-intensity activity may be less beneficial in the context of insufficient sleep, or high levels of sedentary behaviour. In the case of the Canadian 24-hr guidelines, prescriptions are made about how time should be spent in the day between these different behaviours. The findings in this thesis contribute to the understanding of the interrelationship between behaviours, and how they may be composed to be of health benefit. The findings of this thesis suggest that people with type 2 diabetes are more susceptible to changes in cardiometabolic risk and glycaemic control through their daily composition of time-use.

In general, physical activity guidelines for people with type 2 diabetes (79) have focused on a one-size-fits-all approach. For example, it is recommended to achieve 30 – 60 minutes of MVPA per day, or 150 – 300 minutes per week in these guidelines. However, this should be considered in the context of low public adherence of MVPA, especially in people with type 2 diabetes (4,5). The findings from this thesis suggest that beneficial health outcomes can be achieved across a range of different time use compositions. The findings are encouraging in the context of multimorbidity (e.g., chronic pain, peripheral neuropathy) and diabetes symptoms (e.g. fatigue)
that may preclude adherence to regular engagement in exercise, but not necessarily affect the reduction of sedentary behaviour through more light activity or standing behaviours. Current 24hr movement (136) and physical activity (56,79) guidelines do not quantify exactly how sedentary behaviour should be reduced, with a lack of clarity of whether this should be achieved through standing, light activity or exercise. There may be a number of reasons for this: one is that much of the evidence supporting sedentary behaviour reduction looks at acute interruptions to prolonged sedentary time, such as with 3 – 5 minute physical activity interruptions (220). Another is that the sedentary behaviour intervention trials have favoured the measurement of sedentary behaviour reduction (129), as opposed to changes in the composition conferred by sedentary behaviour reduction. This could be an area for future research, which would help quantify how sedentary behaviour should be reduced through the modification of multiple behaviours. In the OPTIMISE Your Health trial the role of whole of day time-use modification can be investigated, as too can the effect of intermittently breaking up sitting with short activity breaks within the same trial. This is especially relevant where broader time-use changes, which increase light-intensity physical activity and standing may be more feasible for some individuals as opposed to more intensive sedentary behaviour activity breaks which, outside of the experimental setting, are seldom performed in day to day life (200). The current evidence suggests that substantial time-use changes to sedentary behaviour levels are feasible within intervention contexts (129).

The OPTIMISE Your Health intervention, the protocol of which is described in this thesis, will add an important contribution to the evidence base. The intervention aims to reduce sitting time to 50% of waking hours with more standing and stepping behaviours, across work and outside of work contexts, and so too aims to break up sitting with short activity breaks. The whole-of-day approach to health behaviour change is seldom adopted within current primary and secondary health care. For example, in Australia, physical activity lifestyle change is often mediated through the referral to an accredited exercise physiologist, with public health funding provided where a patient is being treated for a chronic disease. This involves the supervision of exercise within the billable hour, as well as some take-home education. Referrals by general practitioners to exercise physiologists remain disappointingly low, especially in patients with
non-English speaking backgrounds (221). As the OPTIMISE Your Health intervention, and
OPTIMISED interventions (abbreviated version of OPTIMISE) can be delivered remotely, and
without hands on instruction, the intervention could be administered by primary care
practitioners. This is relevant when health care consultation has seen substantial shift towards
remote consultation with telehealth in Australia (222,223). In a similar way, the OPTIMISE
intervention could also be promoted in preventative care, with prevention of diabetes a
potential avenue of consideration. By supporting environment change with a sit-stand
workstation, a wearable fitness tracker that has regular reminders to move, and health
coaching troubleshooting for the multiple contexts of sedentary behaviour accumulation,
broader daily time-use composition changes may be realised. These changes can be an adjunct
therapy alongside traditional healthcare such as that conducted within an exercise physiology
consultation.

As the technology of wrist-worn devices such as the Fitbit improve, there is increased potential
for their use in surveillance and public health intervention initiatives. Despite being less
accurate when compared to research grade measures (224), when deployed at larger scale and
with many days of observation these devices may overcome these limitations and be able to
observe changes in health behaviours in real-time. Within a research or clinical context, this
approach with fitness tracker wearables can provide greater resolution as to whether an
intervention is adhered to, or supplement (or eventually replace) research grade monitors that
presently only measures daily activity up to 7 – 10 days. These factors can be monitored
remotely in real-time by both user and provider alike. Harnessing cloud-based data enables the
opportunity for health care professionals to provide “just-in-time” tailored interventions,
providing care that could address behaviour change relapse as it occurs (225). Using the
technology in people with type 2 diabetes also provides an opportunity to improve the self-
management of their physical activity levels, with the potential to link these metrics with
glucose and dietary monitoring (226). The potential of wrist-worn trackers in public health
extends beyond physical activity and sedentary behaviour monitoring. Wrist-worn trackers
have predicted onset of influenza (227), assisted with earthquake crisis management (228) and
detected COVID-19 infection (229).
As COVID-19 transmission becomes endemic in modern society, the management of diabetes becomes more crucial. With the onset of new virus variants, lockdown restrictions may be re-imposed, and these will likely precipitate greater sedentary behaviour and lower physical activity levels. This is a dilemma given physical activity and reducing sedentary behaviour are key constructs of glycaemic control and cardiometabolic disease risk mitigation. The changes to physical activity and sedentary behaviour observed in this thesis following the pandemic restrictions would theoretically be associated with significant increases in cardiovascular morbidity and all-cause mortality risks (230). Engaging in physical activity (even below the physical activity guidelines) are associated with less adverse effects and hospitalization from COVID-19 (231,232) with stronger benefits observed in people with diabetes (233). In addition, physical activity not only improves immunity itself (234), but physical activity and lower sedentary behaviour levels are associated with improved immunogenicity of COVID-19 vaccines (235,236). Therefore, maintaining and increasing physical activity, and reducing sedentary behaviour could be considered as an effective countermeasure against coronaviruses. Pandemic-related government policy could leverage physical activity and sedentary behaviour surveillance in the future, potentially by monitoring consumer wearable fitness tracker data. From this an evidence-informed approach could be adopted to ensure physical activity is maintained and sedentary behaviour is mitigated during pandemic lockdowns (237). Overall, the COVID-19 pandemic emphasizes the need for renewed public health effort towards sitting less and moving more, especially in people living with chronic disease.

7.5 Directions for future research

Over the course of this PhD candidature, opportunities for future research have presented themselves that are directly in relation to the continuation and completion of studies reported on in this thesis. Research conducted in this thesis has also helped identify other directions for future research not immediately available for research following the candidature.
7.5.1 Future research directly relevant to the studies reported in this thesis

The Maastricht study is continuing recruitment of their baseline sample, and the research team has expressed interest for prospective follow-up data collection pending funding. The Maastricht and AusDiab studies can also have their data pooled with other studies to increase statistical powering and increase the diversity of the sample, which were limitations of the respective studies. This has been achieved by collaborations such as PROPASS (238) which seeks to unite multiple studies using accelerometers from around the globe in consortium for these purposes. This form of linkage has the potential to improve the quality and resolution of investigations and therefore extend the capacity for hypothesis generation. Similarly, older studies that have used hip, waist, or wrist-worn accelerometers are retrospectively being adapted to improve their interpretation of sedentary behaviour time using machine learning methods (239). This would in turn allow for more robust and sample rich investigations of sedentary behaviour into the future.

These epidemiological observational studies do however need corroboration by randomised controlled trials. The OPTIMISE Your Health Trial will be completed by December 2025, which will present opportunities for numerous investigations. The trial has the potential to determine a specific dose-response of sedentary behaviour reduction and its effect on glycaemic control. This can be investigated directly with the CoDA analytical approach developed in this thesis. In addition, the role of metabolic health moderators and their influence on the response to the intervention could be explored. Moderators could include diabetes duration (years since diabetes diagnosis), number of medications, type of medications (e.g., biguanides or sulphonylureas) (240), as well as moderation by metabolic biomarkers such as insulin sensitivity. It may also be feasible to understand the broader effect of the COVID-19 pandemic on activity levels beyond the first lockdown period and investigate how the current snapshot approach of measuring activity (i.e., with activPAL activity monitoring) correlates with longer-term measurement of the Fitbit. Long-term measurement of sedentary behaviour and physical activity have the potential to be a more representative assessment of free-living behaviours than short term measures as they provide greater resolution of data. With more longer-term data the understanding of how these behaviours cause changes in long term markers of disease
such as cognitive function or HbA1c can be improved. Grant funding for the purpose of improving the accuracy of Fitbit devices and improving their ability to detect behaviours has already been sought by the candidate and collaborators (Appendix G). As the Fitbit software is proprietary, a partnership with Fitbit would help overcome the closed-source barriers and understand to a greater degree what is occurring within the device, leading to improved detection of sedentary and standing behaviours. This would suitably help address the validity concerns of these devices (215).

Along with completing the OPTIMISE trial there has been valued experience gained in adapting the sit less and move more intervention approach to the Finnish population. Following extensive international collaboration, a grant application to the Academy of Finland was successful, with the candidate listed as an investigator on the project (Appendix G). One of the postulated mechanisms potentially driving the detrimental associations of sedentary behaviour with adverse health outcomes is the presence of inactive muscle physiology. The OPTIMUS trial aims to investigate the role of muscle activity, as opposed to strictly interpretation of posture (sitting, standing, stepping), on glycaemic control and cardiometabolic health. Participants are randomised to intervention or control groups and measured with electromyography sensing garments and activPAL thigh monitors over a period of six months. Both the OPTIMISE and OPTIMUS trials share broad similarities and outcome measures, therefore there is the potential for data harmonisation between the two projects. This study will contribute insights as to the role of inactive muscle physiology, the effect of interrupting it, and the implications for cardiometabolic health, glycaemic control, and diabetes management.

7.5.2 Other directions for future research

Aside from the directions that are directly available after candidature, the work presented in this thesis highlights many limitations and gaps that could be addressed with future research.

The compositional data analysis work highlights that broad changes to daily time-use may induce important alterations to metabolism. Thus far, many experimental and intervention sedentary behaviour trials have reduced sedentary behaviour with one behavioural alternative, rather than multiple. An exception to this was a study with a four day, three arm experimental
trial where participated were instructed to adhere to a daily composition featuring less sedentary behaviour and more standing and light walking, or a sedentary daily composition with one hour of moderate-vigorous activity, which were compared to a composition high in sedentary behaviour (193). The authors determined that the composition with more light activities and standing induced comparable improvements in insulin sensitivity to that of the exercise arm (193). Further experimental and longitudinal trials could be conducted to compare compositions higher in standing, with compositions higher in stepping, and within different cohorts such as people with metabolic impairment and diabetes.

Understanding sedentary behaviour, specifically its reduction across the metabolic spectrum requires more investigation, including the influence of metabolic impairment, medications, and diabetes duration. Whilst the studies presented in this thesis suggest that the metabolic response to sedentary behaviour reduction is greater in people with metabolic impairment and type 2 diabetes, there is new evidence suggesting that people with type 2 diabetes with longer diabetes duration may see diminished benefits to health following a physical activity intervention (241). Homer et al. (242), when drawing comparisons with previous experimental research (186), hypothesised that patients with greater reliance on multiple medications and with a longer diabetes duration may have greater impairments in insulin sensitivity leading to less benefit when interrupting sedentary time with brief activity bouts. This shares alignment with diabetes epidemiology that suggests that most people with type 2 diabetes that go into diabetes remission (<6.5% HbA1c) have a relatively short diabetes duration, and low medication usage to start with (243). Collectively, this evidence suggests that there may be an optimal time frame for intervention, which requires further investigative research.

More sedentary behaviour-based intervention trials, as well as their implementation will be necessary to influence wider healthcare adoption of this management approach. The OPTIMSE Your Health trial embeds an abbreviated trial in the form of OPTIMISED that delivers a more cost-effective and less resource intensive program that could feasibly be provided by health care practitioners. Future trials could also explore how sedentary behaviour interventions, compare with traditional exercise and weight loss interventions. Combinations of the
intervention approaches could also be explored. For example, the stair-case approach postulated in Chapter 4, suggests that sedentary behaviour interventions (and the shift towards more upright and ambulatory activities) could be combined with exercise interventions, in a stepwise approach (Figure 3).

Figure 3. The ‘staircase approach’ to health behaviour change

Dunstan et al. (2021). Sit less and move more for cardiovascular health: emerging insights and opportunities. *Nature Reviews Cardiology.* (244)

In other words, once capacity and physical tolerance is developed with the sedentary behaviour intervention, exercise could be the next transitional step in a clinical treatment model. Ultimately, the benefit of sedentary behaviour reduction is that it can feasibly be achieved over the course of the day without significant impact on occupational or leisure time. As such, the long-term feasibility, acceptability, and maintenance of reducing sedentary behaviour compared to traditional health care modes needs prospective investigation as well.

7.6 Conclusions

In conclusion, this thesis extends current knowledge on sedentary behaviour and health, focusing on the assessment of sedentary behaviour time-use within free-living contexts in people at risk of and with type 2 diabetes. The chapters within this thesis describe novel methods and their applications using both cross-sectional and longitudinal designs. To date,
few sedentary behaviour intervention studies have focused on people with type 2 diabetes. Few of these have investigated the role of sedentary behaviour reduction for glycaemic control and mitigation of cardiometabolic disease. This precludes ecological inferences about the relationship of sedentary time and its alternatives with glycaemic control and related cardiometabolic risk markers as well the implications of these relationships for longer-term management of health. In the relative absence of strong ecological and field-based data, this thesis reports findings from the use of a novel methodology in the form of compositional data analysis to identify favourable compositions of time-use, which are relevant to sedentary behaviour interventions and may assist health care practitioners aiming to reduce sedentary behaviour with both upright and ambulatory alternatives. Difference by diabetes status were identified, with associations stronger in people with type 2 diabetes than those with more normal glucose metabolism. These findings reinforce the importance of sedentary behaviour as a key target for clinical management of metabolic impairment. One avenue to explore these findings further is via a randomised and prospective trial, detailed in Chapter 5, the OPTIMISE Your Health trial. Whilst this trial is still ongoing, the contemporary COVID-19 pandemic restrictions that interrupted it have been identified as a new barrier to sedentary behaviour interventions in people with type 2 diabetes. The changes to physical activity and sedentary behaviour observed during these restrictions are expected to negatively impact on glycaemic control and cardiometabolic risk. Further research is required to corroborate the findings of this thesis. Potentially favourable compositions of sitting, standing, and stepping time-use should be investigated prospectively, as should their long-term impact on health markers. With the COVID-19 pandemic continuing, ensuring a healthy time-use composition of daily activity remains a public health priority, especially for people living with type 2 diabetes.
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Appendices

Appendix A – Author contributions to research related to this thesis

Publications related to thesis


Contribution statement

CB conducted analysis and wrote the manuscript. DD, GH, NO, were involved in the conception of the present study’s design, advised on the analyses, and editing of the manuscript. AC was involved in editing of the manuscript. PS was involved in and advised on the analyses. SC, JB, AS, advised on the analyses. The authors read and approved the final manuscript.

Approximate percentage contributions:

Brakenridge CJ 50%, Healy GN 10%, Sethi P 10% Carver A 2.5%, Bellettiere J 2.5%, Salim A 5%, Chastin SFM 5%, Owen N 5%, Dunstan DW 10%.

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Funding for this research was obtained by DD, NO, EE, SJHB, GNH, RMD, DG, MM, EW, NC, PG, LG, TC, BF, MAS. EW is the trial data analyst and developed the statistical analyses plan. PN, MM, TC, LG developed the economic evaluation plan and text section. MB provided input on the device-based measurement section. RG provided extensive support in writing the text. All authors have contributed to the design of the trial. The first draft of this manuscript was produced by CB and all authors have reviewed, edited, and approved the final version.

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**Contribution statement**

CB conducted the analysis, wrote the manuscript, recruited participants, and devised the original study design. AS devised the statistical modeling and advised on the writing of the statistical analyses section. RG and KR recruited participants and advised on the writing and editing of the manuscript. AC, GNH, NO, DWD were involved in the conception of the study design, advised on the analyses, and editing of the manuscript.

**Approximate percentage contributions:**

Brakenridge CJ 50%, Salim A 25%, Grigg RV 5%, Carver A, 2.5%, Rickards K 2.5% Owen N 5%, Healy GN 5%, Dunstan DW 5%.

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As principal supervisor, I certify that the above contributions are true and correct, and my contribution to the paper was 5%:

David Dunstan  
Date: 19/05/2022
**Co-author signatures:**

I acknowledge that my contribution to the above paper is 25%:

Agus Salim  
Date: 23/05/2022

I acknowledge that my contribution to the above paper is 5%:

Ruth Grigg  
Date: 14/06/2022

I acknowledge that my contribution to the above paper is 2.5%:

Alison Carver  
Date: 23/05/2022

I acknowledge that my contribution to the above paper is 2.5%:

Kym Rickards  
Date: 12/05/2022

I acknowledge that my contribution to the above paper is 5%:

Neville Owen  
Date: 07/06/2022

I acknowledge that my contribution to the above paper is 5%:

Genevieve Healy  
Date: 31/05/2022
Manuscripts currently under review related to thesis


Contribution statement

CB conducted the study analysis and wrote the manuscript. DD, GH, NO, AC, were involved in the conception of the present study’s design, advised on the analyses, and editing of the manuscript. FD was involved in editing of the manuscript. AK, BDG, NCS were involved in original acquisition of the data, provided advice on the design, and provided critical review of the manuscript. SJPME, HHCMS, HB were involved in original acquisition of the data, and provided expert review of the manuscript. All authors read and approved the final manuscript.

Approximate percentage contributions:

Brakenridge CJ 55%, Koster A 5%, de Galan BE 5%, Carver A 5%, Dzakpasu F 2.5%, Eussen SJPM 2.5%, Savelberg HHCM 2.5%, Bosma H 2.5%, Owen N 5%, Schaper NC 5%, Healy GN 5%, Dunstan DW 5%

Candidate declaration:

I acknowledge that my contribution to the above paper is 55%:

Christian Brakenridge [Redacted] Date: 30/05/2022

As principal supervisor, I certify that the above contributions are true and correct, and my contribution to the paper was 5%:

David Dunstan [Redacted] Date: 30/05/2022

Co-author signatures:
I acknowledge that my contribution to the above paper is 5%:

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Date: 30/05/2022

I acknowledge that my contribution to the above paper is 5%:

Bastiaan de Galan

Date: 30/05/2022

I acknowledge that my contribution to the above paper is 5%:

Alison Carver

Date: 30/05/2022

I acknowledge that my contribution to the above paper is 2.5%:

Francis Dzakpasu

Date: 03/06/2022

I acknowledge that my contribution to the above paper is 2.5%:

Simone Eussen

Date: 31/05/2022

I acknowledge that my contribution to the above paper is 2.5%:

Hans Savelberg

Date: 30/05/2022

I acknowledge that my contribution to the above paper is 2.5%:
Appendix B – Supplementary materials for Chapter 4

As the manuscript in Chapter 4 is awaiting submission to a scientific journal the supplementary materials are included below.

Supplementary Material 1. Complete linear regression associations of time-use composition with glycaemic control and cardiometabolic risk markers

<table>
<thead>
<tr>
<th></th>
<th>Sitting vs Other Behaviours(^a)</th>
<th>Stand vs. Sit(^b)</th>
<th>Step vs Sit(^b)</th>
<th>Step vs Stand(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(\beta) [95% CI](^c)</td>
<td>(\beta) [95% CI](^c)</td>
<td>(\beta) [95% CI](^c)</td>
<td>(\beta) [95% CI](^c)</td>
</tr>
<tr>
<td>WC, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 # female</td>
<td>1 [-1.5, 3.49]</td>
<td>-1.31 [-4.27, 1.65]</td>
<td>-0.41 [-3.02, 2.19]</td>
<td>0.9 [-2.62, 4.42]</td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>0.41 [-2.99, 3.8]</td>
<td>3.59 [-0.25, 7.44]</td>
<td>-4.29 [-8.05, -0.54]</td>
<td>-7.89 [-12.7, -3.07]</td>
</tr>
<tr>
<td>Model 1 #T2D</td>
<td>1.79 [-0.75, 4.34]</td>
<td>0.6 [-2.36, 3.56]</td>
<td>-3.71 [-6.4, -1.02]</td>
<td>-4.32 [-7.86, -0.77]</td>
</tr>
<tr>
<td>FPG, mmol/L(^c)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model</td>
<td>Coefficient [Lower, Upper]</td>
<td></td>
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<tr>
<td>----------------</td>
<td>---------------------------</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>0.12 [0.1, 0.15]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 # female</td>
<td>-0.01 [-0.05, 0.04]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>-0.02 [-0.06, 0.03]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1 # T2D</td>
<td>0.05 [0.02, 0.08]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>0.06 [0.03, 0.08]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2 # Prediabetes</td>
<td>-0.02 [-0.06, 0.02]</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2 # T2D</td>
<td>0.04 [0.01, 0.08]</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2hPLG, mmol/L

<table>
<thead>
<tr>
<th>Model</th>
<th>Coefficient [Lower, Upper]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.27 [0.21, 0.32]</td>
</tr>
<tr>
<td>Model 1 # female</td>
<td>-0.09 [-0.19, 0.02]</td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>-0.03 [-0.11, 0.05]</td>
</tr>
<tr>
<td>Model 1 # T2D</td>
<td>0.15 [0.1, 0.2]</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.05 [0.03, 0.07]</td>
</tr>
<tr>
<td>Model 2 # Prediabetes</td>
<td>-0.04 [-0.11, 0.04]</td>
</tr>
<tr>
<td>Model 2 # T2D</td>
<td>0.06 [0.02, 0.09]</td>
</tr>
</tbody>
</table>

HbA1c, mmol/L

<table>
<thead>
<tr>
<th>Model</th>
<th>Coefficient [Lower, Upper]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.11 [0.08, 0.13]</td>
</tr>
<tr>
<td>Model 1 # female</td>
<td>-0.03 [-0.08, 0.01]</td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>0 [-0.04, 0.05]</td>
</tr>
<tr>
<td>Model 1 # T2D</td>
<td>0.06 [0.03, 0.09]</td>
</tr>
<tr>
<td>Model 2</td>
<td>0.05 [0.03, 0.07]</td>
</tr>
<tr>
<td>Model 2 # Prediabetes</td>
<td>0 [-0.04, 0.05]</td>
</tr>
<tr>
<td>Model 2 # T2D</td>
<td>0.06 [0.02, 0.09]</td>
</tr>
</tbody>
</table>

ISI-M

<table>
<thead>
<tr>
<th>Model</th>
<th>Coefficient [Lower, Upper]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>-0.34 [-0.46, -0.23]</td>
</tr>
<tr>
<td>Model 1 # female</td>
<td>0.13 [-0.09, 0.35]</td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>-0.08 [-0.37, 0.21]</td>
</tr>
<tr>
<td>Model 1 # T2D</td>
<td>0.01 [-0.23, 0.25]</td>
</tr>
<tr>
<td>Model 2</td>
<td>-0.07 [-0.18, 0.04]</td>
</tr>
<tr>
<td>Model 2 # Prediabetes</td>
<td>-0.09 [-0.36, 0.18]</td>
</tr>
<tr>
<td>Model 2 # T2D</td>
<td>0.04 [-0.19, 0.27]</td>
</tr>
</tbody>
</table>

CMR, SD

<table>
<thead>
<tr>
<th>Model</th>
<th>Coefficient [Lower, Upper]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1</td>
<td>0.49 [0.43, 0.56]</td>
</tr>
<tr>
<td>Model 1 # female</td>
<td>0.07 [-0.06, 0.19]</td>
</tr>
<tr>
<td>Model 1 # Prediabetes</td>
<td>-0.12 [-0.28, 0.03]</td>
</tr>
<tr>
<td>Model 1 # T2D</td>
<td>-0.03 [-0.14, 0.09]</td>
</tr>
</tbody>
</table>

**FPG** = Fasting plasma glucose; 2hPLG = 2h glucose measure in oral glucose tolerance test; HbA1c = glycaed haemoglobin; ISI-M = Matsuda Index described in methods; CMR = clustered cardiometabolic risk score.

*Coefficient for ilr1 parameter, representative of higher levels of sitting time and lower levels of remaining behaviours

**Coefficient for ilr2 parameter, representative of higher levels of time spent in first behaviour, and lower levels of time spent in the second behaviour

*Outcomes transformed with natural logarithm

Model 1 = adjusted for age, sex, education, smoking status, and dietary intake score.

Model 2 = Model 1 + adjusted for waist circumference, except the waist circumference outcome itself and CMR which were comprised.
of waist circumference. Interaction terms indicated by ‘#’: sex and diabetes status added to test their independent effect on the coefficient estimates. Associations statistically significant (p<0.05) are labelled in bold.
Supplementary Material 2. Linear and generalised additive spline modelling and splines stratified by diabetes status

<table>
<thead>
<tr>
<th>Waist circumference (cm)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step: Sit (linear)</strong></td>
<td><strong>Step: Sit (generalised additive model)</strong></td>
</tr>
<tr>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
</tr>
<tr>
<td><strong>Stand: Sit (linear)</strong></td>
<td><strong>Stand: Sit (generalised additive model)</strong></td>
</tr>
<tr>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
</tr>
</tbody>
</table>
Fasting plasma glucose (log transformed)

Step: Sit (linear)

Step: Sit (generalised additive model)

Stand: Sit (linear)

Stand: Sit (generalised additive model)
<table>
<thead>
<tr>
<th>2h post-load glucose (log transformed)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Step: Sit (linear)</strong></td>
</tr>
<tr>
<td><img src="image1.png" alt="Graph" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Graph" /></td>
</tr>
<tr>
<td><strong>Stand: Sit (linear)</strong></td>
</tr>
<tr>
<td><img src="image5.png" alt="Graph" /></td>
</tr>
</tbody>
</table>
Glycated haemoglobin HbA1c (log transformed)

Step: Sit (linear)

Stand: Sit (linear)

Step: Sit (generalised additive model)

Stand: Sit (generalised additive model)
Matsuda index ISI – M (log transformed)

Step: Sit (linear)

Step: Sit (generalised additive model)

Stand: Sit (linear)

Stand: Sit (generalised additive model)
Clustered cardiometabolic risk score (CMR)

<table>
<thead>
<tr>
<th>Step: Sit (linear)</th>
<th>Step: Sit (generalised additive model)</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
</tr>
<tr>
<td><img src="image3.png" alt="Graph" /></td>
<td><img src="image4.png" alt="Graph" /></td>
</tr>
</tbody>
</table>
Waist circumference (cm)

Step: Sit (generalised additive model)

Stand: Sit (generalised additive model)

Fasting plasma glucose (log transformed)

Step: Sit (generalised additive model)

Stand: Sit (generalised additive model)
2h post-load glucose (log transformed)

Step: Sit (generalised additive model)  
Stand: Sit (generalised additive model)

Glycated haemoglobin HbA1c (log transformed)

Step: Sit (generalised additive model)  
Stand: Sit (generalised additive model)
Matsuda index ISI-M (log transformed)

Step: Sit (generalised additive model)

Clustered cardiometabolic risk score

Step: Sit (generalised additive model)

Stand: Sit (generalised additive model)
Supplementary Material 3 – Combined proportions of standing and stepping and associations with glycaemic control and cardiometabolic risk markers

Combined proportions of standing and stepping and associations with fasting plasma glucose diabetes status

Heatmaps of fasting plasma glucose (FPG) and association with composition of waking day as composed of standing and stepping time. Remaining proportion of day made up of sitting time (not illustrated), therefore where stepping time = 0; and standing time = 0; sitting time = 16hrs.

Mean Composition Reference denotes the sample’s mean composition across the three components as per Table 1 geometric means. Red space corresponds to higher levels of FPG (difference from the mean), and blue space corresponds to lower levels of FPG.
Combined proportions of standing and stepping and associations with 2h post-load glucose by diabetes status

| Heatmaps of 2h post-load glucose (2hPLG) and association with composition of waking day as composed of standing and stepping time. Remaining proportion of day made up of sitting time (not illustrated), therefore where stepping time = 0; and standing time = 0; sitting time = 16hrs. Mean Composition Reference denotes the sample’s mean composition across the three components as per Table 1 geometric means. Red space corresponds to higher levels of 2hPLG (difference from the mean), and blue space corresponds to lower levels of 2hPLG. |
|---|---|---|
| NGM | PREDIABETES | T2D |

<table>
<thead>
<tr>
<th>2hPLG (mmol/L)</th>
<th>2hPLG (mmol/L)</th>
<th>2hPLG (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>&lt;0.25</td>
<td>&lt;0.25</td>
<td>0.5</td>
</tr>
<tr>
<td>0.25</td>
<td>0.25</td>
<td>0</td>
</tr>
<tr>
<td>&gt;2.5</td>
<td>&gt;2.5</td>
<td>-0.5</td>
</tr>
<tr>
<td>&gt;5</td>
<td>&gt;5</td>
<td>-1</td>
</tr>
<tr>
<td>&gt;10</td>
<td>&gt;10</td>
<td>-2</td>
</tr>
</tbody>
</table>
Combined proportions of standing and stepping and associations with glycated haemoglobin by diabetes status

<table>
<thead>
<tr>
<th>NGM</th>
<th>PREDIABETES</th>
<th>T2D</th>
</tr>
</thead>
</table>
| Heatmaps of glycated haemoglobin (HbA1c) and association with composition of waking day as composed of standing and stepping time. Remaining proportion of day made up of sitting time (not illustrated), therefore where stepping time = 0; and standing time = 0; sitting time = 16hrs. Mean Composition Reference denotes the sample’s mean composition across the three components as per Table 1 geometric means. Red space corresponds to higher levels of HbA1c (difference from the mean), and blue space corresponds to lower levels of HbA1c.
Combined proportions of standing and stepping and associations with Matsuda index by diabetes status

<table>
<thead>
<tr>
<th>NGM</th>
<th>PREDIABETES</th>
<th>T2D</th>
</tr>
</thead>
</table>

Heatmaps of Matsuda index (ISI-M) and association with composition of waking day as composed of standing and stepping time. Remaining proportion of day made up of sitting time (not illustrated), therefore where stepping time = 0; and standing time = 0; sitting time = 16hrs. Mean Composition Reference denotes the sample’s mean composition across the three components as per Table 1 geometric. Red space corresponds to higher levels of ISI-M (difference from the mean), and blue space corresponds to lower levels of ISI-M.
Appendix C – Ethics approval for OPTIMISE your health study (Chapter 5)

Certificates of ethics committee approval are listed and attached in the chronological order detailed below:

- Ethics approval for the OPTIMISE your health study. Approved on 14/08/2018.
- Ethics approval for the OPTIMISE-D study. Approved on 28/01/2020.
- Ethics approval for the OPTIMISE your health study with amendments. Approved on 16/06/2020.
ETHICS COMMITTEE CERTIFICATE OF APPROVAL

This is to certify that

Project No: 359/18

Project Title: Office-based Program To Improve Metabolic control in Sedentary Employees with type 2 diabetes: The OPTIMISE your health study

Principal Researcher: Professor David Dunstan

Protocol Version 3.0 dated: 2-Aug-2018

Participant Information and Consent Form Version 3.0 dated: 2-Aug-2018

was considered by the Ethics Committee on 26-Jul-2018, meets the requirements of the National Statement on Ethical Conduct in Human Research (2007) and was APPROVED on 14-Aug-2018.

It is the Principal Researcher’s responsibility to ensure that all researchers associated with this project are aware of the conditions of approval and which documents have been approved.

The Principal Researcher is required to notify the Secretary of the Ethics Committee, via amendment or progress report, of

- Any significant change to the project and the reason for that change, including an indication of ethical implications (if any);
- Serious adverse effects on participants and the action taken to address those effects;
- Any other unforeseen events or unexpected developments that merit notification;
- The inability of the Principal Researcher to continue in that role, or any other change in research personnel involved in the project;
- Any expiry of the insurance coverage provided with respect to sponsored clinical trials and proof of re-insurance;
- A delay of more than 12 months in the commencement of the project; and,
- Termination or closure of the project.

Additionally, the Principal Researcher is required to submit

- A Progress Report on the anniversary of approval and on completion of the project (forms to be provided);

The Ethics Committee may conduct an audit at any time.

All research subject to the Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Hospital Ethics Committee is a properly constituted Human Research Ethics Committee in accordance with the National Statement on Ethical Conduct in Human Research (2007).

SPECIAL CONDITIONS

None

SIGNED:

Please quote project number and title in all correspondence
Institutional Human Research Ethics Approval

Project Title: Understanding how to provide broad-reach support for working adults with type 2 diabetes to sit less and move more

Chief Investigator: A/Prof Genevieve Healy

Supervisor: None

Co-Investigator(s): Prof David Dunstan, Prof Neville Owen, Prof Elizabeth Eakin, Prof Stuart Biddle, Dr Ana Goode, Dr Paul Gardiner, Melanie Townsend, Ruth Grigg

School(s): School of Public Health, The University of Queensland

Approval Number: 2019003086

Granting Agency/Degree: Diabetes Australia General Grant

Duration: 30 September 2020

Comments/Conditions:

- HREA Form, 08/01/2020
- Appendix A – Recruitment, 08/01/2020
- Appendix B - participant information sheet and consent, 08/01/2020
- Appendix C example scripts, 08/01/2020
- Appendix D – surveys, 08/01/2020
- Project Description_DART FINAL, 08/01/2020
- Y20G-HEAG_Offer Ltr, 08/01/2020

Note: if this approval is for amendments to an already approved protocol for which a UQ Clinical Trials Protection/Insurance Form was originally submitted, then the researchers must directly notify the UQ Insurance Office of any changes to that Form and Participant Information Sheets & Consent Forms as a result of the amendments, before action.

Name of responsible Sub-Committee:
University of Queensland Medicine, Low & Negligible Risk Ethics Sub-Committee
This project complies with the provisions contained in the National Statement on Ethical Conduct in Human Research and complies with the regulations governing experimentation on humans.

Name of Ethics Sub-Committee representative:
Associate Professor Diann Eley
Chairperson
University of Queensland Medicine, Low & Negligible Risk Ethics Sub-Committee

Signature ___________________________ Date 28/01/2020
Ethics Committee

Certificate of Approval of Amendments

This is to certify that amendments to

Project: 359/18 Office-based Program To Improve Metabolic control In Sedentary Employees with type 2 diabetes: The OPTIMISE your health study

Principal Researcher: Professor David Dunstan

Amendment:
1. Amendments to Protocol, PICF, and supporting documents;
2. Addition of COVID-19 Snapshot Survey;
3. Changes to research personnel – Appointment of Ashleigh Homer, Brianna Fjeldsoe, Tracy Comans, Francis Dzakpasu, Ana Goode, and Len Gray

Attachments:
Protocol version 10.0 dated 11-May-2020
PICF version 10.1 dated 2-Jul-2020
Ethically Defensible Plan version 2.0 dated 11-May-2020
Advertisement version 2.0 dated 11-May-2020
Trialfacts Promotional Material version 5.0 dated 11-May-2020
COVID-19 Snapshot Survey version 1.0 dated 11-May-2020

have been approved in accordance with your amendment application dated 11-May-2020 on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

SPECIAL CONDITION: All research projects approved by the Alfred Hospital Ethics Committee are subject to, and must be carried out in compliance with, the most recent applicable COVID-19 government and relevant institution’s restrictions.

It is now your responsibility to ensure that all people associated with this particular research project are made aware of what has actually been approved and any caveats specified in correspondence with the Ethics Committee. Any further change to the application which is likely to have a significant impact on the ethical considerations of this project will require approval from the Ethics Committee.

Professor John J. McNeil

Date: 16-Jun-2020
Chair, Ethics Committee

All research subject to Alfred Hospital Ethics Committee review must be conducted in accordance with the National Statement on Ethical Conduct in Human Research (2007).

The Alfred Ethics Committee is a properly constituted Human Research Ethics Committee operating in accordance with the National Statement on Ethical Conduct in Human Research (2007).
Appendix D – Supplementary materials for Chapter 5

The following supplementary items, relating to the OPTIMISE Your Health protocol and methodology paper (Chapter 5) published in the *BMC Public Health* journal, are accessible through [https://doi.org/10.1186/s12889-022-13123-x](https://doi.org/10.1186/s12889-022-13123-x)

- Additional file 1. Research funding.
- Additional file 2. Participant information and consent form.
- Additional file 3. Inclusion and exclusion criteria.
- Additional file 4. Intervention handbook.
- Additional file 5. Example activity feedback report.
- Additional file 6. Intervention strategy list.
- Additional file 8. COVID-19 Snapshot Questionnaire.
- Additional file 9. Questionnaire measures.
- Additional file 10. Adverse events report.
- Additional file 11. SPIRIT checklist.
Appendix E – Supplementary materials for Chapter 6

The following supplementary items, relating to Chapter 6 published in the *Journal of Medical Internet Research Diabetes*, are accessible through https://doi.org/10.2196/36181

- **Multimedia Appendix 1.** COVID-19 pandemic restrictions timeline in Melbourne, Australia, 2020.
- **Multimedia Appendix 2.** Self-reported changes in work, physical activity, sedentary behaviour, motivation, and musculoskeletal discomfort following COVID-19 pandemic lockdown restrictions.
- **Multimedia Appendix 3.** Linear regression activity comparisons prior to lockdown restrictions and during for each participant.
Appendix F – Media releases related to thesis

Media relating to Chapter 5 – The OPTIMISE Your Health trial

Newspaper article in The Advertiser relating to the OPTIMISE Your Health trial: Moving on Diabetes
Getting moving to help control chronic disease

BRIGID O’CONNELL

SPENDING more of the working day standing and moving could be the magic recipe to improve the health of the one million Australian adults with type 2 diabetes.

As COVID restrictions ease and office workers return to buildings, the Baker Heart and Diabetes Institute is recruiting for a world-first study to test if using a standing desk and being given advice on how to move during the working day can improve glucose control.

Head of physical activity at the Baker, David Dunstan, said research had shown it was possible to reduce sedentary time in an office setting, while blood glucose control and insulin levels could be improved in type 2 diabetes by increasing movement.

But recruiting 250 office workers for the 18-month study was the first real-world test. “Our skeletal muscles are our largest users of glucose in the body, so when we’re up and active those muscles help our body clear and regulate blood glucose for energy,” Prof Dunstan said.

“We know the more optimal diabetes control reduces the risk of those devastating complications down the track, like heart and kidney disease, amputations and blindness.

“If we can intervene early and really shift our habits and social norms, we may make inroads into improving the diabetes management in the future.”

Prof Dunstan said given extra sedentary time increased the risk of developing type 2 diabetes and also hampered disease control, he hoped the trial would be attractive to those looking to forge healthy habits.

“Figures around the world have shown that time spent sedentary has certainly increased over the lockdown restriction phase and the ongoing working from home phase,” Prof Dunstan said.

“Getting back into the office is a chance for a reset and an opportunity to start thinking of a different outlook to how we undertake our work during the typical working day.”

OPTIMISE trial participants are given a height-adjustable desk, fitbit and health coach support. Regular blood tests will measure glycaemic control, blood vessel function and heart health.

Simon Massouras, an IT teacher at St John’s Regional College in Dandenong, Victoria, has lost 5kg since joining the study. The 53-year-old – who was diagnosed eight years ago following a period of long work days, no exercise and poor diet – said he hoped the increased movement would allow him to go off his daily diabetes medication.
Television news article on Channel 7 relating to the OPTIMISE Your Health trial: How a simple workplace change could help fight diabetes

Video available at https://youtu.be/4WiQW9Ti09c
Office is best fit for health

Pandemic was proof

EXCLUSIVE

GRANT MCMURTHY

INCIDENTAL activity while moving around the office or travelling to work may be even more beneficial than deliberate exercise for some people, new research suggests.

In a quick fix, researchers were able to accurately monitor the movements of Melbourne office workers before and during Covid lockdowns, raising concerns about the effect of restrictions on type 2 diabetes.

Months before the pandemic, scientists at the Baker Institute placed Fitbits on a group of diabetics to monitor and encourage increase activity during their time working in offices.

When the lockdown hit and the study participants began working from home, the devices continued to produce data showing just how severe the effect was, as well as surprising revelations about the value of deliberate and incidental activity.

Researcher Christian Brakenridge said that once lockdown hit, the previously active 11 study participants could be seen to be sitting for an extra hour a day and shedding 1500 steps – a tenth of their pre-pandemic activity.

"Pretty much immediately we saw changes because they were the type of people who are keen to change their lifestyle," Mr Brakenridge said.

"Even a drop of about 500 steps, or an increase of 500 steps, is associated with a 2.9 per cent change in risk of death and cardiovascular disease. So, even though these changes might seem kind of small and widespread at the public level, they actually have pretty meaningful implications for the rate at which our population endures those ill-health effects."

As well as Fitbits, the 11 office workers were provided with sit-stand desks to encourage movement in the office as well as weekly coaching to help manage their diabetes.

Results of the Baker study, published in the open access journal JMIR Diabetes, track their activity over a combined 2447 days, highlighting a dramatic increase in sedentary behaviours as well as short periods of intense activity during permitted daily outdoor periods.

However, the monitoring revealed that even the unprecedented effort of walking around suburbs made by so many people during lockdown was not enough to offset the missed steps taken as part of a normal working day.

"When they did go for walks it was longer than what it was before the pandemic," Mr Brakenridge said.

"But they missed the rest of that time doing incidental activity – commuting, incidental walking around the office – and on average overall, the activity levels reduced."

"The pandemic restrictions were important for reducing the transmission of the virus, but they unfortunately also have other implications for chronic disease management."

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The Conversation article on the COVID-19 pandemic, sedentary behaviour, and participation in the OPTIMISE Your Health trial

New figures show global diabetes prevalence has increased by 16% in the past two years, with 537 million adults (aged 20-79) now estimated to be living with the chronic condition.

Over this same time period, COVID has stopped us doing some of the things that help prevent and manage diabetes. One particularly concerning example is an increase to sedentary behaviour (sitting down for long periods of time), which was already at dangerous levels pre-COVID. Some estimates indicate the pandemic added an average three hours to our sitting time each day.

Now lockdowns have eased in many places, it is vital we get moving again – and in the right way – to change this picture.

Reducing sitting time is a good starting place to help people with diabetes, pre-diabetes and other chronic conditions to reach healthier levels of physical activity.
COVID saw us sitting longer – and diabetes rose globally by 16% in 2 years. Time to get moving

Read more: Fewer diabetes patients are picking up their insulin prescriptions – another way the pandemic has delayed health care for many

A growing global problem

Data from the International Diabetes Federation’s 10th Diabetes Atlas, officially launched today, shows about 10% of the world’s population aged 20–79 now live with diabetes, and diabetes prevalence is predicted to steadily increase to around 784 million adults by 2045.

Most of these people live with type 2 diabetes, a chronic condition that affects the way the body processes blood sugar (glucose). In type 2 diabetes, repeated fluctuations in blood glucose levels eventually mean the body doesn’t respond properly with insulin – the hormone produced that allows glucose to go from the blood to the cells.

This can progress to common diabetes complications such as blindness, nerve damage, heart disease and kidney disease. Recent reports point to an even wider range of diabetes impacts like increased risk of liver disease, dementia, depression, and some cancers.

Our research highlights regular movement as a key way to help manage diabetes and help prevent complications. Getting moving effectively improves glucose control, blood pressure, vascular health and memory.

Read more: A disease that breeds disease: why is type 2 diabetes linked to increased risk of cancer and dementia?

Moving out of lockdown

As we transition to COVID-normal, we must leave lockdown levels of physical inactivity and sedentary behaviour behind.
Reducing sitting time is a good “first step” because it appears more achievable for many and less daunting than a new exercise regime, especially for people who have been highly inactive or who live with a chronic health condition.

Simple lifestyle strategies to reduce sitting time and replace it with either standing or, even better, light physical activity improve metabolism, and for people with type 2 diabetes can prevent and help “sponge up” rising blood glucose levels if insulin isn’t being produced properly.

Breaking up sitting every hour with just two or three minutes of walking can make a difference to glucose control compared with prolonged and uninterrupted sitting. And some evidence shows greater time spent doing light activities daily like household chores, playing with pets, or light garden work, can provide greater blood sugar control over 24 hours than structured workouts.

We are currently testing how these small changes influence diabetes in a clinical trial. Our goal is to help desk workers with diabetes reduce and break up their sitting time.

Lorys’ story

One of our trial participants, Lorys, 64, was gutted when he was diagnosed with type 2 diabetes 11 years ago.

Like many people, he was leading a sedentary lifestyle. A demanding job involving long hours at the computer meant he was sitting for most of the day, stressed and anxious about his health. Diabetes medication wasn’t improving his blood glucose levels as much as he would have liked. Then the pandemic arrived and working from home exacerbated the problem because he was doing less everyday activity, such as walking to and around the office.

As part of the trial, Lorys has started using a sit-stand workstation and an activity tracker to encourage regular short walks throughout the day. He’s focussed on gradual lifestyle changes, small steps that feel achievable and have already added up to make a big difference.

Since the start of this year, Lorys’ HbA1c level – a key diabetes health marker – has almost halved. He’s lost weight and says his mental outlook is more positive. He says he no longer thinks of diabetes as a “death sentence”.

Read more: Got pre-diabetes? Here’s five things to eat or avoid to prevent type 2 diabetes

5 ways to quit the sit
Whether we have type 2 diabetes, pre-diabetes, or just want to get back to a healthier lifestyle post-lockdowns, most of us can benefit from some simple changes:

1. try using a height-adjustable (sit-to-stand) desk. Start standing for a few minutes each day and gradually scale up to standing or walking for 30 minutes of every hour

2. use phone meetings or phone calls as a prompt to stand

3. try walking work meetings or catching up with friends for a walk

4. after finishing a work task or an episode of your favourite TV show, take a short walk around the block

5. set a calendar reminder or use a wearable device to prompt you to stand up and move regularly throughout the day.

The body is made for motion.

It’s been a tough couple of years, especially for people living which chronic health conditions. But it’s not too late to make changes to prevent and manage diabetes and its complications.
Appendix G – Work completed during candidature outside central aim of the thesis

Grant application to the Academy of Finland

Academy of Finland: “OPTIMUS: A Randomized Controlled Trial to Influence Sustained Glycaemic Control by Reducing Muscle Inactivity Time in Middle-Aged and Older Office Workers with Type 2 Diabetes” (Pesola A, Owen N, Dunstan D, Juutinen Finni T, Healy GN, Brakenridge CJ, Lamberg S); AU $1,109,565; 2021 – 2024. AWARDED.

Primary investigator Dr. Arto Pesola conducted a laboratory visit to the Baker Heart and Diabetes Institute in 2019. I collaborated with Dr. Pesola on several different investigations. One of the main ventures was using electromyographical sensing garments to measure deskwork sedentary behaviour, and then countermeasures to prolonged sedentary behaviour (e.g., body weight resistance activities, standing, light walking). We presented on the findings of these in an internal laboratory meeting. In the presentation and following discussion we hypothesised that chronic muscular inactivity was the predominant process behind the detrimental effect of excessive sitting. Electromyographical sensing pants interpreting quadriceps, hamstrings, and gluteal muscles can measure this inactivity and activity, therefore increasing the resolution and validity of measurement of these processes over traditional measures such as accelerometers / inclinometers. This is especially the case when one can be either an active sitter, or passive sitter (electromyographically silent sitting behaviour).

Similar to previous findings on sedentary behaviour suggesting that sedentary behaviour does not differ between active and inactive populations (245), recent evidence has highlighted that exercise does not change daily muscle inactivity levels (246). Therefore, reducing muscle inactivity levels may need to be conducted across the day with greater volumes of light and incidental muscle activity, and potentially independent of posture. We sought to adapt the OPTIMISE Your Health protocol for use in Finnish community-dwelling adults with type 2 diabetes. We included the provision of an under-desk pedal system to facilitate decreases in muscle inactivity time (when muscles are metabolically silent), when participants are sitting at their desks.
Dr. Pesola, myself, and my PhD supervisors created a grant application to the Academy of Finland. After many drafting rounds we submitted it, and it was subsequently accepted for funding.

An abbreviated grant application for the OPTIMUS trial is depicted below.
Research plan

1 Aim and objectives

1.1 Significance of the research project in relation to current knowledge, premise underpinning the research:

**Rising diabetes rates: preventing diabetes-related complications is a priority.** Type 2 diabetes (T2D) prevalence is high among middle-aged and older (45-65 y) workers – up to 7.7% - with a substantial impact on work productivity, risk of absenteeism and inability to work (Schofield et al. 2014). These risks increase with diabetes duration (Chaker et al. 2015; Lavigne et al. 2003). Cardiovascular disease (CVD) is the most common long term complication of T2D, predominantly related to chronic hyperglycaemia (Cavalot et al. 2006). The importance of glycaemic control (HbA1c ≤ 7%) in people with T2D is underscored by the landmark findings of the UK Prospective Diabetes Study’s 10-year follow up, whereby each 1% reduction in HbA1c (absolute) was associated with relative reductions in diabetes-related mortality (-21%), myocardial infarction (-14%) and microvascular events (-37%) (Stratton et al. 2000). One potential strategy to address this risk is through reducing and breaking up prolonged sitting time: a strategy which has been demonstrated to be effective and acceptable in adults with T2D – at least acutely. What is now required is evidence from Phase II efficacy trials on the long term impact of reducing and breaking up sitting time in the vulnerable population we propose to study - middle-aged and older office workers with T2D.

**Reducing chronic postprandial hyperglycaemia in T2D is a daily lifestyle consideration.** Relative to their nondiabetic counterparts, those with T2D are more likely to spend a large proportion of the day (~9h) in a state of postprandial hyperglycaemia (van Dijk et al. 2011). Compared with fasting glucose (FBG), postprandial glucose (PPG) is a stronger correlate of HbA1c, particularly when HbA1c levels are good to fair (<7.3% to < 9.2%) (Ketema and Kibret 2015). Laboratory experiments and clinical study findings indicate that this postprandial state is accompanied by oxidative stress, which in turn triggers a biochemical inflammatory cascade, endothelial dysfunction and sympathetic hyperactivity (O’Keefe and Bell 2007). Such postprandial glucose excursions, when repeated multiple times throughout the day, can create an environment conducive to the development of atherosclerotic risk factors, and diabetic and cardiovascular complications (O’Keefe and Bell 2007). Additionally, in those living with T2D, PPG is an independent predictor of future cardiovascular events, above and beyond fasting glucose levels (Cavalot et al. 2006), and has also been suggested to be a key driver of the reduced productivity of workers with T2D through adverse effects on cognitive function and mood (Sommerfield, Deary, and Frier 2004). Thus, there is a need to better understand whether making sustained changes in a ubiquitous risk exposure in people’s daily lives – prolonged periods of time spent sitting, particularly in the workplace –can lead to improvements in HbA1c and other cardiometabolic risk factors in those with T2D.

**Too much sitting is a new and potentially modifiable contributor to the complications of T2D.** Our team has reported that the mean daily (objectively measured) sitting time in Australian adults is 8.8h/d and Finnish office workers’ muscles are inactive for 80% of working hours (Healy et al. 2015; Pesola et al. 2014). Time spent sitting, particularly in prolonged unbroken bouts, is associated with prevalent diabetes and related risk factors, and that these relationships are independent of moderate-vigorous physical activity (MVPA) (Bellettiere et al. 2018; Healy et al. 2011). Some of the strongest evidence for the detrimental effects of excessive sitting is for CVD risk. Indeed, a recent meta-analysis of nine prospective cohort studies comprising more than 720,000 participants concluded that CVD incidence risk associated with total self-reported sedentary time is nonlinear, with increased risk evident for >10h/d of sedentary time (Pandey et al. 2016). Furthermore, the increased risk of CVD incidence associated with sedentary time was
insufficient of baseline CVD risk factor burden and MVPA levels. Such findings are of particular relevance to T2D, since more than 80% of persons with T2D die of CVD-related causes (Laakso 2010).

**Insights from the group’s previous research suggest that reducing and breaking up sitting time could provide a novel and feasible management strategy in T2D.** The group’s most recent findings (Dempsey et al. 2016) showed for the first time in adults with T2D, the acute (1d) beneficial effects on glucose metabolism of interrupting prolonged sitting, resulting from both light ambulation and simple resistance (muscle strengthening) activities (half-squats, calf raises and gluteal contractions) for three min every 30 min over seven hours (i.e., 14 breaks per condition; Fig 1).

![Fig 1: Effect of 3 trial conditions on net 7-h postprandial iAUC for (A) plasma glucose (mmol h L⁻¹) and (B) serum insulin (nmol h L⁻¹) in metformin-/diet-controlled men and women with T2D (n=24). Mean ± SEM (Dempsey et al. 2016)](image)

The magnitude of the PPG reduction following the acute interruptions to prolonged sitting time in persons with T2D was substantially greater (-39%) than what have been previously reported in overweight or obese adults (Dunstan et al. 2012). Because decreases in PPG appear to be the greatest contributor to subsequent decreases in HbA1c (Ketema and Kibret 2015), these findings underpin our scientific rationale for a trial to examine the longer-term effects on glycaemic control in middle-aged and older adults with T2D, via reducing and breaking up prolonged daily sitting.

**Muscle inactivity is the main mechanism why prolonged sitting decreases glycaemic control.** The large lower body muscle groups are inactive during sitting (Pesola et al. 2015). Blood flow slows down at the vicinity of inactive muscle fibers and contraction-mediated glucose uptake decreases due to low muscle fiber energy demand, resulting in muscle insulin resistance (Bergouignan et al. 2011; Rynders et al. 2018; Hamilton et al. 2018). In case of prolonged muscle inactivity, single bout of exercise is not sufficient to reverse the decrements in whole body glucose intolerance, but frequent light-intensity muscle activity that breaks up the prolonged muscle inactivity periods is needed (Duvivier et al. 2018; Rynders et al. 2018). Accordingly, breaking up prolonged muscle inactivity by frequently activating large muscle groups is important for maintaining the signaling pathways affecting insulin sensitivity (Bergouignan et al. 2013; Hamilton et al. 2007). Therefore, muscle inactivity is one of the main mechanisms why prolonged sitting decreases glycaemic control. This mechanism is manifested in type 2 diabetic people due to poorer baseline level of insulin resistance (Dempsey et al. 2018). To date relatively few studies have assessed muscle activity during habitual life, but have been limited mostly to laboratory conditions because of sophisticated and demanding setups required for EMG recordings. **Our group has developed novel electromyography (EMG) methodology that is integrated in elastic shorts, providing a possibility to monitor muscle inactivity and activity time directly from muscles during 1-3 days of habitual living with 1000 Hz sampling rate (Fig 2A).** By measuring the effects of muscle inactivity reduction directly from muscles in type 2
diabetic participants, that are particularly susceptible to the risks of prolonged muscle inactivity, we can provide a paradigm shift in the understanding how the risks of sitting can be reduced.

The following examples from our previous work illustrate the potential of EMG over contemporary physical activity measuring methods (like accelerometers):

- **Based on our group's research, muscle inactivity time measured directly from muscles during habitual living is adversely associated with HDL and triglyceride concentrations** in a cohort of physically active individuals (Pesola et al. 2015).

- **EMG is the most accurate measure of physical activity at low intensities (Fig 2A).** Even though thigh muscles are inactive almost 70% of the measurement time, the activity time consists of more than 12 000 quick (1.4 s) bursts obtained at an average intensity below that of walking (5.8% of EMG during maximum isometric voluntary contraction) (Tikkanen et al. 2013). Such short muscle activities can be metabolically meaningful in type 2 diabetic participants (Dempsey et al. 2016).

- **Our group has reported that overweight individuals have more muscle inactivity during sitting, but more muscle activity during standing, therefore being exposed to a larger EMG increment when transitioning from sitting to standing, as compared to their normal weight peers (Fig 2B)** (Pesola et al. 2016). Replacing sitting with standing has been more effective in improving metabolic outcomes in overweight than normal weight individuals, but the mechanism is unknown (Thorpe et al. 2014; Miyashita et al. 2013; Bailey and Locke 2015; Brocklebank et al. 2017). The difference in EMG can be one explanation for the observed differences in metabolic effectiveness of reduced sitting.

- **EMG measures physical activity also during non-ambulatory activities** which are
unrelated to acceleration of movement (Fig 2C). Examples are standing and simple muscle activities, which both can improve glucoregulation as compared to prolonged sitting (Dempsey et al. 2016; Thorp et al. 2014).

- **Tailored counseling targeting reduced sitting, a similar behavioural intervention as proposed here, can specifically reduce daily muscle inactivity time (Pesola et al. 2014).** Instead, exercise for fitness did not change daily muscle inactivity patterns (Finni et al. 2014).

**Multi-component interventions can reduce sedentary time.** Our group has an established track record in conducting some of the first pragmatic sedentary behaviour intervention trials demonstrating the feasibility and efficacy of multi-component interventions with office workers (Pesola et al. 2017; Healy et al. 2016). In our cluster-randomized controlled trial (ISRCTN28668090), 133 office workers with young children were randomized to either an individualized counseling intervention (lecture, face-to-face tailored counseling with goal setting and behavioural contracts, two follow-up calls during the first 6 months), or a no-treatment control groups (Finni et al. 2011). The intervention effectively reduced sedentary leisure time [-21.2 (95% CI -37.3 to -5.1) min/8 hours, likelihood ratio P<0.001], increased light activity time [13.4 (-2.2 to 29.0) min/8 hours, likelihood ratio P = 0.008] and breaks per sedentary hour [1.0 (-0.2 to 2.2), likelihood ratio P = 0.010] at 3 months and the results were sustained at the 12 months follow-up (Pesola et al. 2017). In our NHMRC-funded (APP1002706) cluster-randomised workplace intervention trial (the Stand Up Victoria study), 231 desk-bound office workers (overall sitting time 10.3h per 16h day at baseline) from 14 worksites of one organisation were randomised to either a multi-component organisational, environmental (sit stand workstation), individual (in-person/telephone health coaching) intervention or to a usual practice control (Dunstan et al. 2013). Over three months, the multi-component intervention group significantly reduced their total daily sitting time by -1.3 [95% CI: –1.7, –0.9] h/d and their prolonged sitting at work by >1h/d more than controls (Healy et al. 2016). Our epidemiological and acute intervention studies indicate that changes in sitting time of this magnitude would be expected to confer an improved cardiometabolic risk profile (Healy et al. 2015; Pesola et al. 2015) and diminished CVD risk (Pandey et al. 2016), but this needs to be scientifically tested in a rigorous ‘real-world’ randomised controlled trial.

**Portable under-desk pedal machines are a practical, unobtrusive and effective strategy to reduce muscle inactivity in a seated posture.** A typical strategy to prevent the metabolic risks of prolonged sitting is to reduce the time spent in sitting posture per se. However, office workers face many barriers when trying to reduce their sitting time. The nature of computer-based work and exposure to furniture designed for a seated posture have been considered to be the main factors influencing sitting time, whereas behavioural strategies, such as standing meetings, are challenging to implement because social norms facilitate sitting (Hadgraft et al. 2016). Worksite interventions that include environmental supports like activity permissive workstations are more effective than those that do not (Neuhaus et al. 2014). Based on user’s self-report, portable pedal machines are an effective, useful, functional, convenient, and comfortable environmental strategy to counteract sedentary behaviour (Bastien Tardif et al. 2018). However, lower body discomfort may increase after 30 minutes of continuous use, but this can be minimized with optimized positioning of the pedals as well as education to pedal in intervals (Baker et al. 2019). In a randomized controlled multi-component workplace trial, overweight adults working in sedentary jobs pedalled on an average of 37.7% of all days they had access to the pedal machine, for an average of 31 min/day (Carr et al. 2013). In overweight middle-aged sedentary workers, using a pedal machine increases quadriceps and hamstring muscle activity (+150%), total body energy expenditure (+150%, to 128 kcal/h or 1.7 METs), and does not impair cognitive performance as compared to working at a sedentary workstation (Carr et al. 2014). In a randomized cross-over trial in overweight and obese adults, activating muscles by cycling at 2 METs for 2.5 hours during an 8-hour work day produced improvements in 24-hour mean glucose concentration, with 6-h
The postprandial glucose integrated area under the curve (iAUC) being 44% lower than during a control day spent sitting (Crespo et al. 2016). The effects of cycling were greater than those of walking (24% lower 6-h postprandial glucose iAUC as compared to sitting), even though the total energy expenditure was similar between cycling and walking. One possible reason may be a greater quadriceps and hamstring muscle activity during cycling than walking (Hamilton, Hamilton, and Zderic 2018). Therefore, portable pedal machines show potential in decreasing muscle inactivity time and in producing a metabolically meaningful stimulus in a seated posture. The energy expenditure and muscle activity increment when using the pedal machine is comparable or greater to that when transitioning from sitting to standing (Gao et al. 2017). However, use of portable pedal machine may be less prone to the behavioral barriers of reducing sitting at a workplace setting (Hadgraft et al. 2016).

The portable pedal machine is used as one intervention component in this trial. It provides an assistive strategy to reduce muscle inactivity time when sitting is necessitated by working tasks, therefore complementing the strategies that target reductions in sitting time.

1.2 Research questions and/or hypotheses:

To determine, in an RCT with a usual-care control condition, the efficacy of a 6-month multicomponent intervention incorporating tailored health coaching, a portable pedal machine, and Smartphone-based self-monitoring and behavioural prompting tool on:

- **Primary outcomes**: Overall daily muscle inactivity time and glycaemic control (HbA1c).
- **Secondary outcomes**: Overall sitting time, sitting time accumulated in prolonged bouts (≥30 min); postprandial glucose metabolism assessed as incremental area under the curve (iAUC) for glucose and insulin during a 2h, 75g oral glucose tolerance test (OGTT); body composition (fat and lean mass); arterial stiffness (pulse wave velocity); blood pressure (BP); and fasting lipid levels. We will also examine other covariates and potential confounders including physical activity, diet, medication use, illness and health-related quality of life.

**Hypotheses (two tailed):**

1. After the six month intervention, middle-aged and older office workers with T2D receiving the intervention will differ from the controls on both the primary and secondary outcomes.
2. The decrease in muscle inactivity time is associated with the changes in glycosylated haemoglobin

1.3 Expected research results and their anticipated scientific impact, potential for scientific breakthroughs and for promoting scientific renewal:

Diabetes treatment already costs the healthcare system about 9% of the total healthcare budget each year, and the increased frequency of complications associated with poor glycaemic control contributes substantially to ill health, disability and early death. Better glycaemic control is associated with lower diabetes-related mortality, myocardial infarction and microvascular events. This is important, because coronary heart disease is responsible for up to 80% of deaths for people with T2D. PPG is an independent predictor of future cardiovascular events. This study is **significant** because it will be the first long-term RCT to provide level II evidence about the efficacy of an evidence-based multi-component intervention for reducing muscle inactivity time in people with T2D. We will determine the extent to which the striking acute changes in PPG metabolism that have been observed in adults with T2D can be translated to longer-term changes and benefits for overall glycaemic control (HbA1c). The multi-component intervention is **original** (such an approach has never been tested with clinically relevant outcomes), **relevant** (it targets a major public health issue; >350 000 Finns have T2D), and **feasible** (it will be conducted by a team of internationally recognised researchers who are leaders in this field). An international
expert network published a highly cited consensus statement of the definition of sedentary behaviour in 2017 (Tremblay et al. 2017). *In the paper they suggest that use of EMG as a measure of sedentary behaviour could advance our understanding of the health implications of sedentary behaviour.* Therefore, the EMG recordings of this study can provide a paradigm shift in sedentary behaviour field by reporting how an intervention targeting reductions in muscle inactivity (by pedaling while sitting, by standing, and by ambulation), translates to improved glucoregulation in people living with type 2 diabetes. EMG is *sensitive* to detect the expected trial effectiveness, and as a most *direct* measure of muscle inactivity, it is a *relevant* exposure measure for the expected biomarker changes.

1.4 Special objective of call (concerns Academy Programmes and other thematic calls):

2 Implementation

2.1 Work plan and schedule:

**Study design:** This is a six month, controlled-trial design, in which middle-aged and older office workers with T2D (n=250) will be randomly assigned to one of two conditions: 1) a multi-component intervention to reduce sitting time; 2) a usual-care control condition. The intervention group’s outcomes will be compared at three and six months to those of the control condition. We have selected a duration that exceeds the median intervention duration (16 weeks) for the 18 physical activity studies in T2D included in a meta-analysis in which improved glycaemic control was observed (Umpierre et al. 2013). The trial will adhere to the CONSORT Statement extension for non-drug interventions and be registered on the ISRCTN Clinical Trials registry.

**Sample size:** With an estimated 20% attrition based on our previous intervention trials, 2-tailed significance of 2.5% (correcting for 2 primary outcomes), 125 participants per group are required for 80% power to detect minimum differences of interest (MDI) of 0.5% in HbA1c and for 97% power to detect MDI of 1h/16h-day in muscle inactivity time, assuming standard deviations (SD) of 1.6 and 1.5 and a pre-post correlation (r) of 0.7 and 0.6 respectively. A 0.5% HbA1c decrease is clinically meaningful (∼10% reduction in diabetes-related mortality) (Stratton et al. 2000) and about average for physical activity advice interventions that achieve behaviour change (Umpierre et al. 2013). The minimum detectable differences for secondary outcomes with 80-90% power, 5% significance are: 0.5h/16h-day sitting (1.3, r=0.6), 0.6–0.7 h/16h day prolonged sitting (1.8, r=0.6); 1.0–1.1 mmol/L fasting glucose (3, r=0.6); 23–26 pmol/L fasting insulin (70, r=0.6); 0.35–0.40 SD 2-h IAUC for post-load glucose and insulin (r=0.5); 0.5–0.6 mmol/L fasting triglycerides (1.5, r=0.6); 0.08–0.09 mmol/L fasting HDL (0.3, r=0.8); 0.26–0.30 mmol/L fasting LDL (0.9, r=0.7); 5.2–6.0 mmHg systolic and 3.1–3.6 mmHg diastolic BP (15 and 9, r=0.5).

**Timeline:** The study will be conducted across 4 years with a rolling recruitment over 30 months.

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2.2 Research data and material, methods, and research environment

**Participants:** We will recruit overweight/obese (BMI 25 to <40 kg/m²) men and women aged 45–65 years with clinician-diagnosed T2D (treated by diet alone or with oral hypoglycaemic agents; not insulin), who are working at least 0.8 full-time equivalent in a desk-based occupation and able to obtain employer permission to install the provided portable pedal machine at their work desk. In working adults, ages 45–65 years covers both the largest prevalence of T2D (Du\nnstan et al. 2002) and the ages during which diabetes-related complications begin to manifest. Ineligibility will be based on HbA1c <6.5% (indicative of good control) or >10% (reflects uncontrolled); pregnancy; current smoker; non-Smartphone user; regularly engaged in moderate-intensity exercise ≥ 150 min/week and strength training ≥2 x week for >3 months; and/or major illness/physical problems (acute or chronic) that may limit participation in the intervention.

**Recruitment and screening:** Participants living in the Mikkeli area (50km radius from Active Life Lab) will be recruited via multiple strategies. Our investigator team has experience in the recruitment of large (n>100) samples of preclinical populations for lifestyle-intervention trials. PI Pesola’s study (ISRCTN28668090) involving a 12 months lifestyle intervention recruited 133 adults doing office work and having young children, over a 12 month period, demonstrates strong recruitment feasibility. The recruitment process will be assisted by Active Life Lab’s positioning close to the local healthcare. We reach two hundred at-risk individuals each week because of close collaboration with the local healthcare and common procedures for health screening. Based on this recent experience, we estimate that we will need to generate 1290 expressions of interest and undertake HbA1c screening in 909 participants to recruit 250 who meet the eligibility criteria. We will use a targeted recruitment strategy that includes clearly defining study eligibility in our recruitment materials, as well as providing brief information to eligible participants to assist their understanding of the components of the intervention. Recruitment and screening will begin in month 6 of the first year and will occur on a rolling basis over the subsequent 30 months to recruit 250 participants. Screening will target persons who are aged 45–65 with T2D via educating the local doctors of the new study and the eligibility criteria, recruitment letters to the local healthcare, radio/print advertising, targeted mail-outs through the Finnish Diabetes Association member database, community presentations and social media. Potential candidates will be provided with a pathology request form (via mail) for HbA1c testing at a local pathology centre to confirm eligibility.

**Randomisation:** After baseline testing, participants will be randomised, in random blocks of sizes 4–8, across one stratum (men/women), using the NHMRC Clinical Trials Centre randomisation service. Although it is not possible to blind research staff and participants to the group assignment, assessment of the primary outcomes and data analysis will be performed blinded.

**Multi-component Intervention.** Our multi-component intervention will consist of three elements: (1) health coaching (individually tailored education, training and support for muscle inactivity time reduction); (2) provision of a portable pedal machine (environmental restructuring, Fig 3A); and (3) provision of an activity tracker and a Smartphone-based self-monitoring and behavioural prompting tool (Fig 3B). It will be delivered over six months, consistent with previous lifestyle intervention trial evidence (Eakin et al. 2007). The intervention target is a decrease in muscle inactivity time by 1h per day, sustained during the six month intervention. Muscle inactivity time will be replaced by seated muscle activities when sitting is necessitated by work demands (health coaching and pedals), and increased standing and ambulation, as in our recent acute intervention studies (health coaching and smartphone) (Pesola et al. 2014; Dempsey et al. 2016).

1. **Health coaching:** This will consist of two in-person and eight telephone-delivered sessions over six months, to support initiation and maintenance of the muscle inactivity-time
changes. In-person meetings will occur at baseline (‘initial’) and again at the three month assessment (‘booster’), with project staff trained in motivational interviewing and using intervention protocols based on our previous trials (Neuhaus et al. 2014; Finni et al. 2011). The first meeting will occur in the participant’s workplace for installation of the portable pedal machine, with the second meeting in the workplace or the Active Life Lab, as per participant preferences. Consistent with a protocol shown to be feasible, acceptable and effective in our previous telephone-delivered lifestyle-change programs (Pesola et al. 2017; Laukkanen et al. 2015; Dunstan et al. 2013), and supported by a systematic review of the efficacy of telephone-delivered physical activity interventions (Eakin et al. 2007), telephone calls from the same staff member during the course of the intervention will occur on a tapered schedule: one call per week for the first three weeks to one call every three weeks (ie eight calls over the remaining 21 weeks). The initial in-person meeting will provide feedback on baseline levels of muscle inactivity time, assess and enhance motivation, and identify/set goals related to opportunities to decrease muscle inactivity time in both the home and work environment. A participant workbook will be adapted from our previous interventions. The workbook will address sitting time and health, common barriers to reducing sitting time, and information to facilitate goal setting and self-monitoring. Telephone follow-up calls will be brief (~10min) and used to check on progress in reducing muscle inactivity time (via pedalling, frequent ambulation and increased standing) at home and at work, address problems, revise goals as needed and reinforce goal attainment. An intervention protocol checklist will be used by health coaches as a guide during each call, with the checklist completed after each contact. All intervention contact attempts, completions and duration of calls will be recorded.

2. **Portable pedal machine**: To facilitate changes in muscle inactivity time in the workplace, a portable pedal machine (Fig. 3A; Desk Cycle 2 pedal machine) will be provided for the 6-month duration of the study. The pedal machine can be placed below the existing workstation. It allows participants to easily and quietly activate their muscles while still interfacing with their computer. The first in-person health coaching session in the participant’s workplace will provide the opportunity to familiarize them with this type of pedal machine, and demonstrate how to use the pedal machine effectively and safely. Subsequent telephone contacts will confirm that the pedal machine is being used to decrease muscle inactivity time, and the participants will keep a log sheet on the use of pedal machine during EMG measurement periods.

3. **Smartphone-based monitoring and behavioural prompting**: A wrist-worn activity monitor will be provided for each participant to continuously self-monitor their daily movement patterns (via the steps function) in real-time. Through the already developed and tested Rise & Recharge mobile app (iOS and Android), participants can set prompts to interrupt their idle states and also receive reinforcing feedback in real-time on interruptions to prolonged periods of sedentary behaviour. Briefly, the Rise & Recharge display (Fig. 3B) breaks down the day into 30-minute slots, denoted by grey dots that change to a coloured dot when sufficient movement to register as a break is achieved (>15 steps). Research staff will set up the wrist monitor and the app during the initial face-to-face intervention session and encourage participants to use the device.

4. **Control (usual care) condition**: To minimise attrition, usual care participants will receive a thank-you letter following each assessment (baseline, 3 and 6 months), plus standard, off-the-shelf diabetes self-management education brochures (from Finnish Diabetes Association), and a monthly generic project newsletter, containing updates and non-tailored information on diabetes education and various health behaviours. A modified (3 month) version of the intervention will be offered after the six month assessment. There is no evidence that simply providing written material for the management of T2D improves glycaemic control.
Figure 3A. DeskCycle 2 pedal machine. B. ‘Rise & Recharge’ app works in conjunction with wrist-worn movement trackers to deliver prompts and positive feedback in real time, focused on interrupting prolonged periods of sitting with brief physical activity breaks.

Measurement. There will be baseline, three and six months assessments at the Active Life Lab’s clinical research facility (~4h/person each testing session). Interviewer-administered questionnaires will be completed at each assessment visit. Participants will receive verbal and written requests (with confirmation of compliance at data collection time) to refrain from any moderate–vigorous physical activity, alcohol, and caffeine for 24h before the assessment to minimise any impact of these factors on biomarker measures. Objectively assessed EMG will be collected in the three, and sedentary and physical activity time in the 10d preceding the respective on-site assessments. On the testing day, participants will report to Active Life Lab in the morning (8am) having fasted for at least 8h. After completion of body composition, BP and arterial stiffness testing, an indwelling venous catheter will be inserted by a trained nurse for collection of blood measurements at half-hourly intervals during a 2h 75-g OGTT. All testing protocols outlined below are well established in our laboratory and used in our previous intervention trials.

- **EMG**: will be measured with shorts made of knitted fabric similar to elastic clothes, with capability to measure EMG from the skin surface of the quadriceps and hamstrings muscles (Myontec Ltd, Kuopio and Suunto Ltd, Vantaa, Finland, Fig 2). Bipolar electrode pair located on the distal part of the quadriceps and hamstrings. Four different sizes of shorts (L, XL, XXL, XXXL) will be used used. Electrode paste (Redux Electrolyte Crème, Parker Inc., USA) will be used on the electrode surfaces to improve and stabilize conductivity between the skin and electrodes. The shorts will be worn for two three days and the nights in between, at each time point, equalling nine days of EMG data per individual across the study. After every measurement period the shorts (electronics module detached) will be washed. The EMG shorts have been tested for validity, repeatability and feasibility by our group (Finni et al. 2007; Pesola et al. 2014; Tikkanen et al. 2014).

- **Bloods**: FPG, PPG and serum insulin (each 30min during a 2h, 75-g OGTT), HbA1c and fasting lipids (total cholesterol, triglycerides, high-density lipoprotein cholesterol) will be measured by a NATA-/RCPA-accredited laboratory using standard methods. Serum for insulin assays will be frozen at –80°C and measured in a single batch to minimise inter-assay variability. The glucose/insulin iAUC will be calculated using the trapezoidal method.

- **Sitting time/physical activity**: Overall sitting time, time in prolonged (≥30 min) bouts of sitting, and moderate-to-vigorous physical activity time, will be assessed using a highly accurate posture-based activity monitor (Lyden et al. 2012)(activPAL3™ model) worn on the thigh, 24h/d for 10d, in combination with an activity diary. Our research team has extensive experience (>2000 participants) in the collection and analysis of such data.

- **Body composition and anthropometry**: Total body and regional lean tissue mass, fat mass and percentage of body fat will be measured using Tanita MC-780 MA scanner. Weight, height, and waist and hip circumference will also be assessed using standard techniques.

- **Blood pressure and arterial stiffness**: An oscillometric device Arteriograph will be used to assess BP and arterial stiffness (aortic pulse wave velocity, aortic augmentation index and
central systolic blood pressure). The measurement, using a simple upper arm cuff, resembles normal blood pressure measurement and the procedure takes only 2–3 min. Participants will be required to sit quietly for a minimum of 5 min, after which three separate readings will be taken. The average of the latter two readings will be calculated.

- **Diet**: Assessed by three-day food diary and analysed for energy, macronutrients and other nutrients using the Nutri Flow software (Nutri Flow Oy, Oulu, Finland).
- **Medication use and illness/adverse events**: At each visit, study personnel will record information on medicine use (medicine name, dose and dosage), and any recent illnesses or any adverse event the participant attributes as ‘study-related’.
- **Health-related quality of life and mental wellbeing**: This will be assessed from the validated RAND-36 Health Related Quality of Life questionnaire and the WHO-5 wellbeing index.
- **Physical function measures**: Sit to stand test (10 times), timed up and go-test.

### Statistical analyses

Differences between groups in primary and secondary outcomes during (3 months), and at the end of the intervention (6 months) will be tested using mixed models accounting for repeated measures, and adjusting for baseline values and potential confounders. Outcomes are all continuous and expected to be either normal or log-normal, in which case log-transformation will be used. Possible confounders will be narrowed down to a number that can be modelled without overfitting, based on an objective criterion not open to manipulation (backwards elimination, p<0.2 association with the outcome) (Pocock et al. 2002). Analyses will follow intention-to-treat principles. Sensitivity to missing data handling will be evaluated by comparing results for completers’ analyses and alternative methods that are appropriate for different missing data scenarios (eg selection-covariate adjusted completers’ analysis and multiple imputation) (Groenwold et al. 2012). Analyses will be performed in R version 13.5 or higher. Significance is set at p<0.05 two-tailed, with significance adjustment for the two primary outcomes.

### 2.3 Risk assessment and alternative implementation strategies:

Recruitment of the participants for the study is a critical point of the research project. Thus, if the data collection through the primary strategies is unsuccessful or proves to be too slow, we will expand recruitment to additional areas near Mikkeli (such as Jyväskylä, Pieksämäki and Savonlinna), which are only a driving distance away from Mikkeli (100 km). Should there exist problems with inclinometer or health marker data collection, we will try to repeat the measurements, or use established imputation methodologies as detailed in Statistical analyses.

### 3 Research team and collaborators

#### 3.1 Project personnel and their relevant merits:

**Arto Pesola (Ph.D.)** works as a research manager in Active Life Lab in Xamk. His research focuses on sedentary behaviour physiology (Pesola et al. 2015), application of EMG methodology in sedentary behaviour research (Pesola et al. 2016), as well as on behavioural physical activity interventions in children and adults (Pesola et al. 2017, 2018). He has published 27 peer-reviewed articles which have gained more than 1100 citations (h-index 12, h-index divided by years from the first paper (m-index) 1,7, illustrating an outstanding impact). As a PI of current Ministry of Education funded project studying the effect of free bus rides on children's sedentary time (OKM 2019), a previous SuperPark project (Pesola et al. 2018), a researcher in several previous projects (InPact ISRCTN28668090/Ministry of Education, EMG24 Academy of Finland 2009-2010/#128643), and a project manager in a 1,4 m€ smart wellbeing laboratory project (ERDF303855, ERDF303855), Dr Pesola has gained experience in management of demanding
projects including novel research methodology. In 2014-2015 Dr Pesola worked as an expert member in a working group for Finnish sedentary behaviour recommendations invited by the Finnish Ministry of Social Affairs and Health. He has also worked as an active member of an international Sedentary Behaviour Research Network, which published the latest widely cited definition of sedentary behaviour in 2017 (Tremblay et al. 2017). Dr Pesola was awarded Young Investigator Award in biomedicine by Finnish Society of Sports Sciences in 2017. This project could provide an excellent starting point for his independent academic career and PhD project supervision.

Post-doc researcher Christian Brakenridge (Ba Clin Ex Phys, PhD) is currently completing his PhD at the Baker Heart and Diabetes Institute, Melbourne Australia and will complete his PhD in 2022. Mr Brakenridge has extensive experience delivering large workplace health interventions, as well as clinical experience prescribing exercise to patients with T2D. With the completion of his PhD, Christian will be well suited for post-doctoral research on the OPTIMUS project.

PhD researcher Suvi Lamberg (MSc in health sciences) is currently working as a senior lecturer in physiotherapy in South-Eastern Finland University of Applied Sciences.

3.2 Collaborators and their key merits in terms of the project:

Taija Juutinen Finni, Professor of Kinesiology at the University of Jyväskylä, Finland, a title of docent in exercise physiology at University of Eastern Finland. She is an internationally recognized biomechanics researcher with an H-index of 28 (WoS) and research grants > 2 M€. She has established the wearable EMG method in assessment of daily physical activity as will be used in this project. She has supervised 9 PhD students to completion and currently supervises 6. She is a senior editor of biomechanics and motor control section in the Scandinavian Journal of Medicine and Science in Sports (IF 3.6), editorial board member of Clinical Biomechanics, fellow of European College of Sport Science.

Professor Neville Owen has been the primary scientific driver in developing the research field of sedentary behavior and health. Publication numbers and citations rank him first internationally in the field. His research program covers observational-study evidence on health consequences and determinants of sedentary behaviour, the development of measurement methods, randomised controlled trials examining the feasibility and benefits of behavioural change, and laboratory and field-based studies to identify mechanisms underlying the effects of sedentary behaviour on chronic disease risk. He will provide conceptual, methodological and strategic guidance for all aspects of the proposed project.

Professor David Dunstan is Head of the Physical Activity Laboratory at the Baker Heart and Diabetes Institute in Melbourne and an NHMRC Senior Research Fellow. His research focuses on the role of physical activity and sedentary behaviour in the prevention and management of chronic diseases. He has published 175 peer-reviewed papers, including publications in high impact journals such as Circulation, Diabetes Care, Diabetologia, Obesity Reviews, Journal of the American Society of Nephrology, Journal of the American College of Cardiology. He will provide conceptual, methodological and strategic guidance for all aspects of the proposed project.

A/Prof Genevieve Healy is a NHMRC Career Development Fellow at the Cancer Prevention Research Centre in the School of Public Health at the University of Queensland, and an honorary research fellow at the Baker IDI Heart and Diabetes Institute, and Curtin University. Her PhD research reported some of the first evidence regarding the importance of regularly interrupting sedentary time for heart health. Her current research builds on this work to examine population-
level variations in prolonged sedentary time as well as the feasibility and acceptability of reducing this behaviour in key settings, such as the workplace. A/Prof Healy will assist with respect to the health coaching aspects of the intervention.

4 Responsible science

4.1 Research ethics:

All protocols will be submitted for ethical approval to the Central Finland Health Care District Committee on Research Ethics. All procedures follow Finnish legislation on Personal Data Act (22.4.1999/523) and Medical Research Act (9.4.1999/488 and 10.9.2010/794). All research activities will follow good scientific and clinical practices according to the updated guidelines of the National Advisory Board on Research Integrity in Finland. The participants will be recruited to the study on a voluntary basis, will be given truthful and realistic information on the procedures involved in the study, will be asked to sign an informed consent, and have the right to withdraw from the study at any time. The project will follow the principles of good scientific practice and ethical guidelines of the Academy.

4.2 Promoting open science:

We will publish all scientific articles in open access journals and aim to publish research data alongside the articles (considering data confidentiality). The green open access will be preferred or parallel publishing option will be negotiated with the publisher. We will also write articles to non-academic audiences in various national magazines targeted and make press releases of the most important results to be disseminated via newspapers and magazines. Accumulation of the findings will be placed in a project web-page.

4.3 Promoting equality and non-discrimination:

Gender equality will be taken into account when recruiting the personnel and by providing a research environment in which it is possible to combine career and family life. Non-discrimination is a central principle in all aspects of the research and project management.

5 Societal effects and impact

5.1 Effects and impact beyond academia:

There is the potential for our approach to be applicable and scalable at a population level, if successful. Indeed, our findings will have immediate translational application, informing clinical, public health and occupational health guidelines. This will provide the large – and rapidly increasing – numbers of middle-aged and older working Finns living with diabetes access to a simple, realistic approach to better manage their condition.

5.2 Considering principles of sustainable development:

Physically active lifestyle promotes several objectives of sustainable development and social sustainability. Accessible physical activity interventions, such as the components tested in this trial, improve equality in wellbeing accessibility (e.g. you can be active at the workplace instead of driving to a gym during non-work time), sustainable employment (promotion of healthy working years), a carbon neutral society (decreased private car usage via increased physically active commuting) and lifestyle respectful of the carrying capacity of the nature.
6 Bibliography

6.1 List of all the sources used in the research plan:

Baker Heart and Diabetes Seed Grant application

Baker Seed Grant: “The Integration of Lifestyle into Personalised Medicine Approaches: A machine learning-based algorithm for high-resolution and cost-effective characterization of sedentary behaviour” (Salim A, Brakenridge CJ, Owen N, Dunstan D); AU $95,000; 2022 – 2023.

Following the successful publication of the manuscript “The Associations of COVID-19 Lockdown Restrictions with Longer-Term Activity Levels of Working Adults With Type 2 Diabetes: Cohort Study” in JMIR Diabetes we set out to make further improvements to the Fitbit’s valid interpretation and characterisation of sedentary time.

Below follows the grant application that was created and submitted during my PhD candidate. It was developed iteratively with collaborators David Dunstan, Neville Owen and Agus Salim as project lead.

<table>
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<th>Baker Seed Fund Application</th>
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**Project Title:** Machine learning-based algorithm for high-resolution and cost-effective characterization of sedentary behaviour

**Project Leader:** David Dunstan, Agus Salim

**Date of Submission** 07/02/2022

Please submit your applications by email to the Commercialisation unit: guy.krippner@baker.edu.au.

1. **Provide a brief description of the unmet clinical need**

   Include the specific indication and how patients would be selected. Identify the limitations of existing technologies 190 words

Wearable physical activity (PA) trackers are being used in research settings as intervention and measurement tools, and increasingly are providing health-related information to consumers. Fitbit leads the market for wrist-worn fitness trackers in Australia. While Fitbit is known to have good concordance with research-grade accelerometers for light and moderate-intensity physical activities, little is known about Fitbit’s accuracy for measuring sedentary time. High sedentary time is associated with excess mortality, and increased cardiovascular risk. We and others
have reported that longer bouts of uninterrupted sitting time are also associated with incident CVD\(^2\) as well as worse cardiometabolic health\(^3\), metabolic syndrome and diabetes\(^4\). Fitbit generates a massive amount of minute-by-minute data, so it has the enormous potential to use high-resolution data and be a cost-effective method for capturing individual-specific sedentary behavior. However, being a wrist-worn device, Fitbit is known to overestimate steps\(^5\) for activities involving wrist movement such as when playing a video game. To accurately characterize sedentary behaviour, we need to develop a machine learning method that can correct its tendency to overestimate step counts and to discriminate sitting and standing postures, which are not discriminable from step counts alone.

2. Provide a brief description of technology

Summarise key features of technology; highlight one key piece of data; describe how technology meets unmet need; provide an estimate of the market size; highlight competitive advantage; how would the product be used 695 words

We are the world leaders in understanding and influencing the adverse consequences for diabetes and heart disease of large amounts of time spent sitting, and identifying the patterns of sitting time that are particularly high risk. Here, we propose to use a machine learning method, specifically the Hidden Semi-Markov Model (HSMM) to estimate key parameters of sedentary behaviour (total sedentary time and average bout duration) from Fitbit data. To improve detection of sedentary time, we will use other data produced by Fitbit, in addition to the minute-by-minute step count. These additional data are already part of the Fitbit system but some are not accessible to the wearer.

As a proof of concept, we have developed a HSMM model utilizing both Fitbit generated step-count and heart rate data. Heart rate data can be useful in distinguishing sitting from standing posture because standing would result in increased heart rate relative to sitting. Heart rate can also differentiate anomalously high step counts due to activities that involve wrist movement only. This is because physical activities will lead to increase in heart rate, so any increase in step counts without significant increase in heart rate is likely due to acceleration in the wrist only. We fitted the model to data from 11 intervention participants followed for more than a year\(^6\). The results show that while both algorithms overestimate the proportion of time spent on sedentary behavior by 11.1\% (SD = 7.5\%) for Fitbit and by 12.2\% (7.9\%) for our algorithm, our novel algorithm estimates the average sedentary bout to be 33 mins (SD=9 mins), very close to the estimates obtained using research-grade activPAL (mean=38 mins, SD = 9 mins). This constitutes a significant improvement over Fitbit-classification that consistently underestimate average sedentary bout (mean = 21 mins, SD = 5min). The integration of heart rate data clearly helps the differentiation of intermittent standing from sitting position and has led to an improved characterization of average sedentary bout, although we contend that heart rate data on its own is not enough. Overestimation of sedentary time clearly indicates the current failure of both Fitbit and our algorithm to discriminate prolonged standing from sitting. We plan to improve the algorithm by leveraging on the raw Fitbit 3-axis accelerometer data. These accelerometer data are used by Fitbit to estimate step counts but they are not accessible to users.
We will work in partnership with Fitbit (Dunstan has an established relationship) to acquire the raw accelerometer data. Over recent decades, several machine learning models have been developed to estimate posture using 3-axis accelerometer data\(^7,8\). We will improve and implement the posture-recognition algorithms and embed them within our algorithm. We hypothesize that this would result in better discrimination between sitting and standing, leading to more accurate estimation of both total time and average bout of sedentary behaviour, which we can also benchmark against cardiometabolic risk markers.

The algorithm will be validated using data from Baker-based OPTIMISE trial participants\(^9\) for whom Fitbit and the research-grade activPAL data, and a range of cardiometabolic risk markers that have already been shown to be associated with the sedentary time and to be able to be modified with changes in sedentary time, are available. We currently have data from 44 participants from various demographic backgrounds (gender, ethnicity, level of education). As the OPTIMISE trial recruitment is ongoing, we expect the number of participants to increase. Successful validation of our algorithm for Fitbit data (worldwide market share=7.3%) will put us in a strong position to submit a nationally-competitive grant for funding to extend our methods and apps to data from other devices with higher market share, especially Apple (market share = 19.3 %) and Xiaomi (market share = 19.6\%)\(^10\).

We expect that upon successful validation, the algorithms can be commercialized both as part of Fitbit and as standalone Android Apps, as well as providing them freely-available for research and academic purposes. Importantly, the accurate assessment of sedentary time (and the identification of high-risk patterns such as large volumes of prolonged unbroken sitting time across the day) will have significant future clinical and public health applications, especially so for those living with, or at risk of developing, type 2 diabetes and cardiovascular disease.

### 3. Proposal and budget

Describe the key experiment to advance translation; provide indicative milestones and timeline; define go/no go decision(s); Budget: FTE, direct costs, external costs **250 words**

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References


