Sedentary behaviour, musculoskeletal pain conditions and type 2 diabetes

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Dzakpasu, F. Q. S. (2023). Sedentary behaviour, musculoskeletal pain conditions and type 2 diabetes [PhD Thesis]. Australian Catholic University. https://doi.org/10.26199/acu.8z582

Sedentary Behaviour, Musculoskeletal Pain Conditions and Type 2 Diabetes

by

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MPH (Global Health and Advocacy), ChM (Urology), MBBS, BSc (Biomedical Science)

A thesis submitted in total Fulfilment of the requirements of the degree of

Doctor of Philosophy (PhD)

Mary MacKillop Institute for Health Research

(Behaviour, Environment and Cognition Research Program)

Faculty of Health Sciences

Australian Catholic University

January 2023

Declaration

This thesis contains no material that has been extracted in whole or in part from a thesis that I have submitted towards the award of any other academic qualifications (degree or diploma) in any other tertiary institution.

No other person's work has been used without due acknowledgement in the main text of the thesis.

All research procedures reported in the thesis received the approval of the relevant Ethics/Safety Committees (where required).

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Acknowledgement

Despite some challenges, it has been a good journey, especially in the early stages of the evolving COVID-19 pandemic. I have been fortunate to be mentored by some of the greatest authorities in the field of Physical Activity and Behavioural Epidemiology who were dedicated and committed to my research work, and for whom I would like to give acknowledgement. First and foremost, my sincere gratitude goes to my Primary (Principal) Supervisor (Associate Supervisor 'on paper'), Professor David W. Dunstan, the Head of the Baker-Deakin Department of Lifestyle and Diabetes, who was also formally with the Behaviour, Environment and Cognition Program at the Mary MacKillop Institute for Health Research (MMIHR), Australian Catholic University (ACU) for his mentorship. I can recall my first meeting with him when I was looking for a PhD supervisor. The discussion and his advice at that meeting motivated and encouraged me through my successful PhD application. Thank you for accepting me as one of your PhD students and guiding me through my research skills development to make this PhD thesis a reality.

I am honoured and grateful to have Professor Neville Owen, a Senior Scientist at the Physical Activity Laboratory of the Baker Heart and Diabetes Institute, and a Distinguished Professor at the Centre for Urban Transitions, Swinburne University as one of my Associate Supervisors. He mentored and shaped my understanding of the conceptual frameworks of scientific work, which has contributed enormously to the works presented in this thesis. Also, I would like to express my sincere gratitude to Doctor Alison Carver, my other Associate Supervisor, and my formal ACU-based Co-Supervisor, now a Senior Research Fellow at the National Centre for Healthy Ageing, Central Clinical School, Monash University. Her dedication, commitment, and encouragement throughout my candidature period contributed to my research skills development.

Also, my sincere thanks to Associate Professor Orly Lacham-Kaplan ('official' Principal Supervisor) and Associate Professor Anthony Barnett, ('official' Co-Supervisor) both at MMIHR-ACU for accepting to occupy their respective roles (as ACU-based supervisors 'on paper') when Professor David W. Dunstan and Doctor Alison Carver left ACU at the latter part of my candidature. Though they were not directly involved in the supervision of this thesis, these arrangements and their presence ensured a smooth continuity of my candidature. Also, I would like to acknowledge Professor Takemi Sugiyama, my formal Co-Supervisor at ACU who left for the Centre for Urban Transitions, Swinburne University early in my candidature. Additionally, thanks to Professor Ester Cerin of MMIHR-ACU for stepping in as my ACU-based Principal Supervisor when Associate Professor Orly Lacham-Kaplan left the University at the thesis amendment stage to enable me to get my PhD over the line.

Furthermore, I would like to acknowledge some collaborators who have contributed to my PhD thesis. First, my thanks go to Professor Flavia Cicuttini and Associate Professor Donna Urquhart of Monash University for their expert advice on musculoskeletal pain conditions and their contributions to

some of the studies presented in this thesis. Secondly, I am grateful to a team of collaborators at the Maastricht University in the Netherlands, especially Associate Professor Annemarie Koster, Professor Nicolaas Schaper, and Professor Bastiaan E. de Galan. They played a pivotal role in my successful application to solicit an external dataset from the Maastricht Study. Also, their contributions to the manuscript that came out of the Maastricht Study dataset are very much appreciated.

My sincere appreciations go to the team at the Physical Activity Laboratory of the Baker Heart and Diabetes Institute where I spent my entire PhD candidature period for the opportunities offered and where I was also able to access the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) dataset for one of the thesis' empirical studies. Also, I acknowledged the administrative support I had from MMIHR-ACU throughout my candidature.

I thank my family, especially my sisters and my late mother who sadly passed away just before the commencement of my PhD, for their continuous support and prayers, as well as everybody who has contributed in diverse ways to this thesis. Finally, my greatest thanks go to the Almighty God for His abundant grace and mercy throughout this wonderful journey.

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Abbreviations

AAS	Active Australia Survey
ADA	American Diabetes Association
ADL	Activities of Daily Living
AGEs	Advanced glycation end-products
AIC	Akaike information criterion
AMED	Allied and Complementary Medicine Database
AusDiab	Australian Diabetes, Obesity, and Lifestyle Study
BMI	Body mass index
BPS	Bodily pain scale
CCD	Census Collector District
CESD	Centre for Epidemiology Studies Short Depression Scale
CINAHL	Cumulative Index to Nursing and Allied Health Literature
CKD	Chronic kidney disease
CMRS	Cluster metabolic risk score
CONSORT	Consolidated Standards of Reporting Trials
CRP	C-reactive protein
CVD	Cardiovascular disease
DALYs	Disability-Adjusted Life-Years
DHD-index	Dutch Healthy Diet index
DHS	Department of Human Services
DPHACTO	Danish PHysical ACTivity cohort with Objective measurements
DVD	Digital Video Disc
EU	European Union
FTE	Full-time equivalent

GBD	Global Burden of Disease
GDP	Gross domestic product
GMS	Glucose metabolism status
GMUSC	Global Alliance for musculoskeletal Health
HbA_{1c}	Glycated haemoglobin
HDL	High-density lipoprotein
HOMA-IR	Homeostatic Model Assessment of Insulin Resistance
HRQoL	Health-related quality of life
hs-CRP	high-sensitivity C-reactive protein
iAUC	Incremental area under the curve
ICC	Intraclass (correlation) coefficient
IFG	Impaired fasting glucose
IGT	Impaired glucose tolerance
IL	Interleukin
ilr	isometric log-ratio
IPAQ	International Physical Activity Questionnaire
LAR	Leptin-adiponectin ratio
LBP	Lower back pain
LIPA	Light-intensity physical activity
LMICs	Low- and middle-income countries
LOCF	Last-observation-carried-forward
lrEM	log-ratio Expectation-Maximisation
MAR	Missing at random
METs	Metabolic equivalents
MIPA	Moderate-intensity physical activity
MPQ	McGill Pain Questionnaire

MSK	Musculoskeletal
MSP	Musculoskeletal pain
MVPA	Moderate-to-vigorous intensity physical activity
N/A	Not applicable
NCDs	Non-communicable diseases
NGM	Normal glucose metabolism
NGT	Normal glucose tolerance
NHANES	National Health and Nutrition Survey
NMQ	Nordic Musculoskeletal Questionnaire
NRS	Numeric Rating Scale
OGTT	Oral glucose tolerance test
OR	Odds ratio
PICO	Population, Intervention, Control/comparison and Outcome
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P	PRISMA-Protocol
PROSPERO	International prospective register of systematic reviews
QualSyst	Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields
RAGEs	Advanced glycation end-product (AGE)-receptors
RCS	Restricted cubic spline
RCT	Randomised control(led) trial
RevMan5	Review Manager version 5.4.1
SAS	Statistical Analysis System
SB	Sedentary behaviour
SE	Standard error
SF-36	36-Item Short-Form Health Survey questionnaire

SF-MPQ	short-form McGill Pain Questionnaire
sICAM-1	soluble Intracellular adhesion molecule-1
T2D	Type 2 diabetes
TNF-α	Tumour necrosis factor
TV	Television-viewing
UBP	Upper back pain
UK	United Kingdom
USA	United States of America
VAS	Visual Analog Scale
VIF	Variance Inflation Factor
VIPA	Vigorous-intensity physical activity
VRS	Verbal Rating Scale
WC	Waist circumference
WHO	World Health Organisation
WOMAC	Western Ontario and MacMaster Universities Osteoarthritis Index
YLD	Years lived with disability

Abstract

Sedentary behaviour (too much sitting, as distinct from too little physical activity or exercise) is of rising public health concern. It has been associated with increased risks of multiple chronic diseases, including cardiovascular conditions, metabolic disorders such as type 2 diabetes (T2D), and all-cause mortality. Also, there is growing evidence of potential risk associations with musculoskeletal pain (MSP) conditions. Importantly, MSP conditions have emerged as common comorbidities in people living with cardiometabolic conditions, especially so in those living with T2D.

The co-occurrence of excessive sedentary behaviour, T2D and MSP conditions, which is much more common in older adults is concerning. MSP conditions can be a barrier to regular physical activity participation in adults. An adequate level of moderate-to-vigorous intensity physical activity (MVPA) has been a cornerstone in the management of T2D and has also been known to be beneficial for pain management. The coexistence of T2D and MSP conditions may render many adults physically inactive and vulnerable to engaging in prolonged periods of sitting during waking hours, due at least in part to functional impairment and pain. Consequently, being physically inactive and engaging in excessive sedentary behaviour may have further detrimental impacts on both T2D and MSP conditions. Currently, the coexistence of MSP conditions and T2D in adults and the potential relationships with sedentary behaviour have been largely unexplored.

This thesis, therefore, aimed to explore the evidence on sedentary behaviour, MSP conditions, and T2D with the broad aim of understanding the associations of sedentary behaviour with pain related to musculoskeletal systems in adults and whether such potential relationships differ in those living with and without T2D.

To address this aim, an existing prospective dataset from an epidemiological study, the Australian Diabetes, Obesity and Lifestyle Study (AusDiab) and a cluster-randomised control trial, the Stand-Up Victoria Study, as well as a cross-sectional dataset from the Maastricht Study were analysed. First, a systematic review (*Study 1*), was conducted using the standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines with the purpose of identifying the existing evidence on associations of sedentary behaviour in occupational and non-occupational settings with MSP conditions, and to identify knowledge gaps to inform the thesis' empirical studies. This review (*Study 1*) found evidence of cross-sectional associations of both occupational and non-occupational sedentary behaviour with MSP conditions, with the associations in the occupational domain being dependent on the nature and the physical demand of the occupation. Evidence on prospective associations was inconclusive; however, there was a probable indication of a protective association of sedentary behaviour (device-measured) with some MSP conditions in tradespeople. Additionally, reducing desk-based (office) workers' sitting time was observed to be correlated with reduced MSP conditions or

discomfort. Also, the review identified a lack of a sufficient number of device-measured sedentary behaviour-based studies as well as prospective studies as key literature gaps.

Secondly, three empirical studies informed by the knowledge gaps from the systematic review were conducted. *Study 2 (Maastricht Study dataset – data of 2827 participants were analysed)*: In this study, logistic regression and restricted cubic spline statistical methods were utilised to examine the linear and non-linear cross-sectional associations of device-measured daily sitting time with MSP outcomes in adults with normal glucose metabolism (NGM), prediabetes, and T2D. Evidence of a cross-sectional association was observed between device-measured daily sitting time and knee pain (in a linear function). The association was only significant in those with T2D but not in those with prediabetes or NGM. No significant associations were observed for neck, shoulder, or low back pain; however, the relationships appeared to be curvilinear but statistically non-significant.

Study 3 (AusDiab dataset – 4099 participants' data were analysed): This study utilised a multilevel growth curve modelling to examine the prospective relationships of the common leisure-time sedentary behaviour, television-viewing (TV) time with bodily pain in adults with and without T2D over 12 years. The findings showed that bodily pain severity increases with age, and an increased volume of TV time at any given time point was significantly associated with increased bodily pain severity. The observed relationship was more pronounced in those with T2D than those without. In reference to those with NGM, the effect of T2D and prediabetes on bodily pain severity increased with increasing TV time, significantly so only in those with T2D when the TV time threshold increased above 2.5 hours per day.

Study 4 (Stand Up Victoria Study dataset – pooled data of 224 participants were analysed): Using compositional data analysis framework, prospective relationships with changes in multisite MSP of changes in desk-based workers' sitting, standing, and stepping, as well as the short-bouts and long-bouts of these behaviours at three- and 12-months were examined. Further, compositional isotemporal substitution modelling was performed to examine the impact of reallocating time among these behaviours on MSP outcomes. The findings demonstrated that in the short term (at three months) increased standing relative to changes in stepping and sitting composition was significantly associated with increased multisite MSP outcomes, and increased stepping relative to changes in sitting and standing was significantly associated with reduced multisite MSP outcomes. Reduced sitting relative to changes in standing and stepping was not significantly associated with multisite MSP changes at three months. Further, no significant associations were observed for changes in short-bouts relative to long-bouts of these behaviours with the MSP outcomes. In the longer term (at 12 months), there were no significant associations observed for the relationships. Noteworthy, increased standing appeared not to worsen multisite MSP outcomes in the long term. Additionally, reallocating time from sitting at baseline to standing or stepping at follow-ups with the other behaviour held constant at the mean could

favourably impact multisite MSP outcomes. Likewise, favourably reallocating time from baseline to follow-ups between the short and long bouts of a given behaviour while volumes of time spent in other behaviours are kept constant may have beneficial impacts on multisite MSP outcomes, especially in the longer term at 12 months.

In summary, the findings indicate that there is evidence of cross-sectional associations of sedentary behaviour with MSP conditions. The cross-sectional evidence appears stronger for knee pain, with evidence observed for both self-reported and device-measured sedentary behaviour, an association which seems to be driven mainly by the presence of T2D. Furthermore, the thesis found evidence of a prospective association of increased sedentary behaviour with increased bodily pain severity, a relationship which was more pronounced in those with T2D than those without. Additionally, reducing desk-based workers' sitting by increasing standing and stepping, would unlikely have adverse impacts on MSP outcomes, especially in the long term. These findings provide some implications for practice and future research in this context. They could also help to inform future work directed at developing an improved understanding of the potential biological mechanisms of sedentary behaviour's role in T2D/MSP conditions relationships in adults.

Keywords: activity behaviours, adults, bodily pain, chronic pain, desk-based workers, glucose metabolism status, growth curve model, sedentary time, sitting time, time-use composition

Chapter 1: Introduction

1.1 Background

Sedentary behaviour has emerged as a public health challenge globally [1]. It is defined as behaviours (sitting, lying, and inclined postures) during waking hours characterised by a total energy expenditure of less than or equal to (≤) 1.5METs/hour [1-3]. Sedentary behaviour is one component of the physical activity continuum and lies at the lower end of the spectrum. It is distinct from physical inactivity which is typically described as either non-engagement in any form of physical activity or failure to meet the minimum recommended guidelines for moderate-to-vigorous intensity physical activity (MVPA) [1, 2]. An overview of the physical activity spectrum is illustrated in Figure 1.1. More time spent in upstream activity behaviours of the spectrum has been shown to be beneficially associated with multiple indicators of better health outcomes and has been the centrepiece of clinical and public health recommendations [4, 5]. In recent decades, public health researchers have intensified interest in understanding the impacts of excessive volume of time spent in downstream activity behaviours, specifically sedentary behaviour [1-3, 5].

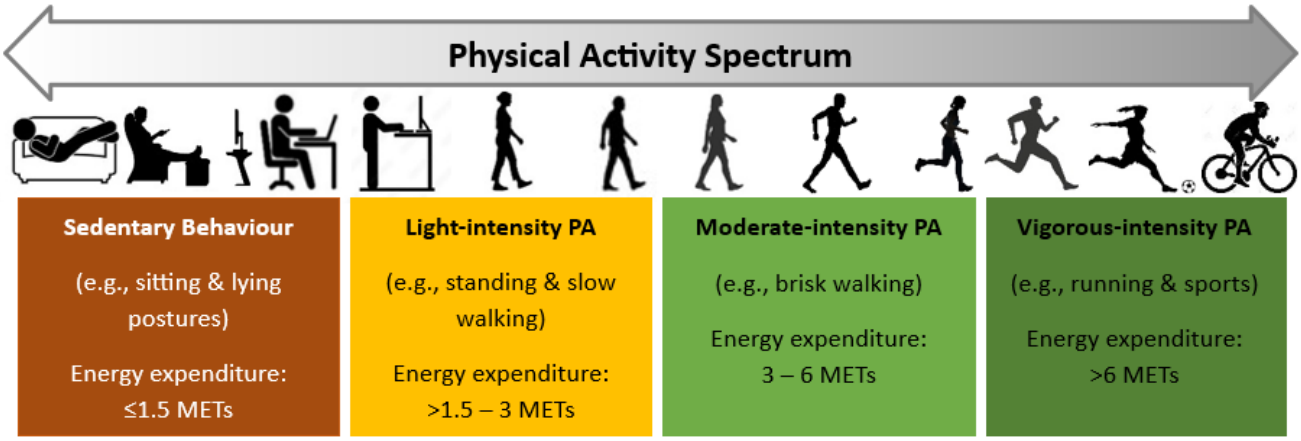


Figure 1.1: Physical Activity (PA) Continuum

There is increased acknowledgement of the negative health impacts of sedentary behaviour, especially the risks are exacerbated among the most vulnerable populations [6]. Specifically, it has been identified that the prevalence of sedentary behaviour in vulnerable adults, especially older adults and those living with cardiometabolic disorders such as cardiovascular diseases and type 2 diabetes (T2D) is considerably higher than in the less vulnerable populations and without these disorders [7]. Globally, T2D accounts for over 90 per cent of all cases of diabetes and contributes substantially to the global burden of non-communicable diseases (NCDs) [8]. Sedentary behaviour negatively impacts multiple health outcomes in people living with T2D, particularly in those who are also physically inactive [9, 10].

Musculoskeletal pain (MSP) conditions, which are those disorders that affect musculoskeletal structures such as bones, cartilage, muscles, tendons, ligaments, nerves and surrounding tissues [11, 12] have emerged as a common co-morbidity increasingly reported in adults with T2D [13, 14]. MSP conditions are mostly associated with bodily pain and functional limitations [11, 12]. Although multiple factors are likely to play a role in the rising prevalence of MSP conditions in adults, particularly in those with T2D, it is also possible that sedentary behaviour may be another important contributing factor. From a general population perspective, time spent sitting is shown to be potentially associated with increased risks of MSP conditions [15-17]; although there are suggestions that the relationship could be bi-directional, whereby sedentary behaviour is also the consequence of the presence of MSP conditions [18, 19]. The direction of the relationship between MSP conditions and sedentary behaviour warrants further exploration.

The debilitating effects of MSP conditions in adults, particularly in those with T2D, are not only restricted to impacts on quality of life but also present a barrier to engagement in adequate recommended levels of physical activity, which is considered a cornerstone in the management of T2D [20]. Notwithstanding the impact on physical activity participation, people living with T2D and coexisting MSP conditions are likely to experience worsening glycaemic control when inappropriate pharmacological treatment such as corticosteroids and some non-steroid anti-inflammatory drugs (NSAIDs) are used for pain management [21]. Although the mechanisms explaining the pathophysiology of MSP conditions in T2D [22, 23] are still unclear, there are suggestions that environmental and behavioural risk factors may also play important contributing roles. Interestingly, evidence from population-based studies has shown there are detrimental associations of sedentary lifestyle (or behaviour) and some environmental attributes with outcomes related to MSP conditions [24, 25]. Furthermore, epidemiological evidence indicates sedentary behaviour is associated with increased adiposity [26, 27]; being overweight and/or obese increases the risk of T2D [28, 29] and has also been associated with an increased risk of MSP conditions [30]. A probable biological mechanism could be the heightened systemic inflammatory processes induced by adiposity [31, 32]. Systemic inflammatory changes are thought to play a significant role in the pathophysiology of T2D as well as MSP and bodily pain-related conditions [33, 34]. Also, there is emerging evidence that sedentary time is associated with elevated systemic inflammatory processes [35]. Given that there is growing evidence which indicates that time spent in sedentary behaviour is higher in those living with T2D than those without T2D [7], it could be plausible that excessive volume of sedentary behaviour may partly contribute to the rising prevalence of MSP conditions in T2D.

Evidence of associations between high volumes of sedentary behaviour and chronic diseases, including T2D incidence, has resulted in revisions to public health physical activity guidelines whereby reductions in sedentary behaviour and breaking up prolonged uninterrupted sitting are encouraged [10, 36-39]. Furthermore, experimental studies have reported improved biomarkers related to glycaemic control in T2D with brief activity interruptions to prolonged sitting [40-42]. For instance, interrupting prolonged

sitting with light-intensity physical activity (LIPA), which may include intermittent bouts of standing, light walking and simple resistance exercises showed improved blood glucose response and insulin sensitivity in T2D [41, 43]. Thus, there are potential benefits of LIPA interruptions during prolonged sitting bouts in people with T2D. It has been suggested that LIPA in vulnerable populations such as older adults and those living with T2D could be a safe and more acceptable approach to reducing high volumes of sitting [9] and provide a steppingstone to more active lifestyles. Also, desk-based workers spend higher proportions of their waking hours sitting (sedentary behaviour) in the office which can increase their occupational health risks [44]. Therefore, LIPA interruptions, including intermittent standing to break up prolonged sitting, could be beneficial in reducing overall sitting time in desk-based workers. An estimated proportion of time spent in the different components of the physical activity spectrum in adults is illustrated in Figure 1.2 (Image adapted from Grace & Dunstan [5]), with LIPA time having the potential to displace a substantial amount of sedentary time [5].

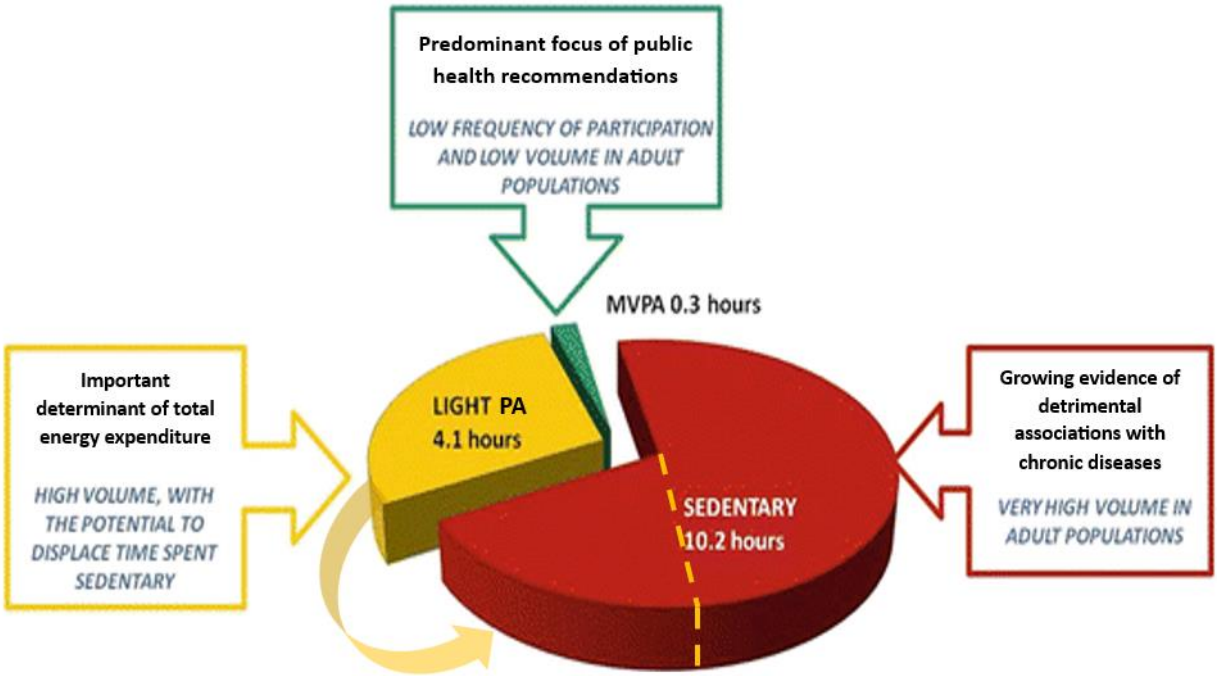


Figure 1.2: Estimated (device-measured) proportions of time spent in the physical activity spectrum in adults. *The arrow illustrates the potential scope for increasing light-intensity physical activity through displacing portions of time spent in sedentary behaviour.*

The prevalence of sedentary behaviour among adults increases with age and is much higher in older adults, particularly at the stage when their physical activity participation declines [6, 45]. Among adults of working age, sedentary time is mostly accumulated in occupational settings [44]. There is inconclusive evidence on the relationships of sedentary behaviour in different occupational settings with health outcomes [46-48]. Nevertheless, recent evidence suggests that desk-based workers can have higher tendencies to accumulate higher volumes of sitting time [44, 49], which has been shown to be associated

with adverse health outcomes [44, 50]. In contrast, proponents of the "physical activity paradox" concept suggest sedentary behaviour in occupational groups that engage in more labour-intensive occupations may have protective associations with health outcomes [51-53]. However, prior literature on the relationships of sedentary behaviour with MSP conditions has not been explicit on sedentary behaviour accumulated in different occupational settings and the potential relationships with MSP conditions outcomes [17, 54].

The growing evidence of adverse associations of higher volumes of sitting (sedentary behaviour) in desk-based workers has led to an increased interest in workplace interventions to reduce desk-based workers sitting time [55-58]. Evidence indicates that workplace strategies that consciously or unconsciously increase workplace active movements, such as the use of height-adjustable workstations can be effective in reducing substantial amounts of desk-based workers' daily accumulated sitting time [56-58]. Importantly, there is emerging evidence of possible beneficial associations of changing desk-based workers' sitting behaviour through breaking up prolonged sitting time and passively increasing physically active behaviours with cardiometabolic risk markers [59-61]. Also, plausible beneficial impacts on outcomes related to MSP conditions of reduced desk-based workers' sedentary behaviour, especially prolonged uninterrupted sitting have been suggested [46, 48, 62-64]. Therefore, exploring further this emerging evidence would be promising, given that MSP conditions are among the most common ill-health complaints of workers which account for absenteeism and lost productivity [65-68].

At present, the evidence indicates that most workplace sedentary behaviour reduction strategies among desk-based workers, especially those utilising sit-stand workstations have substantially reduced sitting time mainly through increases in standing time with only modest changes in ambulatory (stepping or walking) time [69]. Few studies have examined the MSP impacts of changing desk-based workers' time spent sitting, standing, and stepping brought about by workplace interventions to reduce sedentary behaviour. Specifically, there is a lack of evidence on prospective associations of changing desk-based workers sitting, standing, and stepping behaviours with MSP outcomes. Nonetheless, there is inconclusive evidence that suggests increased prolonged static standing could have undesirable associations with MSP outcomes [46, 62, 63]. Similarly, few studies have documented that reducing desk-based workers' sitting time could be beneficially associated with MSP outcomes [46, 48, 62-64].

The drawback of this previous evidence on the relationships between changing desk-based workers' sitting or standing behaviour with MSP outcome, however, is that those previous studies mainly focussed on the absolute changes in the behaviours in isolation [46, 62, 63]. These waking hours activity behaviours are time-use behaviours which are composite data [70]; therefore, changes in time spent in any component of these activity behaviours, sitting, standing, and stepping are interdependent [70]. There is a paucity of studies exploring the interdependency attribute of changing desk-based workers' activity behaviours and the potential relationship with MSP outcomes. In this context, there are suggestions that

the relative balance of time spent in different activity behaviours in a composition is an important determinant of overall health outcome [71-73]. In other words, time spent in any component of activity behaviours, sitting, standing, or stepping relative to the other activity behaviours has a greater predictive value of health outcome than the absolute time spent in any individual activity behaviour [71-73]. Therefore, employing methodological approaches that can explore this interdependency characteristic of time-use activity behaviours could provide insights relevant to understanding the MSP impacts of reducing sedentary behaviour among desk-based workers [70, 73, 74].

In summary, there is growing evidence of a rising prevalence of MSP conditions in adults, which is now also commonly reported in those living with T2D and the consequent impacts on effective glycaemic management [21, 75]. However, there has been little research on the potential contributions of behavioural risk factors to MSP conditions in T2D. New insights from experimental studies indicate that interrupting prolonged sitting with LIPA may be beneficial for glycaemic control in people living with T2D [40, 41, 76]. Further, a study has demonstrated that displacing sedentary time with physical activity of any intensity may improve pain and disability in people with MSP conditions [77]. That said, there are strong merits for exploring the relationship between sedentary behaviour and MSP conditions, and whether such relationships would be different in people living with and without T2D. Also, it would be informative in this regard of understanding the relative balance of displacing portions of daily accumulated sedentary behaviour (sitting time) with physically active behaviours including standing and stepping time on MSP outcomes. To this end, the main focus of this thesis, therefore, was to use observational data from population-based epidemiological studies as well as randomised controlled trial data of a subgroup of population who were desk-based workers to better understand the potential relationships of sedentary behaviour with MSP conditions in a population of adults living with and without T2D.

1.2 Challenges of musculoskeletal pain conditions in type 2 diabetes

Aside from the known complications of long-standing T2D due to the effects of uncontrolled hyperglycaemia, MSP conditions such as those involving joints, are also a common multimorbidity in some people living with diabetes, particularly T2D [78]. There is evidence that T2D is associated with a higher risk of developing and progression of some MSP conditions such as those involving joints [23, 79, 80]. For instance, systematic review-based evidence indicates that T2D is positively associated with knee osteoarthritis [80] and carpal tunnel syndrome [79]. Notably, the coexistence of MSP conditions in older adults with T2D can impede routine daily functional and physical abilities such as active transport to destinations. Compounding this problem is the absence of a clear understanding of pathophysiological mechanisms underpinning MSP conditions in T2D [21-23, 81, 82].

The causes of chronic pain conditions, including pain associated with MSP conditions are generally multifaceted with the interplay of socioeconomic, metabolic, physical, biological as well as psychological factors [83, 84]. Some potential mechanisms of MSP conditions in people with diabetes, in general, have been put forward [22, 81]. However, it is plausible that such mechanisms may not progress in isolation, but rather intertwine and possibly be mediated by other factors [22, 81]. Apart from some individual intrinsic factors, including old age and duration of T2D which is the most common, behavioural factors such as sedentary behaviour as well as environmental factors which can influence, and shape a person's decision-making could play some role in this complex. There is growing evidence of the potential associations of sedentary behaviour and some environmental attributes with MSP conditions [24, 25, 75, 85]. A review study, for instance, has indicated there is a plausible association between sedentary behaviour and MSP condition, specifically, back pain [85]. Likewise, findings from a large prospective study suggest environmental walkability index and sedentary behaviour influence outcomes of MSP conditions in adults [25]. Therefore, evidence from studies exploring the relationships of sedentary behaviour with MSP conditions in those with T2D may provide some relevant insights into the roles of sedentary behaviour in MSP conditions pathways in T2D.

1.3 Summary of evidence gaps

Despite the compelling epidemiological evidence of detrimental associations between sedentary behaviour and health outcomes [5, 10, 86], there is yet inconclusive evidence on the associations of sedentary behaviour with MSP conditions. Further, it is unknown whether such associations would potentially differ in those with or without T2D. Also, there is convincing evidence of associations between T2D and MSP conditions, however, there are no specific explanatory mechanisms for MSP conditions in T2D [80, 87, 88]. Also, the plausible moderating role of T2D in the associations of sedentary behaviour with MSP conditions has not been explored. Additionally, there is limited evidence on the benefits of replacing portions of time spent in sedentary behaviour (sitting) with physically active behaviours (standing or stepping) on MSP condition outcomes.

1.4 Thesis aims

The overarching aim of this thesis is to explore the associations of sedentary behaviour with MSP conditions and related outcomes in adults living with and without T2D. It is hypothesised that the accumulation of high volumes of sedentary behaviour (sitting time) would be associated with a greater risk of MSP conditions in adults living with and without T2D, and this would be more pronounced in those with

T2D. Further, it examines whether displacing large portions of daily time spent sitting with standing or stepping will positively impact MSP conditions.

To address this broad aim of the thesis, statistical modelling methods were used to analyse existing epidemiological datasets (from the AusDiab Study [89] and the Maastricht Study [90]) and a randomised controlled trial dataset (from the Stand Up Victoria Study [55]). Evidence synthesised in this thesis aims to provide some new insights into the relationships of sedentary behaviour with MSP conditions in adults with and without T2D.

1.4.1 Thesis objectives

The following objectives guided the studies that were undertaken to achieve the overarching aim of the thesis:

1. To examine the associations of sedentary behaviour with MSP conditions and whether the associations differ between those with and without T2D.
2. To examine whether hypothetically substituting portions of total daily accumulated sitting time with standing or stepping may beneficially impact MSP conditions in adults.

Chapter 2: Literature Review

2.1 The dual burden of type 2 diabetes and musculoskeletal pain conditions

Despite improvements in life expectancy in recent decades [91, 92], the global mortality burden attributable to non-communicable diseases (NCD) has risen steadily [93, 94]. The 2016 data on the global burden of diseases indicate that NCDs accounted for 61.4% of worldwide Disability-Adjusted Life-Years (DALYs) [95]. Furthermore, DALYs attributable to T2D and MSP conditions are high and have increased proportionately in the last 3 – 4 decades [95, 96]. Epidemiological data indicate that there is a rising trend of T2D and MSP conditions, which is possibly due to the ageing global population and improved life expectancy [97-99]. Whilst recent global data from 2010 – 2019 indicate that the absolute number of DALYs has remained stable, there has been an over 80% increase in the DALYs from T2D [98].

T2D is a metabolic disorder characterised by hyperglycaemia, hyperinsulinemia, insulin resistance and dyslipidaemia which predisposes to an increased risk of cardiovascular disease [100, 101]. The aetiology of T2D involves a complex interaction of biological, epigenetic and environmental factors. However, the fundamental pathophysiology that underpins T2D is progressive insulin resistance and to some extent relative defect in insulin secretion [100]. There are several risk factors which mediate T2D aetiology, including non-modifiable factors such as old age and family history, as well as modifiable risk factors, for example, overweight/obesity and lifestyle behaviours such as sedentary behaviour, physical inactivity and unhealthy dietary behaviour [100, 102]. The rising prevalence of T2D, a key contributing factor to cardiovascular disease-related deaths, substantially accounts for the increase in NCDs' DALYs globally [103-105]. For instance, Zhou and colleagues [104] pooled data from 751 population-based studies between 1980 and 2014 and found that the prevalence of T2D in adults substantially rose from 108 million to 422 million within those 35 years.

With the growing global population, as a result of rising life expectancy and an ageing population with decreased mortality [92, 104, 105], people living with T2D are expected to increase exponentially [98, 106-109]. The pace of the rise in T2D prevalence could pose some threats to global public health expenditure, both in high-income countries (HICs) and low- and middle-income countries (LMICs) alike [106, 110-112]. Of concern though is the rapidly rising prevalence of T2D in LMICs in recent decades [104, 108, 109, 113]. For instance, the age-standardised prevalence of T2D in adults has been reported to be much higher in LMICs compared to HICs [104], and the rate of growth in the burden of T2D is much higher in LMICs [113]. Also, LMICs are projected to experience the greatest increase in T2D-related burden in the coming decades [109]. This will further constrain the healthcare budgets of these resource-limited countries, especially the health cost of managing T2D and related complications, as well as comorbidities including MSP conditions [104, 105].

MSP conditions are ubiquitous, with most presenting as either acute or persistent chronic pain, as well as functional disability [12, 114, 115]. The impacts of MSP conditions can be devastating, limiting a person's activity and dexterity [116, 117]. Furthermore, MSP conditions negatively impact health outcomes and well-being, including fatigue, psychological problems, and sleep difficulties [12, 14, 118]. Chronic diseases such as mental disorders, cardiovascular conditions, chronic respiratory conditions, and metabolic disorders such as T2D are commonly associated with MSP conditions [13, 14]. In Australia, for example, T2D is identified as the most common chronic disease that coexists with MSP conditions in those requiring hospitalisation [119].

Worldwide, the contribution of MSP conditions to the global disease burden has increased significantly [99, 120], with a recent report indicating that from 1990 – 2019 there have been increases in incident cases (59.86%), deaths (116.02%), and DALYs (77.39%) of MSP conditions [99]. A previous report on the global data between 1990 and 2016 showed a similar trend of the MSP conditions' burden [95]. Global disease burden data in 2016 for NCDs indicate MSP conditions are the second highest contributor to "years lived with disability" (YLD) in the world [97]. Low back pain and neck pain have been identified as the leading cause of YLD worldwide [95, 121]. Furthermore, global mortality attributable to MSP conditions is considerable, due partly to the ageing population globally [14, 122]. According to WHO data, between 1986 and 2011, MSP condition-related mortality increased by 67% worldwide [122]. Epidemiological evidence indicates MSP conditions increase the risk of mortality which is possibly due to an increased risk of multi-morbidities [123, 124]. Evidence synthesised from a meta-analysis of pooled data from observational prospective cohort studies, for example, concluded that osteoarthritis increases the risk of mortality due to cardiovascular conditions [124].

Although MSP conditions exist across life-course, the prevalence increases with age [14, 125, 126]. The continued shift towards an ageing population globally [97], coupled with the rising prevalence of NCDs such as cardiovascular diseases and T2D, as well as their associated risk factors, e.g., obesity and sedentariness the global MSP condition-related burdens are expected to keep rising [97, 99, 127]. In Europe, for instance, the Survey of Health, Ageing and Retirement in Europe (SHARE) study observed the prevalence of MSP conditions as ranging between 18.6% and 45.6% in adults [128]. Furthermore, the worldwide prevalence of MSP conditions is much higher among older adult populations [97, 126, 129]. According to the Australian Bureau of Statistics 2014-15 data, 61% of Australians aged between 25 and 64 years old reported living with MSP conditions, with the prevalence being much higher in those between 75 and 84 years, at 72% [119]. The United States NHIS study has also documented that more than one in every two adults in America lives with a MSP condition, with the rate almost three-fourth in those above 65 years [130]. Additionally, the prevalence is increasing across all world regions, especially, in LMICs [114]. The WHO's Study on global AGEing and adult health (SAGE) data, for example, highlights a high prevalence of MSP conditions in most LMICs [125].

Aside from the disability burden, MSP conditions present considerable economic burdens in terms of health care costs to individuals and society, as well as work loss due to disability [120, 131, 132]. In 2015, the mean proportional increase in MSP conditions DALYs globally correlated with the gross domestic product (GDP) per capita for the year 2015 [133]. In the US, the economic cost (including direct and indirect costs) of MSP conditions accounts for about 5.7% of the total GDP of America [130]. In work settings, MSP conditions account for substantial productivity and economic cost [131]. The cost of productivity lost due to MSP conditions in the European Union (EU), for example, is relatively high and estimated at about 2% of the EU GDP [131].

2.1.1 Assessment and classification of T2D

Type 2 diabetes is a gradually progressive disorder with a high level of undiagnosed cases in the population, as a result, there are variations in T2D cases at different places and over time [134, 135]. Some epidemiological studies often rely on self-reported data for known T2D cases; however, the definitive assessment of T2D is by clinical diagnostic methods, including, fasting blood or plasma glucose test, oral glucose tolerance test (OGTT), and glycated haemoglobin (HbA_{1c}) test [100, 134]. For the OGTT, the standard recommended by the World Health Organisation (WHO) and the American Diabetes Association (ADA) is the "75g OGTT test". T2D is defined as fasting blood or plasma glucose ≥ 7.0 mmol/L or a 2-hour postprandial glucose ≥ 11.1 mmol/L or an HbA_{1c} cut-point > 6.5% (48mmol/mol) [134]. Prediabetes state definition according to ADA criteria [134, 136], as well as the definition of normal glucose metabolism (NGM), is provided in Table 2.1.

Table 2.1: Definitions of glucose metabolism status by assessment methods.

Classifications	Diagnostic methods		
	FBG	2-hour OGTT	HbA1c
NGM	< 5.6 mmol/L	IGT < 7.8 mmol/L	< 5.7% (<39 mmol/mol)
Prediabetes	5.6 – 6.9 mmol/L (IFG)	7.8 – 11.0 mmol/L (IGT)	5.7 – 6.4% (39 – 46 mmol/mol)
T2D	≥ 7.0 mmol/L	≥ 11.1 mmol/L	> 6.5% (48 mmol/mol)
FBG – Fasting blood glucose, NGM – Normal glucose metabolism, OGTT – Oral glucose tolerance test, HbA1c – Glycated haemoglobin, IFG – Impaired fasting glucose, IGT – Impaired glucose tolerance, T2D – Type 2 diabetes			

2.1.2 Measurement of MSP conditions in epidemiological research

Measurements of MSP conditions in epidemiological studies can be based on subjective and/or objective methods [137-140]. Objective methods which involve physical and diagnostic examination by medical professionals [138] are often regarded as a more accurate approach. However, in large population-based studies, subjective methods are typically utilised because of the cost-effectiveness, time-saving and convenience of administering the self-report instruments [141]. Other study designs such as surveillance studies sometimes rely on clinical records as a method to collect data on MSP conditions [142, 143].

Currently, there is no universally accepted standardised method for measuring MSP conditions. There has been an attempt, however, to develop a standardised survey instrument for MSP conditions. For instance, the Global Alliance for Musculoskeletal Health (GMUSC) has developed and piloted a "musculoskeletal (MSK) survey module" for estimating the population-based prevalence of MSP conditions [144]. That said, epidemiologic studies have systematically examined the agreement between subjective and objective methods [143, 145-147]. A study, for example, examined the agreement between physical examination and a self-reported questionnaire to assess shoulder pain and found that there is reasonable agreement between these two methods for measuring shoulder pain [143]. Legault and colleagues [146], likewise, reported a good agreement between a self-reported questionnaire and the clinical records method of collecting data on MSP conditions. Commonly used self-reported instruments have shown acceptable validity and reliability in psychometric studies [148-150]. For instance, Orebro Musculoskeletal Pain Questionnaire is reported as a valid and reliable tool for assessing MSP conditions [151, 152]. Similarly, the reliability of Nordic Musculoskeletal Questionnaire has been examined through test-retest and validated against clinical history and found to be an accurate instrument for screening and collecting surveillance data on MSP conditions [150, 153, 154].

There are some self-report instruments specifically designed to measure attributes related to MSP conditions, for example, the quality and severity of pain, individuals' affective responses, sensory characteristics, and coping ability of pain, as well as a disability associated with MSP conditions [140, 155-158]. Most of these instruments have been shown to have adequate accuracy for assessing outcomes related to MSP conditions [159, 160]. For instance, the multiple-dimension self-report questionnaires such as Western Ontario and MacMaster Universities Osteoarthritis Index (WOMAC), SF36 bodily pain scale (BPS), and McGill Pain Questionnaire (MPQ), or short-form McGill Pain Questionnaire (SF-MPQ), as well as the single-item questionnaires such as Visual Analog Scale (VAS), Verbal Rating Scale (VRS) and Numeric Rating Scale (NRS) are reported to have acceptable psychometric properties for assessing attributes of pain related to MSP conditions [158, 159, 161, 162].

Though self-report instruments are commonly used for assessing MSP conditions in population-based studies, they have some limitations, which include recall and reporting bias with a high tendency of over-exaggeration or underestimation of pain [163, 164]. Some factors have been identified to contribute to these limitations, including the wording of questions which could influence the understanding and response to the questions [165, 166], as well as variations in the description of anatomical sites and the mode of administering the instrument [166-168]. For instance, studies have indicated that while self-report instruments are reliable, question-wording and the description of pain location could influence the estimations [165, 167]. Similarly, some authors have suggested differences in the mode of administering self-report MSP condition instruments could impact the response and quality of the measured data [166, 168]. Notwithstanding, a population-based study, however, analysed and compared data collected by self-

report manikin (human figure) and written questions on pain related to MSP conditions and found an agreement between these modes of administering self-report questionnaires [169].

2.2 Sedentary behaviour epidemiology

Several epidemiologic studies and systematic reviews have documented evidence of strong associations between sedentary behaviour and risks of metabolic disorders, including obesity, metabolic syndrome, and T2D, as well as cardiovascular diseases, some cancers, and all-cause mortality [10, 86, 170, 171]. The adverse impacts of high volumes of sedentary behaviour (such as prolonged uninterrupted sitting) in apparently healthy populations have also been reported [3, 54, 172]. In most cases, studies that examined the health risk associations of excessive sedentary behaviour (sitting) with adverse health outcomes have often observed that such risk associations are independent of accumulated volumes of MVPA [3, 171, 173]. Data from a prospective study, for example, demonstrated that there is a dose-response association of sitting time with cardiovascular diseases and all-cause mortality irrespective of the level of accumulated MVPA [171]. Also, a meta-analysis has indicated that sedentary behaviour, measured by television-viewing time (TV time), is associated with an increased risk of T2D regardless of the level of MVPA [10].

From a global public health perspective, it is evident from most countries that the average time spent sitting or in sedentary behaviour during waking hours is high [6]. The estimated total volume of sitting time during waking hours per day, for example, is estimated to be about 7.7 hours in the US [174]; 9.0 hours in Australia [175] and 9.5 hours in Canada [176]. Whilst a study of trends in sitting time across Europe found this to be relatively stable between 2002-17, there is evidence that sitting time is increasing in some subgroups of people [177, 178]. These shifts are mainly driven by occupational transitions from a predominantly physically intensive industrialised economy to a service economy that supports prolonged desk-based sitting at work [179]. Additionally, urban planning and built-environment design have influenced discretionary sedentary behaviour, with most built-environment supporting increased leisure-time sitting and a high volume of passive transport [180, 181].

The prevalence of sedentary behaviour increases with age and sitting time is higher in older adults [6, 45]. Evidence from systematic reviews indicates that older adults over 60 years old have a much higher prevalence of sedentary behaviour [45, 182]. One of these reviews documented that 67% of older adults accumulate an average objective device-measured sitting time greater than 8.5 hours/day [45]. Similarly, Harvey and colleagues [182] in another review observed that older adults ($\geqslant$60 years) spend a greater portion of waking hours (65 – 85%) sitting, with a mean accumulated sedentary time of 9.4 hours/day. Also, a Canadian survey report indicates adults above 60 years have a higher prevalence of high sitting time, with a documented average sitting time of 10 hours/day [183]. The high prevalence of sedentary behaviour in

adults has been attributed to diverse reasons. For example, individual intrinsic factors such as health status, retirement, or obesity, as well as environmental factors, including lack of a supportive environment for physical activity and active transport are some of the reasons [184]. However, evidence on sedentary behaviour determinants in older adults is inconclusive [184].

2.2.1 Measurement of sedentary behaviour

In sedentary behaviour research, the accurate estimation of sedentary exposure is by measuring overall sedentary behaviour, for example, total daily sitting time or total sitting time in a specific domain (at home, work, or commuting in a car) [185]. In line with this, objective methods are considered to have higher accuracy. Self-reported instruments have limitations in accurately estimating overall sedentary behaviour and have consistently been shown to underestimate total sitting time in high-level evidence studies [45, 182, 186]. Despite their limitations, self-reported instruments remain popular in large population-based studies where they are considered to be practical to administer and have also been shown to have acceptable psychometric properties [186, 187].

There are several objective methods for assessing sedentary behaviour in research, which are based on direct estimation of energy expenditure by measuring physiological markers (e.g. heart-rate monitoring) or doubly-labelled water (DLW) and indirectly by measuring body acceleration during movement, e.g., the accelerometers [185, 188, 189]. Other instruments detect changes in body posture to measure sitting time and indirectly estimate energy expenditure, e.g., the inclinometers [185, 189]. There are alternative objective instruments for estimating sedentary behaviour which use pressure sensors [185, 189]. Unlike self-report instruments, most objective methods have high accuracy for measuring sedentary behaviour and overcome common limitations associated with subjective (self-report) methods [185]. However, the cost of using some of the available objective instruments limits their use in large population-based surveys [185, 190].

There are, however, substantial differences between device-measured total spent in sedentary behaviour and those measured by self-report instruments [45, 182, 186]. Table 2.2 show the commonly used sedentary behaviour instruments in research.

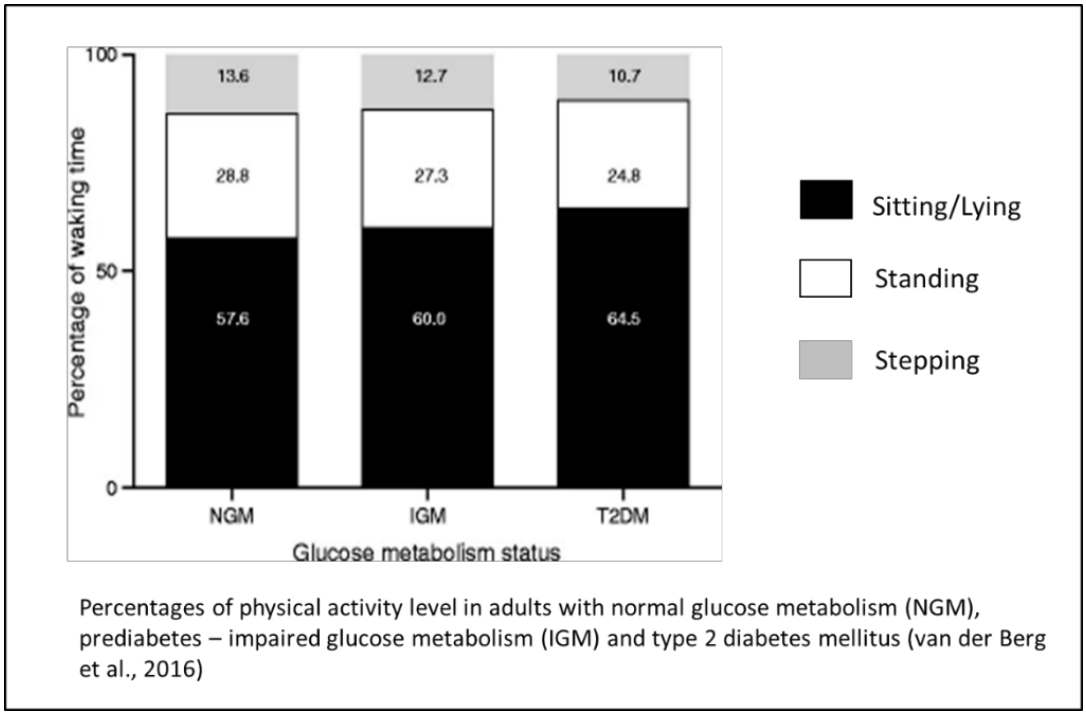
Table 2.2: Common measures of sedentary behaviour (activity behaviours) used in research.

Instrument	Description	Strengths and limitations
Self-report	Measure sedentary behaviour-related domains such as mode, context, duration, as well as pattern or breaks [185] Data are captured by self-administered or interviewer-administered questionnaires [185, 191]. Self-report questionnaire variants [185, 186, 191] • single-item questionnaires (e.g., the single-item sitting question in Global Physical Activity Questionnaire – GPAQ) • multiple-items questionnaires (e.g., 18-items Sedentary Behaviour Questionnaire – SBQ) • domain-specific questionnaires (e.g., domain-specific Adult Sedentary Behaviour Questionnaire – ASBQ) • diaries (e.g., Ecological momentary assessment – EMA) • proxy-report questionnaires in cognitively limited populations	Strengths • Highly utilised in large population-based studies [185, 191] • They are cost-effective, less expensive, and • highly accessible. • Relatively easy to complete with less burden and are accepted by study participants. • Does not influence the behaviour being measured in individuals [190, 191]. • Able to capture qualitative dimensions of sedentary behaviour which cannot be captured by objective devices [185, 191]. E.g., can capture context-specific sedentary behaviour and identify modes of sedentary behaviour, this information can inform intervention strategies [185, 189]. Limitations • Poor validity, recall bias, reporting bias, vulnerability to social desirability bias, and cultural norms influences [189-192]. • Limits data comparison in different populations and across studies, due to the challenges of translating information to achieve linguistic and conceptual equivalence [185, 190]. • Complicated by concurrent behaviour phenomena (e.g., watching television and playing video games), making behaviour-specific measures (e.g., TV time) more limited than global measures, like sitting time [185].
Device-measured Accelerometers e.g., ActiGraphs	Detect body movements and measure real-time acceleration frequency and amplitude which are integrated into movement counts by an algorithm [185, 188, 189]. Estimated energy expenditure is based on the assumption that measured acceleration is proportional to the force generated by muscles that are engaged during the movement [189]. Estimated sedentary time depends on the movement count measured by the accelerometer at a given cut-point [185, 189]. The movement counts cut-point threshold determines, to some extent, the accuracy of the estimated sedentary behaviour [185]. New processing methods, e.g., using raw accelerometer data and machine learning or deep learning algorithms may improve measurement accuracy in the future [193-195].	Strengths • At a specified cut-point threshold can accurately estimate total daily or domain-specific (e.g., time at work) sedentary time. • Useful in detecting incidental movements and/or breaks in sedentary time [185]. Limitations • Limited in capturing contextual data • May influence participants' behaviour leading to reactivity bias [189]. • Some cannot distinguish between sitting, lying or standing postures, hence, standing time may be incorporated into total sedentary time [185, 196]. The triaxial accelerometers (ActiGraphs GT3X, GT3X+, and w GT3X+) are fitted with an inclinometer to distinguish postures, but this function as a sole measure of sitting time is reported not to be valid [196]
Device-measured Inclinometer e.g., activPAL	A discrete thigh-worn device which can determine changes in body posture [185, 189]. The device uses in-built "Intelligent Activity Classification" proprietary algorithms to classify acceleration and gravitational changes in the thigh as either stepping, standing, sitting, or lying [185]. The activPAL collects data on stepping speed, step count, stepping time, standing time, sitting time and lying time. Also, it determines sedentary bouts (breaks in sitting) and postural transition from sit-stand-step or vice-versa, as well as the estimate of energy expenditure [185, 189].	Strengths • The gold standard for measuring activity behaviours • Can be utilised in a different context [185]. Limitation • limited in providing qualitative dimension data, e.g., sedentary behaviour context [185].

2.3 Sedentary behaviour and type 2 diabetes

Epidemiological evidence shows that high volumes of sedentary behaviour significantly increase T2D risk, irrespective of the level of physical activity or the confounding effect of body mass index (BMI) [10, 197-199]. For instance, Wilmot and colleagues [10] synthesized evidence from 10 epidemiological studies and found that higher volumes compared to lower volumes of sedentary time were associated with a 112% increased relative risk of T2D. Also, a large population-based study, the 45 and Up Study, for instance, found that a higher volume of sitting time was independently associated with T2D after accounting for the participants' physical activity time and BMI [198]. Furthermore, associations with T2D have been shown to increase further with any time increase in sedentary behaviour [7, 200]. For example, observational findings from the Maastricht study indicate the odds of T2D increased by 22 percentage points for each hourly increment in sitting time [7].

There is evidence indicating that adults with T2D are more likely to engage in higher volumes of sedentary behaviour than those without T2D [7]. For instance, a study objectively monitored activity behaviours in middle-aged and older adults with an average age of 60 years old, found that those living with T2D spent about 5% more of their waking hours in sedentary behaviour (sitting) than those categorised as having prediabetes, and about 7% more than those with normal glucose metabolism (NGM) as shown in Figure 2.1 (graph taken from the Maastricht Study – van der Berg et al. [7]).



Percentages of physical activity level in adults with normal glucose metabolism (NGM), prediabetes – impaired glucose metabolism (IGM) and type 2 diabetes mellitus (van der Berg et al., 2016)

Figure 2.1: Activity behaviours distributions in adults by type 2 diabetes status.

2.3.1 Sedentary behaviour and cardiometabolic biomarkers of T2D

Excessive sedentary behaviour has been associated with abnormal levels of cardiometabolic risk markers in T2D, including biomarkers of insulin function, adiposity, glucose metabolism and metabolic risk score [201-204]. For example, Cooper et al. [201] have documented from six-month prospective data of 528 newly diagnosed T2D patients that a higher volume of device-measured sitting time was associated with higher insulin levels, increased insulin resistance (HOMA-IR), and decreased HDL-cholesterol, after accounting for the patients' time spent in MVPA [201].

Similarly, Rossen and colleagues [203] reported using compositional data analysis that device-measured sedentary time relative to LIPA and MVPA time was negatively associated with HOMA-IR, HDL-cholesterol and sagittal abdominal diameter in T2D. Also, Healy and others [205] have shown using the isotemporal substitution analytic method that there are cross-sectional associations of device-assessed sitting time with waist circumference (WC) and BMI in T2D. Furthermore, Cooper and colleagues [204] reported that an hour increase in sedentary time was positively associated with increased cluster metabolic risk score (CMRS), independent of the level of time spent in MVPA. (Note: CMRS is computed by summing WC, triacylglycerol, HbA_{1c}, systolic blood pressure and the inverse of HDL-cholesterol).

2.3.2 Interrupting sedentary time in T2D and biomarkers

Recently, most behavioural activity researchers focussing on sedentary behaviour have increased their attention on understanding the impacts of intermittent LIPA breaks in prolonged sitting periods and the associations with indicators of health outcomes [43, 76, 206]. A study, for instance, found that frequent LIPA interruption of prolonged sitting time improved glycaemic control, whereas uninterrupted sitting resulted in worsened glycaemic control in individuals living with T2D [207].

Several experimental studies have shown that active breaks in prolonged sitting are inversely associated with metabolic risk biomarkers in T2D [40-42]. Dempsey and colleagues [40] demonstrated in an experimental randomised crossover trial involving 24 overweight/obese adults with T2D that light-walking and simple resistance physical exercise breaks in-between prolonged sitting attenuated acute responses of postprandial glucose, insulin, C-peptide, and triglyceride. A secondary analysis of the same data found that breaking prolonged sitting with light-walking and simple resistance physical exercise was associated with beneficial changes in postprandial plasma lipidome in individuals with T2D [208]. In a similar randomised crossover design involving 19 adults with T2D who were on non-insulin treatment, Duvivier et al. [41] compared three experimental conditions: Sitting, "Sit-Less" (breaking prolonged sitting with standing and light-walking), and structured exercise. The authors found that the "Sit-Less" condition was associated with significantly lower 24-hour-glucose incremental area under the curve (iAUC) than sitting and non-significantly lower than structured exercise (iAUC in min × mmol/l: "Sit-Less" = 1263 ± 189; Exercise =

1383 ± 194; and Sitting = 1974 ± 324). Also, HOMA2-IR was significantly reduced in "Sit-Less" compared to both structured exercise and sitting conditions [41].

2.3.3 Sedentary time and systemic inflammatory biomarkers in T2D

Systemic inflammatory processes have been implicated in T2D progression and the development of diabetes-related complications, as well as the pathophysiology of prediabetes [209, 210]. Systemic inflammatory reactions related to T2D are mediated through adipose tissue-derived cytokines (adipokines), including interleukin (IL)-6 and tumour necrosis factor (TNF-α) which regulates glucose metabolism and insulin resistivity [210-212]. Increased adiposity in T2D is associated with an increased level of IL-6 which stimulates the hepatic secretion of C-reactive protein (CRP), a systemic biomarker for an inflammatory response [213-215]. Additionally, adiposity is associated with an increased level of leptin, a regulator of insulin sensitivity [212, 216], as well as decreased levels of anti-inflammatory and anti-atherogenic cytokines such as adiponectin in T2D [210, 213]. Also, there are other non-adipose tissue-derived inflammatory biomarkers which have been identified with metabolic processes in T2D. For example, vascular tissue-derived soluble intracellular adhesion molecule-1 (sICAM-1) has been associated with an increased risk of vascular complications in T2D [217].

Evidence suggests sedentary behaviour is positively associated with an unfavourable level of inflammatory biomarkers, including CRP and adipokines such as TNF-α, leptin, adiponectin, and IL-6 [218-220]. Studies have reported in adults living with T2D evidence of associations of higher volumes of sedentary time with unfavourable levels of IL-6 and CRP [221, 222], as well as leptin and leptin-adiponectin ratio (LAR) [222]. The associations were shown to be independent of time spent in MVPA as well as adiposity and glycaemic levels [222].

2.4 Sedentary behaviour and musculoskeletal conditions.

There is some evidence suggesting that sedentary behaviour is associated with some MSP conditions [46, 85, 223]. A systematic review, for instance, indicated that sedentary behaviour is associated with low back pain [85]. Also, longitudinal study findings suggest that increased sedentary time is associated with pain related to MSP conditions [15]. Similarly, a cross-sectional study noted that prolonged occupational sitting is significantly associated with back pain [54]. In addition, Lee et al. [16] documented in a cross-sectional study a correlation between sedentary behaviour and chronic knee-joint pain. Furthermore, intervention studies have indicated a positive effect of sedentary behaviour reduction on outcomes related to MSP conditions [46, 48, 223]. Brakenridge et al. [46], for example, reported in an intervention study that reduced sitting time among workers is associated with reduced low back pain. Also, Barone-Gibbs and

colleagues [48] concluded from a six-month sitting reduction intervention trial that decreased prolonged sitting reduced long-standing low back pain among a group of workers.

Similarly, associations of sedentary behaviour with MSP condition-related attributes such as pain intensity, functional disability and physical functioning are evident [24, 85]. Alzahrani and colleagues [85] observed in a systematic review the detrimental associations of sedentary behaviour with pain intensity and disability. Furthermore, a longitudinal study documented that higher time spent in sedentary behaviour (>2 hours/day of TV time) was associated with low back pain-related disability in women [24]. Also, a sedentary behaviour reduction intervention trial found that increased workplace sitting time was associated with increased risks of MSP symptoms [17].

Nevertheless, MSP conditions could also contribute to excessive sedentary behaviour in adults, partly because of the perceived pain-inhibitory effect of sitting [18, 19]. For instance, findings from a cross-sectional study indicate that sedentary behaviour is associated with a higher inhibitory capacity of pain in people living with chronic MSP conditions, suggesting that sedentary behaviour could be a protective mechanism in pain modulation [18]. Also, a study has noted that patients with knee osteoarthritis spend most of their waking hours in sedentary time [224]. Furthermore, a qualitative study on the perspectives of daily sedentary behaviour among rheumatoid arthritis patients identified common themes, which indicate that arthritis-related pain contributes to patients engaging in more sedentary behaviour [19].

In contrast, some publications have noted no evidence of associations between sedentary behaviour and MSP conditions [225, 226]. For example, Chen and colleagues reviewed 10 prospective cohorts and five case-control studies and found no significant associations between sedentary behaviour and low back pain [225]. However, the only high-quality study among their reviewed studies reported evidence of an association between sedentary behaviour and low back pain [225]. Also, a systematic review has observed that sitting in itself may not be associated with back pain, but prolonged sitting coupled with awkward postures and whole-body vibration may increase the risk of back pain [226].

Furthermore, body locations of MSP conditions may be a determining factor of sedentary behaviour/MSP conditions associations [64, 227]. For instance, some sitting reduction interventions have found intervention strategies to be effective in reducing MSP at selected anatomical sites [46, 64]. Danquah et al. [64], for example, documented that the “Take-a-Stand!” office-based intervention effectively reduced neck/shoulder pain but not back and extremities pain. Likewise, Brakenridge and colleagues found that sitting reduction intervention significantly reduced pain intensity at the lower back but not at the neck, upper back or extremities [46].

2.5 Relationships between type 2 diabetes and musculoskeletal pain conditions

Some MSP conditions are highly prevalent and exclusive in people with diabetes [21, 22, 81, 228], especially T2D which forms a large proportion of diabetes cases globally [8]. Limited joint mobility syndrome or "cheiroarthropathy", for example, is believed to be exclusively prevalent in people with diabetes, with the prevalence rate reported to range between 8% and 58% [229-232]. Other MSP conditions such as carpal tunnel syndrome, adhesive capsulitis, Dupuytren's contracture, stiff hand syndrome, flexor tenosynovitis etc. are frequently associated with diabetes [22, 229]. Also, evidence of a rising prevalence of diabetes-associated joint-related MSP conditions is well documented [21, 230]. Charcot osteoarthropathy, for example, is more commonly associated with diabetes [21].

Epidemiological studies have documented evidence of detrimental associations between T2D and MSP conditions such as arthritis, rheumatoid arthritis, osteoarthritis, and chronic back pains [75, 88, 232-238]. Bhat et al. [238], for example, surprisingly found in a case-control study, a higher prevalence of upper and lower limb MSP conditions in T2D cases than in the non-T2D controls [238]. Moreover, studies have intensively investigated and documented evidence of a potential risk of osteoarthritis in T2D patients [80, 87, 88, 239]. In a systematic review and meta-analysis, for instance, William and colleagues [80] reported increased odds of osteoarthritis incidence and progression in T2D patients (OR = 1.21, 95% CI: 1.02 – 1.41). Also, Eymard et al. [239] found in an intervention trial that T2D increases the risk of joint narrowing in knee osteoarthritis patients. Furthermore, a meta-analysis of pooled data from 25 studies found T2D to be associated with an increased risk of carpal tunnel syndrome, however, the risk was not different in people with type 1 diabetes [79].

Some authors, however, suggest MSP conditions rather predispose to the risk of developing T2D [240]. Findings from a prospective study, for instance, suggest that the presence of osteoarthritis could predispose to an increased risk of T2D, a risk which is age- and gender-dependent, with younger people and older women being at increased risk of T2D [240]. On the contrary, other publications have documented no evidence of associations between T2D and the risk of MSP conditions [88, 241]. For instance, Dario et al. [88] analysed longitudinal data and found no evidence of an increased risk of back pain in people with T2D. Similarly, a group of authors performed a matched case-control study and concluded that T2D is not an independent risk factor for the pathogenesis of hand osteoarthritis [241].

Taken together, there are considerable methodological differences in the designs of the above studies, hence, it is difficult to make a meaningful comparison across the findings. Nevertheless, the findings from the high-level evidence studies appear to suggest T2D may be associated with some MSP conditions and increase the risks of their development and progression [80, 237, 239]. The contrasting findings in the other studies might be due to the confounding effects of some moderating or mediating factors [88, 235, 239]. Also, there is the plausibility that behavioural and environmental exposures may mediate or moderate the observed associations between T2D and MSP conditions [25, 75]. For instance,

Molsted et al. [75] observed that a high prevalence of low back pain in people with T2D was also associated with a high volume of sedentary behaviour.

2.6 Systematic review on sedentary behaviour and musculoskeletal pain conditions

To build on the literature presented above, a formal systematic review of the literature in the context of this thesis was performed. The overarching aim of the systematic review was to explore the existing evidence on associations of sedentary behaviour in occupational and non-occupational settings with MSP conditions in adults. A further aim was to identify some literature gaps to inform the empirical studies in the thesis.

2.6.1 The manuscript

A systematic review titled "Musculoskeletal Pain and Sedentary Behaviour in Occupational and Non-Occupational Settings: A Systematic Review with Meta-Analysis" was conducted as Study 1 of this thesis. The review has been published in the International Journal of Behavioral Nutrition and Physical Activity (IJBNPA). The contributions of the authors on the published Study 1 are provided in Appendix B1.1.

2.6.2 Citation:

Dzakpasu FQS, Carver A, Brakenridge CJ, Cicuttini F, Urquhart DM, Owen N, Dunstan DW. *Musculoskeletal pain and sedentary behaviour in occupational and non-occupational settings: a systematic review with meta-analysis.* Int J Behav Nutr Phys Act. 2021 Dec 13;18(1):159. https://doi.org/10.1186/s12966-021-01191-y

2.6.3 Copy of the published manuscript – PDF

International Journal of Behavioral Nutrition and Physical Activity

REVIEW

Open Access

Musculoskeletal pain and sedentary behaviour in occupational and non-occupational settings: a systematic review with meta-analysis

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Abstract

Background: Sedentary behaviour (SB; time spent sitting) is associated with musculoskeletal pain (MSP) conditions; however, no prior systematic review has examined these associations according to SB domains. We synthesised evidence on occupational and non-occupational SB and MSP conditions.

Methods: Guided by a PRISMA protocol, eight databases (MEDLINE, CINAHL, PsycINFO, Web of Science, Scopus, Cochrane Library, SPORTDiscus, and AMED) and three grey literature sources (Google Scholar, WorldChat, and Trove) were searched (January 1, 2000, to March 17, 2021) for original quantitative studies of adults ≥ 18 years. Clinical-condition studies were excluded. Studies' risk of bias was assessed using the QualSyst checklist. For meta-analyses, random effect inverse-variance pooled effect size was estimated; otherwise, best-evidence synthesis was used for narrative review.

Results: Of 178 potentially-eligible studies, 79 were included [24 general population; 55 occupational (incuding15 experimental/intervention)]; 56 studies were of high quality, with scores > 0.75. Data for 26 were meta-synthesised. For cross-sectional studies of non-occupational SB, meta-analysis showed full-day SB to be associated with low back pain [LBP – OR = 1.19(1.03 – 1.38)]. Narrative synthesis found full-day SB associations with knee pain, arthritis, and general MSP, but the evidence was insufficient on associations with neck/shoulder pain, hip pain, and upper extremities pain. Evidence of prospective associations of full-day SB with MSP conditions was insufficient. Also, there was insufficient evidence on both cross-sectional and prospective associations between leisure-time SB and MSP conditions. For occupational SB, cross-sectional studies meta-analysed indicated associations of self-reported workplace sitting with LBP [OR = 1.47(1.12 – 1.92)] and neck/shoulder pain [OR = 1.73(1.46 – 2.03)], but not with extremities pain [OR = 1.17(0.65 – 2.11)]. Best-evidence synthesis identified inconsistent findings on cross-sectional association and a probable negative prospective association of device-measured workplace sitting with LBP-intensity in tradespeople. There was cross-sectional evidence on the association of computer time with neck/shoulder pain, but insufficient evidence for LBP and general MSP. Experimental/intervention evidence indicated reduced LBP, neck/shoulder pain, and general MSP with reducing workplace sitting.

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Conclusions: We found cross-sectional associations of occupational and non-occupational SB with MSP conditions, with occupational SB associations being occupation dependent, however, reverse causality bias cannot be ruled out. While prospective evidence was inconclusive, reducing workplace sitting was associated with reduced MSP conditions. Future studies should emphasise prospective analyses and examining potential interactions with chronic diseases.

Protocol registration: PROSPERO ID #CRD42020166412 (Amended to limit the scope)

Keywords: Sedentary behaviour (SB), Occupational, Non-occupational, Workplace sitting, Self-reported, Device-measured, Computer time, Vehicle time, Musculoskeletal pain (MSP) conditions

Background

The burden of musculoskeletal pain (MSP) conditions has increased in recent decades, contributing to substantial health care costs [1]. According to 2019 Global Burden of Disease (GBD) estimates, age-standardised disability-adjusted life years attributable to MSP conditions excluding low back pain (LBP) increased from 1990 to 2019 by some 30.7 percentage points [2]; whereas the 2017 GDB report ranked LBP as the second-highest contributor to years lived with disability [3]. The prevalence of MSP conditions has increased in parallel with the rising burden of chronic disease and is most pronounced in those with multi-morbidities [3, 4]. Also, MSP can substantially limit mobility and engagement in regular physical activity, thereby predisposing to increased risk of other chronic conditions [3].

The biological mechanisms contributing to MSP conditions are heterogeneous; nonetheless, obesity, static working postures, physical inactivity, smoking, and aging, as well as cardiometabolic and systemic inflammation, are some factors identified to increase the prevalence of MSP [5, 6]. While there is convincing evidence of beneficial associations of physical activity with outcomes related to MSP conditions [7, 8] there is an additional element to consider in this nexus – sedentary behaviour (SB). Defined as time spent in sitting and/or reclining postures during waking hours, with energy expenditure less than 1.5 metabolic equivalents (METs) [9] – SB is associated with increased risk and unfavourable outcomes of chronic diseases, including cardiovascular disease, metabolic disorders, musculoskeletal diseases, and some cancers, as well as all-cause mortality [10, 11]. Intervention trials have shown that reducing sitting time can result in modest improvements in some biomarkers of health risk [12, 13]. From a population health perspective, excessive time spent sitting is common among older adults, especially in those with co-morbidities such as cardiovascular and metabolic disorders [14, 15].

Epidemiological evidence indicates higher volumes of SB are associated with several MSP conditions, including osteoarthritis, back pain, and neck/shoulder pain [16, 17]. Some of these findings are from low-level evidence cross-sectional studies and there could be potential reverse causality bias [16]; inferring a causal relationship between SB and MSP may therefore be problematic as pain and chronic disease could predispose to engagement in excessive SB [18]. There is, however, an inconsistent body of evidence of associations of SB with MSP conditions and related outcomes from high-level evidence-based studies [19, 20]. Some previous systematic reviews of studies including higher-level study designs have reported no associations of SB with the prevalence of some MSP conditions [19–24], whereas others have reported either positive [20, 25] or negative [26] associations with some MSP-related outcomes such as pain intensity. Methodological differences and limitations within the individual studies reviewed in these systematic reviews could impact the quality of evidence and comparability of these reviews as some of the studies were based on self-reported and surrogate estimates of SB which increases the risk of bias [19, 21, 22, 24, 27]. The emergence of evidence on device-measured SB, especially from studies using the ActiGraph and activPAL devices has improved the quality of SB evidence in recent research outputs [25–27].

There could be other reasons for the equivocal associations, including factors related to the influence of the specific domains of SB (e.g., work, transport, domestic) and the relative exposure of the studied population. This perspective suggests potential contributions of different domains of SB to the risk of adverse health outcomes, which may differ from the effects of total full-day SB [28–30]. Moreover, evidence on differences in health effects of different SB domains has been identified as a key knowledge gap by the 2020 World Health Organisation (WHO) physical activity and SB guidelines development group [31]. Existing systematic reviews have not identified differences according to domains in the associations of SB with MSP conditions.

This distinction is important, partly because, most working adults accumulate SB in both occupational and non-occupational settings. That said, SB could predispose to MSP conditions in certain occupational groups such as desk-based workers who commonly engage in a

prolonged sitting [32, 33]. In this context, interventions to reduce prolonged workplace sitting time by breaking up sitting with standing and/or light walking have shown beneficial associations with a reduction in MSP or musculoskeletal system discomfort among desk-based workers [34, 35]. Thus, SB associations may also reflect plausible biomechanical or biological pathways explaining MSP conditions in those exposed to prolonged static sitting postures [36–38]. Paradoxically, however, in occupational groups such as tradespeople who engage in more labour-intensive manual work, SB may be a protective behaviour against MSP conditions and other chronic diseases [39–41].

We conducted a systematic review to examine evidence on the associations of SB with MSP conditions in observational and experimental/intervention studies of adults. Specifically, we examined and synthesised evidence separately for associations of SB with MSP conditions in the occupational and non-occupational SB domains.

Methods

Review design

We used a standard Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines-based pre-designed protocol (PROSPERO ID: CRD42020166412 – amended to limit the scope of the review) to ensure a transparent review [42, 43]. The a priori research question and search strategy were formulated according to the Population, Intervention, Control/Comparison, and Outcome (PICO) framework [44] to enhance search precision and ensure extensive data extraction to be representative and unbiased [45]. The research question was: *What are the associations of occupational and non-occupational SB with MSP conditions in adults?*

Search strategy

Using a comprehensive search strategy, search terms were identified and combined using Boolean operators to search the following electronic databases: MEDLINE Complete, CINAHL Complete, PsycINFO, Web of Science, Scopus, Cochrane Library, SPORTDiscus, and AMED. Additionally, three online grey literature databases, including Google Scholar, WorldChat, and Trove, were searched to also identify non-peer-reviewed studies to help to minimise publication bias [46]. The search was conducted by one reviewer, for consistency, with the guidance of a librarian (Australian Catholic University, Melbourne) initially on January 5, 2020; and, further updated on November 1, 2020, and March 17, 2021. The search filter was set to limit search results to studies published from January 1, 2000, onwards. This timeframe was chosen because the field of SB is relatively new, the early definitive papers were published at the beginning of this period, and SB research output has grown significantly over the past two decades [9].

The search terms format, guided by the PICO framework, included keywords, terms, and phrases related to SB (Exposure/Intervention); MSP conditions (Outcome); and adults (Population). The search was optimized by adding to the search string, newly identified key terms that consistently appear in titles and abstracts of retrieved studies during the search [47]. A supplementary file (Supplementary Table 1: Search key terms and strings strategy – A sample Medline database search syntax) describing the comprehensive search term framework is attached.

Study eligibility and selection

Inclusion and exclusion criteria

The selection of eligible studies was based on pre-determined inclusion and exclusion criteria. The reviewed studies satisfied all the criteria below:

a. An original quantitative study involving either an observational or intervention/experimental design. This included cross-sectional, case–control studies, and prospective studies, as well as randomized controlled trials (RCTs) and non-randomized experimental study designs.
b. The study was conducted in adults aged 18 years or older and examined relationships between SB (the exposure of interest) and MSP conditions (the outcome of interest).
c. The study included a measure of any kind of MSP condition, including inflammatory and non-inflammatory MSP conditions such as back pain, joint/osteoarthritis, and pain in extremities (except for pain attributable, acutely or recently, to trauma). Autoimmune-related MSP conditions, for example, rheumatoid arthritis and fibromyalgia were not included in this review because the pathophysiology of these conditions is mainly attributable to the processes and progression of specific clinical disease entities with autoimmune causations. Some studies did not measure a specific type of MSP condition but produced a composite measure of MSP conditions. Those that measured arthritis but excluded fibromyalgia were considered for inclusion because the majority of reported cases of arthritis are likely to be osteoarthritis rather than rheumatoid arthritis. There is no universally accepted measure for MSP conditions; therefore, any acceptable measures described in studies provided the basis for considering studies to be appropriately inclusive of MSP conditions.

d. The study clearly defined or stated the measure of SB. Specifically, the study reported a self-report measure or device-based measure of occupational or non-occupational SB. This included population-based or occupational/workgroup cohort studies that measured SB exposures that aligned with the focus of our review.

Studies were excluded if they met any of the criteria described below:

a. all qualitative studies and those quantitative studies involving children and adolescent populations aged below 18 years;
b. studies that did not appropriately define SB; those that used proxy estimates, such as "less active", "inactive" or "does not engage in physical activities"; those that did not make a clear distinction between SB and physical inactivity and included these as overlapping behaviours or used these terms interchangeably;
c. studies that focused on SB as an outcome but did not explicitly examine the relationship of SB with MSP conditions; studies that focused only on the relationship between physical activity and MSP conditions;
d. studies conducted exclusively in clinical groups with existing clinically diagnosed MSP conditions, e.g., knee osteoarthritis patients that focused on symptom severity as outcome measures;
e. opinion or perspective articles, conference papers, editorials, newsletters, and review studies, however, the reference lists of some literature reviews on a similar topic were hand-searched for relevant studies;
f. studies published in languages other than English.

Screening and selection process

A two-stage approach was used to process all identified studies before arriving at the final set of studies for inclusion in this review. First, the reviewer (FD), exported all the retrieved studies into Endnote reference manager software [48], checked and removed duplicate studies. The refined list of studies was exported into collaboration-supported Rayyan systematic review software [49] for screening. One reviewer (FD) initially screened and removed irrelevant studies by title and abstract according to our inclusion and exclusion criteria, but where there was uncertainty regarding inclusion, such studies were considered in stage two screening. The second stage involved retrieval of full-text articles of retained studies, and two reviewers (FD and CB), independently read and assessed the full-text articles for inclusion. Disparities were discussed and resolved among the two reviewers; however, when uncertainty remained, they consulted with three senior reviewers (AC, NO and DD). Records of retained studies as well as reasons for exclusion (at stage two) were documented using a PRISMA flowchart (Fig. 1).

Data extraction

A pre-designed data extraction form was used to organise relevant information from the studies reviewed, to ensure data quality, and to minimise errors [50]. Reviewer FD extracted data from all the studies, and this was verified independently by CB. The verification process involved the comparison of data extracted by CB from randomly selected studies (not less than 20%) with the extracts of FD [51]. Disagreements were resolved harmoniously. Extracted data included:

- Descriptive details – study title, author name, year of publication, place of study, study aim
- Study design – cross-sectional, case–control, prospective, experiment/RCT/non-RCT
- Study population – population-based, occupational/workgroup cohort
- Sample size
- Demographic information of study participants – e.g., gender, mean age or age range, and BMI.
- SB and measures – occupational SB, non-occupational SB, self-report and objective measures.
- Outcome variables and measures – MSP conditions, e.g., back pain, neck/shoulder pain, osteoarthritis, and extremities pain.
- Intervention/experiment detail (when applicable) – type, duration, assessment point(s), effect size, etc.
- Other relevant data relating to the MSP condition outcomes and their measures – e.g., pain intensity and disability.

Study quality assessment

Quality assessment for the included studies was undertaken (independently by two reviewers) using the quantitative checklist of QualSyst (Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields) [52]. Briefly, the quantitative QualSyst checklist is scored on 14 criteria as either "YES = 2", "PARTIAL = 1", "NO = 0" or "NOT APPLICABLE" (N/A) depending on the extent to which each criterion item is satisfied by the study report. Items marked 'N/A' were excluded from the computation of the QualSyst summary score. For each paper, a summary score was computed by summing scores across items and dividing this by the maximum possible score for all relevant items [i.e., 28 – (number of 'N/A' items × 2)]

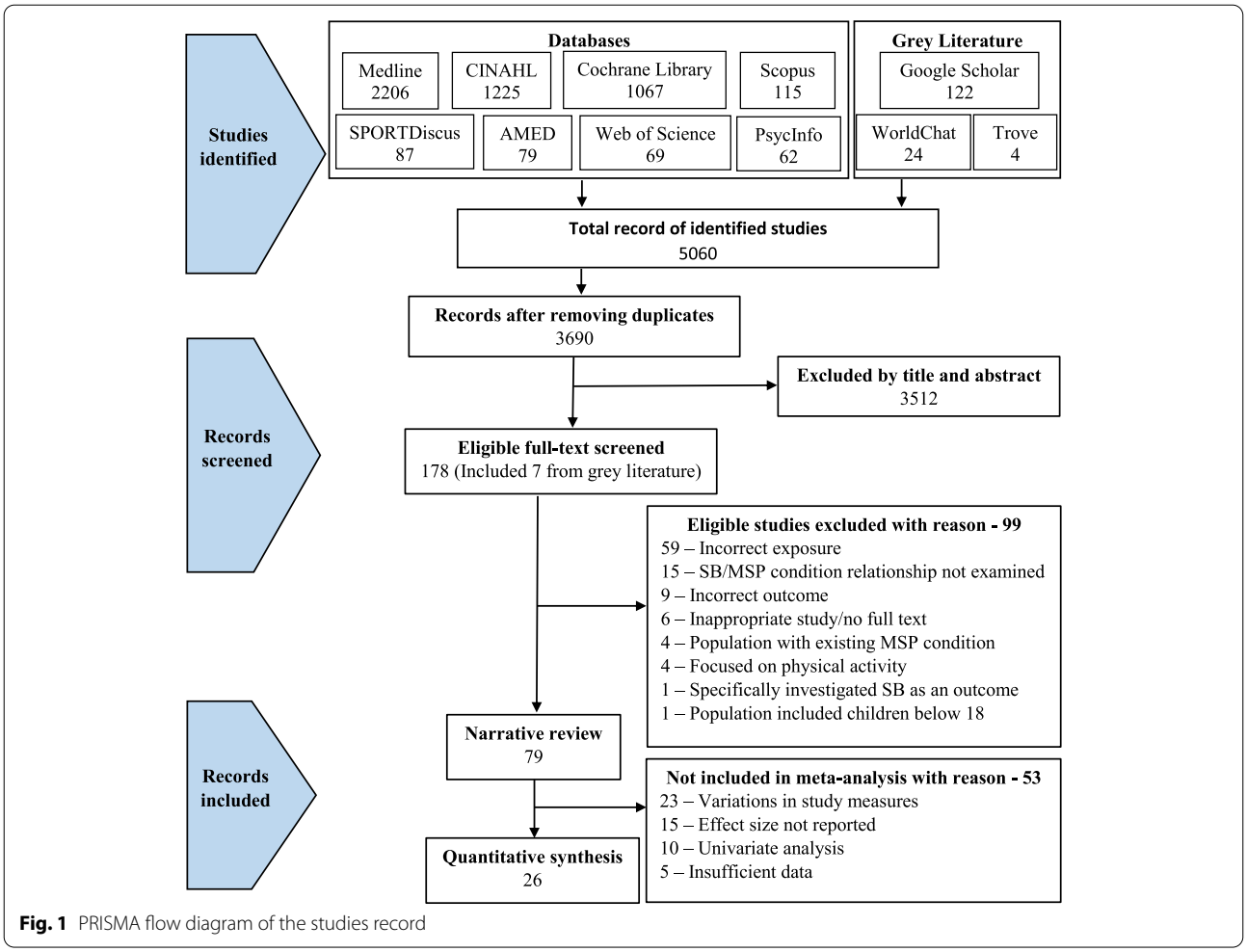

Fig. 1 PRISMA flow diagram of the studies record

[52]. Disparities in the assessments were discussed and resolved between the assessors, and if required, the three senior reviewers arbitrated. Note, however, that the quality assessment score was not a criterion for study selection but was to be considered in the determination of the robustness of our data synthesis.

Data synthesis

The extracted data were first categorised broadly as either general population or occupational cohort studies. Thereafter, they were summarised as either observational or experimental/intervention studies. The observational studies were then further organised according to study design (cross-sectional/case–control and prospective), and experimental/intervention studies were categorised as RCTs and non-RCTs to simplify the evidence synthesis. Within the categories, the SB domain measured was organised into occupational and non-occupational SB, and the measuring instrument into device-measured and self-reported SB. Further, grouping was completed according to measured SB [full-day, leisure-time, workplace sitting, computer time, vehicle time (time spent sitting in a vehicle), and sedentary behaviours (SBs) – time spent watching television, on computer/video gaming, reading or talking on the phone], as well as the type of MSP condition outcomes. The MSP conditions included back pain (low back pain – LBP and upper back pain – UBP); neck/shoulder pain; knee osteoarthritis (pain); extremities pain (upper and lower); and other MSP conditions (included MSP conditions reported no more than three in the reviewed studies; a general MSP/discomfort or collectively measured MSP conditions; and arthritis).

Descriptive tables and narrative text provide a general overview of the studies reviewed. MSP condition outcomes (e.g., back pain, neck/shoulder pain, and knee osteoarthritis) reported in three studies or more with permissible variations in the study designs and measures were quantitatively synthesised. Otherwise, the MSP condition is presented in a narrative review.

Narrative review

In the case whereby meta-analysis was not feasible, individual study findings were systematically described and integrated using the best-evidence synthesis in a narrative text [53, 54]. This commonly used synthesis approach takes into account the quality and the consistency of reported findings of the studies in three levels – strong evidence (≥ 75% of the studies show consistent significant findings in the same direction of ≥ 2 high-quality studies; moderate evidence (consistent significant findings in the same direction of a high-quality and at least a low-quality studies or ≥ 2 low-quality studies; and insufficient evidence (inconsistent findings in ≥ 2 studies or just a single available study). When there were ≥ 2 studies of high quality in a category, our conclusion on the evidence of associations was based on the within- and between-relationships of the high-quality studies.

Quantitative synthesis

Pooled meta-analysis was performed on homogenous data for SB and MSP condition outcomes when permissible. The RevMan5 (Review Manager 5.4.1) inverse-variance approach was used to estimate the pooled effect size (in odds ratio) based on random effect due to the heterogeneity of the data [55]. When there were sufficient studies, subgroup analysis was performed based on self-reported and device-measured SB. To gain insight on how occupation type could mask the association of workplace sitting with MSP conditions, a subgroup analysis by occupation type was performed. Further, subgroup analysis was conducted for studies that reported neck, shoulder, and neck/shoulder pain, and for a subgroup that reported extremities pain. Pooled effect relationships were illustrated by forest plots, and data heterogeneity was estimated by I^2, Tau^2, and Cochran's Chi-square. The robustness of our estimated pooled effect sizes was examined in a sensitivity analysis by excluding studies of low quality from the estimate; we used a funnel plot to illustrate potential publication bias.

In general, evidence synthesised by narrative review (the best-evidence synthesis) or quantitative synthesis (meta-analysis) from observational studies was regarded as either of low quality for cross-sectional/case–control studies-based evidence or high quality for prospective studies-based evidence. Evidence synthesised from experimental/intervention studies was regarded as of moderate/high quality depending on the relative contribution of non-RCT and RCT studies in the evidence.

Results

The search identified 5060 studies (Fig. 1) and 3690 remained after removing duplicates. These studies were screened by title and abstract according to the review's inclusion and exclusion criteria. A total of 178 studies were retained for full-text screening. Of these, we excluded 99 studies (Supplementary Table 2: Studies excluded after full-text screening) after the full-text screening, leaving 79 studies published from 2000 to 2021 for the evidence synthesis, including 26 studies for meta-analysis. The included studies had representation from 36 different countries. Several of these countries were the settings for five or more studies: Australia (10), Denmark (8), Brazil (8), South Korea (5), the USA (5), and the UK (5).

Characteristics of the included studies

The characteristics of the studies are detailed in Tables 1, 2, and 3 for the general population cohorts, observational occupational cohorts, and experimental/intervention occupational cohorts, respectively. Overall, 24 observational studies were categorised as general population cohort studies; 55 studies as occupational cohort studies, which included 40 observational studies and 15 experimental/intervention studies. The occupational category comprised studies of office workers (21); professionals – physicians, specialists, nurses, university staff, teachers, students, and police duty officers (20); tradespeople and manual workers – construction, factory, manufacturing, cleaning, transport, handicraft, sewing machine operators, steel plant workers and beauticians (14); and bus drivers (3), included a study [56] that recruited office workers, professionals, and tradespeople; and another study [57] was also of professionals and tradespeople. Cross-sectional designs and a case–control design accounted for 75% and prospective designs 25% in the general population category, whereas 85% of the observational studies in the occupational category were cross-sectional and 15% had prospective designs. Among the experimental/intervention studies, however, there were six randomised controlled trials (RCTs), two randomised cross-over trials, and two non-randomised experiment without control; one study each of non-RCT, randomised trial (RT) without control, non-RT without control (a pilot study), non-randomised cross-over trial, and a cross-sectional analysis of a dataset from an RCT.

In the general population category, SB was most frequently measured (79%) in the non-occupational domain. In contrast, in the occupational category, SB was most frequently measured (85%) in the occupational domain. Most (i.e., 54 out of 79) of the studies measured self-reported SB. In total, 19 studies investigated device-measured SB, including ActiGraph (general population category, four studies; occupational category, eight studies), activPAL (five – all in the intervention studies of occupational category), and both ActiGraph and activPAL (one intervention study of occupational category).

Table 1 Characteristics of the general population studies

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Sedentary behaviour (SB) domain + Measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect size/*p*-value	Quality score
Study design – cross-sectional						
Non-occupational Sedentary Behaviour						
Aweto et al. 2016 [58] Nigeria	51 – 80 years Sample size = 182 Average: age = 70.17(8.62), BMI = NR %Female: 54.95%	Non-occupational – Sedentary behaviours (TV, reading, listening to music, sitting in a car, lying, talking on the phone) Self-reported	LBP, UBP, Shoulder pain, Neck pain, Knee pain, Ankle pain, Elbow pain, Arm pain – Point and 12-month prevalence %Prevalence: point prevalence = 51.6%; 12-months prevalence = 87.4% Self-reported	Chi-square ($\chi 2$) test	Positive associations of sedentary behaviours with LBP; UBP; Knee pain; and Ankle pain. No association with Neck/shoulder and Elbow pain **LBP:** $\chi 2 = 15.7$, p-value = 0.02; **UBP:** $\chi 2 = 13.6$, p-value = 0.03; **Knee pain:** $\chi 2 = 16.8$, p-value = 0.01; **Ankle pain:** $\chi 2 = 14.2$, p-value = 0.03; **Shoulder pain:** $\chi 2 = 10.6$, p-value = 0.56; **Neck pain:** $\chi 2 = 7.8$, p-value = 0.62; **Elbow pain:** $\chi 2 = 5.6$, p-value = 0.72	0.41
Kang et al. 2020 [59] South Korea	≥ 50 years Sample size = 3,761 Average: age = NR, BMI = NR %Female: 48.3%	Non-occupational – Total SB(≥ 7.5 h/day) Self-reported	Orthopaedic problems (OPPs): LBP, knee pain, and hip pain – 3-month prevalence %Prevalence: men – 17.7% OPPs; women – 28.6% OPPs Self-reported	Multiple logistic regression Adjusted for age, education, income, occupation, marital status, smoking, BMI, physical activity at work, leisure physical activity, alcohol, sleep duration	Positive association of total SB (≥ 7.5 h/day) with OPPs in *men* [OR(95%CI) = 1.45(1.08 – 1.93)], and no association in *women* [OR(95%CI) = 1.04(0.80 – 1.35)] *Men* had a positive association with **knee pain** [OR(95%CI) = 1.80(1.11 – 2.92)], whereas *women* had a positive association with **hip pain** [OR(95%CI) = 2.05(1.35 – 3.11)] No associations of total SB (≥ 7.5 h/day) with LBP in both men and women, knee pain in women, and hip pain in men	0.91

Table 1 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Sedentary behaviour (SB) domain + Measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect size/*p*-value	Quality score
Kim, 2019 [60] South Korea	≥ 65 years Sample size = 301 Average: age = 72.93(0.11), BMI = NR %Female: 58.3% Korea's 6th National Health and Nutrition Examination Survey (KNHANES VI)	Non-occupational – Total SB (≥ 7.5 h/day) Self-reported	LBP; Osteoarthritis; Knee pain; Hip pain – 3-month prevalence %Prevalence: LBP = 30.5; Osteoarthritis = 92.7; Knee pain = 27.3; Hip pain = 12.8 Self-reported	Multiple logistic regression Adjusted for sex, age, obesity, housing type, family income, education, and marital status	Positive associations of total SB (sitting) with LBP, knee pain, hip pain; and no association with osteoarthritis **LBP:** OR(95%CI) = 1.44(1.19 – 1.74), $p < 0.001$; **Knee pain:** OR(95%CI) = 1.41(1.11 – 1.79), $p < 0.05$; **Hip pain:** OR(95%CI) = 1.54(1.1 – 2.03), $p < 0.05$; **Osteoarthritis:** OR(95%CI) = 1.72(0.86 – 3.43), $p = 0.126$	0.91
Kulaivelan et al. 2018 [61] India	All adults Sample size = 1503 Average: age = 48.23(13.12), BMI = 25.97(4.57) %Female: 54.2%	Non-occupational – TV time, TB SB (sitting) Self-reported	LBP – 12-month prevalence %Prevalence: 9.0% Self-reported – MNMQ	Binary logistic regression Adjusted for smoking, income, sleeping hours, scheduled caste	No associations of TV time and total SB (sitting) with LBP **Sitting time (upper quartile):** OR(95%CI) = 1.17(0.85 – 1.62); **TV time(> 2 h/day)**: OR(95%CI) = 1.17(0.82 – 1.66)	0.68
Lee et al. 2019 [16] South Korea	≥ 50 years Sample size = 8008 (Without chronic pain = 6344, chronic pain = 1664) Average: age – without chronic knee pain = 65.2(9.3), chronic knee pain = 61.3(8.7); BMI – without chronic knee pain = 24.0(3.1), chronic knee pain = 24.7(3.3) %Female: without chronic knee pain = 72.6%, chronic knee pain = 27.4% KNHANES VI	Non-occupational – Total SB (< 5, 5–7, 8–10, and > 10 h/day) Self-reported – IPAQ	Chronic knee pain – 3-month prevalence %Prevalence: 20.8% Self-reported	Multivariable logistic regression Adjusted for age and BMI, individual factors (lifestyle factors and health factors), such as smoking, alcohol consumption, occupation, education, household income, physical activity, depression, and sleep duration	Total SB (> 10 h/day) is significantly positively correlated with chronic knee pain, especially in women even with high levels of physical activity **Total SB > 10 h/day** – *Overall:* OR(95% CI) = 1.28(1.02 – 1.61), $p = 0.03$; *Women:* OR(95% CI) = 1.33(1.02 – 1.74), $p = 0.04$; *Men:* OR(95% CI) = 1.17(0.78 – 1.75), $p = 0.46$	0.95

Table 1 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Sedentary behaviour (SB) domain + Measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect size/*p*-value	Quality score
Loprinzi, 2014 [62] USA	≥ 65 years Sample size = 1753 Average: age – T2D = 73.4, without diabetes = 74.3; BMI – diabetes = 30.2, without diabetes = 27.3 %Female: diabetes = 55.1%, without diabetes = 74.3%, All = 57.4% National Health and Nutrition Examination Survey (NHANES)	Non-occupational – Total SB Device-measured – ActiGraph	Arthritis %Prevalence – With diabetes = 43.4%; without diabetes = 33.5% Self-reported	Wald tests and design-based likelihood ratio tests were used to examined statistical differences Adjusted for gender, age, and accelerometer wear time	Positive association of total SB with arthritis in both T2D and non-diabetes ***P*-value:** T2D = 0.001; without diabetes < .0001	0.91
Machado et al. 2018 [63] Brazil	≥ 65 years Sample size = 378 Average: age = 75.5(6.1), BMI = 27.3(4.9) %Female: 70.9% The PAINEL Study	Non-occupational – Total SB Self-reported	LBP – 12-month prevalence %Prevalence: 9.3% Self-reported	Logistic regression Adjusted for age, gender, BMI, income, multimorbidity, depressive symptoms, sleep hours, years of schooling, smoking, physical activity level	No association of total SB with LBP **Sitting time 4.2(2.5) h/day:** OR(95%CI) = 1.03(0.81 – 1.31)	0.73
Mendonça et al. 2020 [64] Brazil	All adults – Severely obese Sample size = 150 Average: age = 39.6(0.7), BMI = 46.1(0.5) %Female: 85.3% 'DieTBra Trial'	Non-occupational – Total SB (Low SB < 1,182.15 min/day) Device-measured – ActiGraph	MSP –Neck, shoulders, elbows, upper back, lower back, wrist/hands, hips/thighs, knees, and ankles/feet %Prevalence: 89.3%(site with high prevalence – ankle/feet = 68.7%), LBP = 62.7%, knees = 53.3%, and UBP = 52.0%) Self-reported	Poisson regression Adjusted for sex, age, skin colour, years of schooling, economic class, and occupation	Low total SB (< 1,182.15 min/day) is associated with hip pain, but no association with shoulder pain and wrist/hands pain **Hip pain:** PR(95%CI) = 1.84(1.05 – 3.21), $p = 0.032$. **Shoulder pain:** PR(95%CI) = 1.76(0.96 – 3.23), $p = 0.066$; **Wrist/hands:** PR(95%CI) = 0.59(0.33 – 1.06), $p = 0.078$	0.95

Table 1 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Sedentary behaviour (SB) domain + Measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect size/*p*-value	Quality score
Mendonça et al. 2020a [65] Brazil	All adults – Severely obese Sample size = 150 Average: age = 39.57(0.72), BMI = 46.12(0.53) %Female: 85.33% 'DieTBra Trial'	Non-occupational – Total SB(Low SB < 1,182.15 min/day); Device-measured – ActiGraph	MSP-related pain intensity %Prevalence: pain – 89.33%, severe pain – 69.33%, and pain in four or more sites – 53.33% Self-reported	Poisson regression Adjusted for demographic data (gender, education, and economic class), diet and exercise (fruit and vegetable consumption and MVPA [min/day]), and clinical characteristics (falls in the last 12 months, fracture, anxiety, depression, arthritis/arthrosis, use of analgesics, and muscle relaxant use)	A longer duration of total SB is associated with the experience of more pain **SB < Median (1182.15):** *Pain* – PR(95%CI) = 0.95(0.86 – 1.06), $p = 0.399$; *Severe pain* – PR(95%CI) = 1.09(0.88 – 1.35), $p = 0.432$; *Four or More Painful Sites* – PR(95%CI) = 1.06(0.79 – 1.44), $p = 0.680$	0.91
Park et al. 2018 [66] South Korea	≥ 50 years Sample size = 5364 Average: age = without LBP = 63.4(8.7), LBP = 67.3(9.1); BMI = without LBP = 24.1(3.1), LBP = 24.4(3.4) %Female: without LBP = 52.3%; LBP = 74.2% KNHANES	Non-occupational – Total SB Self-reported – IPAQ	LBP – 3-month prevalence %Prevalence: 22.8% Self-reported	Multiple logistic regression Adjusted for age, sex, BMI, socioeconomic factors, education, household income, smoking, alcohol, and comorbidities	Positive association of total SB with LBP **Sitting time > 7 h/day:** OR(95%CI) = 1.33 (95% CI, 1.10 – 1.61)	0.95
Ryan et al. 2017 [67] UK	All adults Sample size = 2313 Average: age = 52(18), BMI = 28(5) %Female: 55% Health Survey for England (HSE)	Non-occupational – Total SB Device-measured – ActiGraph	Chronic MSP %Prevalence: 17% Self-reported	Isotemporal substitution Adjusted for age, sex, socioeconomic status, diet, smoking history, alcohol intake, anxiety/depression, and presence of anon-musculoskeletal long-standing illness	Replacing 30 min SB with 30 min MVPA has a small but clinically relevant protective association with the chronic MSP prevalence ratio **Substituting 30 min SB with 30 min MVPA:** PR(95%CI) = 0.71(0.55 – 0.88)	0.95
Sagat et al. 2020 [68] Saudi Arabia	18 – 64 years Sample size = 463 Average: age = NR, BMI = NR %Female: 44.1%	Non-occupational – Total SB (Sitting always or most of the time) Self-reported	LBP intensity %Prevalence: Before quarantine = 38.8%, During quarantine = 43.8% Self-reported	Spearman test for correlation	A significant positive correlation of LBP intensity with sitting during Covid-19 quarantine **Correlations of LBP intensity with sitting:** *Before quarantine* – $r = 0.054$, $p = 0.216$; *During quarantine* – $r = 0.124$, $p = 0.008$	0.59

Table 1 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Sedentary behaviour (SB) domain + Measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect size/*p*-value	Quality score
Smuck et al. 2014 [69] USA	All adults Sample size = 6796 Average: age = NR, BMI = NR %Female: NR NHANES	Non-occupational – Total SB, sedentary bout Device-measured – Acti-Graph	LBP – 3-month prevalence %Prevalence: NR Self-reported	Adjusted weighted logistic regression Adjusted for BMI	Positive association of total SB and mean sedentary bout with LBP **Maximum SB bout [1239(903) min]:** OR(95%CI) = 1.03(1.1 – 1.8); **Average SB bout [50.0(46.9) min]**: OR(95%CI) = 1.09(1.3 – 3.0)	0.91
Vancampfort et al. 2017 [70] China, Ghana, India, Mexico, Russia, and South Africa	≥ 50 years Sample size = 34,129 (China = 13,175; Ghana = 4305; India = 6560; Mexico = 2313; Russia = 3938; South Africa = 3838) Average: age = median (IQR): 62(55 –70) years, BMI = NR %Female: 52.1% SAGE	Non-occupational – Total SB (≥ 8 h per day) Self-reported	Chronic LBP – 1-month prevalence %Prevalence: 8.6%, Arthritis %Prevalence: 29.5% Self-reported	Multivariable logistic regression Adjusted for sex, age, education, wealth, setting, unemployment, living arrangement, and country, comorbid chronic conditions	Positive association of total SB with arthritis and chronic LBP *Arthritis* **Overall:** OR(95%CI) = 1.22(1.03 – 1.44); **50-64 years:** OR(95%CI) = 1.17(0.92 – 1.49); ≥ **65 years:** OR(95%CI) = 1.33(1.07 – 1.67); *Chronic LBP* **Overall:** OR(95%CI) = 1.70(1.37 – 2.11), **50-64 years:** OR(95%CI) = 1.38(0.98 – 1.95), ≥ **65 years:** OR(95%CI) = 1.87(1.43 – 2.44)	0.86
Occupational Sedentary Behaviour						
Anita et al. 2019 [71] Spain	Born between 1940 and 1966 (> 50 years) Sample size = 1059 Average: age = 56.7(7.1), BMI – LBP = 27.1(5.4), No LBP = 27.1(4.2) %Female: 55%	Occupational – Workplace sitting Self-reported	LBP – 1-month prevalence %prevalence = 14.2% Self-reported	Multivariate regression Adjusted for age, sex, depression/anxiety level	No association of workplace sitting with LBP OR(95%CI) = 0.28(0.05 – 1.38), $p = 0.12$	0.77

Table 1 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Sedentary behaviour (SB) domain + Measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect size/*p*-value	Quality score
Occupational and Non-occupational Sedentary Behaviour						
Bento et al. 2019 [72] Brazil	All adults Sample size = 600 Average: age = NR, BMI = NR %Female: 50%	Occupational—Workplace sitting; and Non-occupational—Sedentary behaviours (time spent on TV, on a computer, and/or video games) Self-reported	LBP – Point prevalence %Prevalence: 28.8% Self-reported	Poisson regression Adjusted for age, education, ethnicity, income, smoking, physical activity, depression, hypertension, diabetes, gastrointestinal, renal, and respiratory diseases	No associations od sedentary behaviours nor workplace sitting with LBP **TV time ≥ 3 h:** *Female* PR = 0.96(95%CI = 0.31 – 1.71); *Male* PR(95%CI) = 1.06(0.68 – 1.65); **Computer/video game ≥ 3 h:** *Female* PR(95%CI) = 0.70(0.37 – 1.31); *Male* PR(95%CI) = 0.52(0.24 – 1.14). **Sitting position at work (Always/usually):** *Female* PR(95%CI) = 1.24(0.90 – 1.72); *Male* PR(95%CI) = 0.88(0.56 – 1.38)	0.86
Dos Santos et al. 2017 [73] Brazil	All adults Sample size = 600 Average: age = NR, BMI = NR %Female: 50%	Occupational – Workplace sitting; and Non-occupational – sedentary behaviours (time spent on TV, on a computer, and/or playing video games) Self-reported	Neck pain – 12-month prevalence %prevalence: 20.3% Self-reported – NMQ	Poisson regression to calculate prevalence ratio with a confidence interval Adjusted for gender	No associations of workplace sitting, TV time, and computer time with neck pain **Sitting position (Always/usually):** PR = 1.09(95%CI = 0.78 – 1.52); **TV time > 3 h:** PR = 0.89(95%CI = 0.64 – 1.23); **Computer time > 3 h:** PR = 1.20(95%CI = 0.71 – 2.02)	0.77

Table 1 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Sedentary behaviour (SB) domain + Measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect size/*p*-value	Quality score
Study design – case–control						
Occupational Sedentary Behaviour						
Pope et al. 2003 [74] UK	All adults Sample size = 3385 Average: age = NR, BMI = NR, %Female: Cases = 63.6; Control = 49.4	Occupational – Workplace sitting (≥ 2 h without a break) Self-reported	Hip pain – 1-month prevalence %Prevalence: 10.5% Self-reported	Logistic regression Adjusted for age, sex, and all physical activities	Positive association of prolonged sitting with hip pain **Sitting for prolonged periods – ≥ 2 h:** *(higher exposure vs not exposed):* OR(95%CI) = 1.82(1.13 – 2.92)	0.91
Study design – prospective						
Non-occupational Sedentary Behaviour						
Balling et al. 2019 [75] Denmark	All adults Duration: mean 7.4-years Sample size = 46,826 Average: age = 47.6(15.8), BMI = 24.8(4.2) %Female: 60.3%	Non-occupational – Total SB (sitting time) Self-reported – IPAQ	LBP – Incidence %Incidence: 3.8% Medical records	Cox regression Adjusted for age, sex, mental disorder, education, smoking status, BMI, leisure-time physical activity, and physical activity at work	No association of total SB (sitting) with an incidence of LBP **Sitting 6 to < 10 h:** HR(95%CI) = 0.99(0.89 – 1.10); **10 + hrs:** HR(95%CI) = 0.99(0.86 – 1.16)	0.95
Chang et al. 2020 [76] USA	45 – 79-years at baseline Duration: 8-year Sample size = 1194 Average: age = 58.4(8.9), BMI = 26.8(4.5) %Female: 58.4% Osteoarthritis Initiative (OAI)	Non-occupational – Extensive sitting behaviour over 8 years Self-reported	Knee pain – 12-month incidence %Incidence: 13.0% Clinical diagnosis – radiologic examination	Logistic regression Adjusted for age, gender, BMI, depressive symptoms, comorbidities	No association of extensive sitting trajectory with incident knee osteoarthritis **Moderate frequency sitting trajectory:** RR(95%CI) = 1.02(0.88 – 1.18); **High frequency sitting trajectory:** RR(95%CI) = 1.22(1.00 – 1.50)	0.95
da Silva et al. 2019 [77] Australia	All adults Duration: 3-, 6-, 9- and 12-month follow-ups Sample size = 250 Average: age = 50(15), BMI: 26.5(5.3) %Female: 50%	Non-occupational – Total SB Self-reported	LBP – Incidence %Incidence: 38% at 3-months; 56% at 6-months; and 69% at 12-months Self-reported – 11-point numerical rating scale	Cox regression – completeness of follow-up was calculated using the completeness index Adjusted for age BMI, smoking, and exposure to heavy load	Positive association of sitting time with LBP **Sitting > 5 h:** HR(95%CI) = 1.50(1.08 – 2.09), p = 0.02	0.73

Table 1 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Sedentary behaviour (SB) domain + Measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect size/*p*-value	Quality score
Hussain et al. 2016 [78] Australia	All adults Duration: 5-, 12-years Sample size = 4974 Average: age = NR, BMI = NR %Female: 55.8% Australian Diabetes, Obesity, and Lifestyle (AusDiab) Study	Non-occupational – TV time Self-reported	LBP intensity, LBP disability – 6-month prevalence %Prevalence: 81.9% Self-reported – Chronic Pain Grade Questionnaire (CPGQ)	Multinomial logistic regression Adjusted for age, education, smoking status, dietary guideline index score, and BMI; SF-36 MCS score	High levels of TV time are positively associated with an increased risk of LBP disability in women but not in men. No association of TV time with LBP intensity **TV time ≥ 2 h: *LBP intensity*** *(Men)* Low: OR(95%CI) = 1.15(0.91 – 1.46), $p = 0.25$; High: OR(95%CI) = 1.17(0.86 – 1.59), $p = 0.31$; *(Women)* Low: OR(95%CI) = 1.11(0.88 – 1.40), $p = 0.37$; High: OR(95%CI) = 1.17(0.88 – 1.56), $p = 0.28$; ***LBP Disability*** *(Men)* Low: OR(95%CI) = 1.10(0.84 – 1.43), $p = 0.50$; High: OR(95%CI) = 1.15(0.82 – 1.61), $p = 0.42$; *(Women)* Low: OR(95%CI) = 1.35(1.04 – 1.73), $p = 0.02$; High: OR(95%CI) = 1.29(1.01 – 1.72), $p = 0.04$	0.82
Stefansdottir & Gudmundsdottir, 2017 [17] Iceland	All adults Duration: 5-years Sample size = 737 Average: age = 53(16), BMI = 27(5) %Female: 39% Health and Wellbeing of Icelanders survey	Non-occupational – Total SB Self-reported	General musculoskeletal symptoms – 5-year prevalence %Prevalence: 33.5% Self-reported	Not reported	Positive association of total SB with general MSP **High SB:** OR(95%CI) = 1.7(1.03 – 2.83)	0.50

Table 1 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Sedentary behaviour (SB) domain + Measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect size/*p*-value	Quality score
Occupational Sedentary Behaviour						
Martin et al. 2013 [79]UK	36-year, 43-year, and 53-year old cohorts Duration: Since birth in 1946 Sample size = 2957 Average BMI: 36-year = 24.1(3.7), 43-year = 25.4(4.2), 53-year = 27.4(4.8) %Female: 36-year = 51.3%, 43-year = 51.3%; 53-year = 50.7%	Occupational – Workplace sitting (> 2 h) Self-reported	Knee pain (Osteoarthritis) – 1-month prevalence %Prevalence: 10.2% Self-report and clinical examination	Logistic regression Adjusted for gender, health risk factors, and socioeconomic position	Negative association of workplace with knee osteoarthritis in women, but no association in men **Sitting highly likely:** *(Men) 36 years* OR(95%CI) = 1.13(0.61 – 2.06), *p* = 0.700; *43 years* OR(95%CI) = 0.69 (0.39 – 1.24), *p* = 0.226; *53 years* OR(95%CI) = 0.60 (0.34 – 1.07), *p* = 0.085; *(Women) 36 years* OR(95%CI) = 0.56 (0.33 – 0.94), *p* = 0.029; *43 years* OR(95%CI) = 0.57 (0.36 – 0.89), *P* = 0.013; *53 years* OR(95%CI) = 0.89 (0.56 – 1.43), *p* = 0.653	0.91

NR: Not reported, (M)NMQ: (Modified) Nordic musculoskeletal questionnaire, TV: Television-viewing

Table 2 Characteristics of the observational occupational cohort studies

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Study design – cross-sectional							
Occupational Sedentary Behaviour							
Ayanniyi et al. 2010 [80] Nigeria	All adults Sample size = Computer users = 236; Non-computer users = 236; Total = 472 Average: age – Computer users = 29(4.87), Non-computer users = 31(6.23); BMI = NR %Female: Computer users = 42.4%; Non-computer users = 42.4%	Office workers	Occupational – Computer time Self-reported	Musculoskeletal symptoms (Neck/shoulder pain, UBP, elbows, wrists/hands, LBP, hips/thighs, knees, and ankles/feet pain) – 7- and 12-month prevalence %Prevalence: 7 days point prevalence – Computer users = 55.9%, Non-computer users = 27.5%; 12-months prevalence – Computer users = 93.2%, Non-computer users = 33.9% Self-reported	Regression analysis Adjusted for age, sex, marital status	Positive association of computer time with musculoskeletal symptoms **7-day prevalence:** *2–4 h* – OR = 1.36(95%CI = 0.92 – 1.68, $p < 0.05$); *> 4 h* – OR = 4.12(95%CI = 3.21 – 5.16, $p < 0.05$); **12-Month prevalence:** *2–4 h* – OR = 3.25(95%CI = 1.84 – 4.73, $p < 0.05$); *> 4 h* – OR = 5.04(95%CI = 3.66 – 6.33, $p < 0.05$)	0.73
Benyamina et al. 2018 [81] Canada	All adults Sample size = 2208 Average: age = 35.8(8.1), BMI = NR %Female: 31.1%	Professionals – Car-patrol police officers	Occupational –vehicle time (time spent sitting in a vehicle) Self-reported	LBP – 12-month prevalence %Prevalence: Chronic LBP = 28.1%, acute/subacute LBP = 40.7% Self-reported – NMQ	Multinomial regression Adjusted age, sex, country of birth, income, the region of residency, depressed mood, and anxiety	No association of vehicle time with LBP **Acute/subacute LBP vs No-LBP:** OR(95%CI) = 1.005 (0.998 – 1.012), $p = 0.169$; **Chronic LBP vs No-LBP**: OR(95%CI) = 1.002 (0.993 – 1.010), $p = 0.702$	0.77
Cagnie et al. 2007 [82] Belgium	All adults Sample size = 512 Average: age = NR, BMI = 24.0(3.4) %Female: 41.7%	Office workers	Occupational – prolonged workplace sitting and computer time (> 4 h/day) Self-reported	Neck pain – 12-month prevalence %Prevalence: 45.5% Self-reported – NMQ	Logistic regression Adjusted for age, gender, mental tiredness, and sport	Positive associations of prolonged workplace sitting and computer time with neck pain **Workplace sitting:** OR(95% CI) = 2.06(1.17 – 3.62); **Computer time:** OR(95% CI) = 1.57(1.10 – 2.22)	0.73

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Celik et al. 2018 [83] Turkey	All adults Sample size = 528 Average: age = 38.55(9.79), BMI = 25.44(3.85) %Female: 51.14%	Office workers	Occupational – Total workplace sitting [mean = 4.64(2.21) Self-reported	LBP, UBP, Shoulder pain, Neck pain, Leg pain, Arm pain, Foot pain, Wrist pain %Prevalence: LBP – Female = 60.4%, Male = 49.6%; UBP – Female = 62.6%, Male = 43.0%; Shoulder pain – Female = 50.0%, Male = 31.0%; Neck pain – Female = 61.9%, Male = 42.6%; Leg pain – Female = 39.6%, Male = 26.7%, Arm pain – Female = 33.0%, Male = 20.5%; Foot pain – Female = 45.6, Male = 37.2%; Wrist pain – Female = 33.7%, Male = 19.0% Self-reported	Multiple-linear regression Adjusted for age, BMI, marital status, exercise in daily life, working experience	No significant association of workplace sitting with LBP, UBP, shoulder and wrist pain. Negative association of workplace sitting with neck and extremities pain (arm, leg, and foot) in females **LBP:** *Female* B = –0.07, SE = 0.04, 95%CI = –0.16–0.00, *p* = 0.080; *Male* B = –0.03, SE = 0.04, 95%CI = –0.13–0.05, *p* = 0.458; **UBP:** *Female* B = –0.00, SE = 0.04, 95%CI = –0.09–0.07, *p* = 0.825; *Male* B = 0.06, SE = 0.04, 95%CI = –0.03–0.15, *p* = 0.195; **Neck pain:** *Female* B = –0.110, SE = 0.04, 95%CI = –0.20–(–0.02), *p* = 0.009; *Male* B = 0.04, SE = 0.04, 95%CI = –0.04–0.13, *p* = 0.352. **Shoulder pain:** *Female* B = –0.02, SE = 0.04, 95%CI = –0.10–0.06, *p* = 0.648; *Male* B = 0.01, SE = 0.04, 95%CI = –0.06–0.10, *p* = 0.711; **Leg pain:** *Female* B = –0.08, SE = 0.04, 95%CI = –0.170–0.000, *p* = 0.043; *Male* B = –0.01, SE = 0.04, 95%CI = –0.11–0.07, *p* = 0.687; **Foot pain:** *Female* B = –0.09, SE = 0.040, 95%CI = –0.18–(–0.01), *p* = 0.027; *Male* B = 0.00, SE = 0.04, 95%CI = –0.07–0.08, *p* = 0.891; **Arm pain:** *Female* B = –0.10, SE = 0.04, 95%CI = –0.18–(–0.02), *P* = 0.010; *Male* B = 0.00, SE = 0.04, 95%CI = –0.07–0.08, *p* = 0.919; **Wrist pain:** *Female* B = –0.04, SE = 0.04, 95%CI = –0.12–0.04, *p* = 0.343; *Male* B = 0.03, SE = 0.03, 95%CI = –0.03–0.11, *P* = 0.292	0.73

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Chee & Rampal 2004 [84] Malaysia	All adults Sample size = 906 Average: age = NR, BMI = NR %Female: 100%	Tradespeople – Semiconductor factory workers	Occupational – Workplace sitting (≥ 4 h/day) Self-reported	Neck/shoulder pain, and lower limbs – 12-month prevalence %Prevalence: 80.5% Self-reported – NMQ	Multivariate binary logistic regression Adjusted for age, work task, work schedule, overtime work, whether work environment was too cold, and stress	Positive association of workplace sitting with **neck/ shoulder pain** [OR(95% CI) = 1.6(1.2 – 2.1)]; a negative association with **Lower limbs** OR(95% CI) = 0.5(0.4 – 0.8)	0.91
Chrasakaran et al. 2003 [85] Malaysia	All adults Sample size = 529 Average: age = 31.2(7.4), BMI = NR %Female: 100%	Tradespeople –Semiconductor factory workers	Occupational – Workplace sitting (≥ 4 h/day) Self-reported	Neck, shoulder, arm (elbow and forearm), wrist and fingers, upper leg (hips/thighs/knees), lower leg (ankles/feet) – 12-month prevalence %Prevalence: lower leg (48.4%), shoulder (44.8%), upper leg (38.8%) and neck (29.7%) Self-reported – NMQ	Logistic regression Adjusted for age, number years of work, the stress of work, cold working temperature	Positive association of workplace sitting with NSP, but no association with extremities pain **Neck:** [OR(95% CI) = 2.1(1.3 – 3.2); **Shoulder:** [OR(95% CI) = 1.7(1.2 – 2.5); **Upper leg:** [OR(95% CI) = 0.6(0.3 – 1.0); **Lower leg:** [OR(95% CI) = 0.6(0.4 – 1.0)	0.73
Constantino et al. 2019 [86] Brazil	All adults Sample size = 530 Average: age = NR, BMI = NR %Female: 95.4%	Professionals – Teachers	Occupational – workplace sitting (≥ 2 h/day), computer time(≥ 2 h/day); and Non-occupational – TV time(≥ 2 h/day) Self-reported	Clinically diagnosed MSP disease; musculoskeletal symptoms (back/ neck); and MSP-related disability – 12-month prevalence %Prevalence: > 30% Self-reported – NMQ	Poisson regression Adjusted for age, gender, length of employment, high stress, common mental disorder, physical activity	Negative association of workplace sitting with **lower limbs disability** [Adjusted PR(95%CI) = 0.64(0.43–0.94)]; No association of TV time with **back & neck pain** [Adjusted PR(95%CI) = 1.03(0.88–1.21)]; Positive association of TV time with clinically diagnosed **MSP disease** [Adjusted PR(95%CI) = 1.37(1.02–1.85)]; No association of computer time with clinically diagnosed **MSP disease** [Adjusted PR(95%CI) = 0.78(0.60–1.02)]	0.77

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Dianat & Karimi, 2016 [87] Iran	All adults Sample size = 632 Average: age = 34.5(11.5), BMI = 24.9(4.1) %Female: 58.9%	Tradespeople – Handicraft workers	Occupational – Workplace sitting (> 2 h/day) Self-reported	Neck, shoulders, LBP –1-month prevalence %Prevalence: 76.2% Self-reported – NMQ	Logistic regression Adjusted for age, gender, BMI, marital status, education level, smoking, physical activity, years working	Positive association of workplace sitting > 2 h with **neck pain** in multivariate analysis [OR(95% CI) = 2.85(1.79 – 4.53), $p < 0.001$] Univariate analysis showed a positive association of workplace sitting with **shoulder pain** [OR(95% CI) = 1.54(1.02 – 2.31)];and no association with **LBP** [OR(95% CI) = 0.99(0.66 – 1.47)]	0.86
Dianat et al. 2015 [88] Iran	All adults Sample size = 251 Average: age = 33.2(9.9), BMI: 24.1(4.1) %Female: 39.8%	Tradespeople – Sewing machine operators	Occupational – workplace sitting (> 2 h/day) Self-reported	Neck, shoulders, UBP, LBP, elbows, wrists/hands, hips/thighs/buttocks, knees, and ankles/feet – 12-month prevalence %Prevalence: 9.6% Self-reported – NMQ	Logistic regression Adjusted for demographic (age, gender, BMI, educational level, marital status, smoking, physical activities, and job characteristics, and RULA scores	Positive association of workplace sitting > 2 h with **neck pain** [OR(95% CI) = 3.34(1.40 – 7.95), $p = 0.006$]; and **shoulder pain** [OR(95% CI) = 3.12(1.19 – 8.18), $p = 0.020$] in multivariate analysis However, univariate analysis showed no association of workplace sitting with **LBP** [OR(95% CI) = 1.12(0.41 – 2.99), $p = 0.821$], and **UBP** [OR(95% CI) = 1.04(0.93 – 1.16), $p = 0.102$]; but positive association with **Hand/wrist** [OR(95% CI) = 2.49(1.08 – 5.72), $p = 0.031$]	0.86
Ilic et al. 2021 [89] Serbia	Young to middle-aged Sample size = 499 Average: age = 22.0(2.2) %Female: 67.7%	Professionals – Students	Occupational – Workplace sitting (prolonged sitting) Self-reported	LBP – Point prevalence %Prevalence: 20.8% Self-reported	Logistic regression Adjusted for smoking, BMI, Incorrect body posture, stress, incorrect sitting position, family history of LBP	Multivariate analysis: No association of prolonged sitting with LBP [OR (95%CI) = 1.5(0.5 – 4.2), $p = 0.424$ Univariate analysis – prolonged sitting associated with LBP ($p = 0.018$)	0.82
Hakim et al. 2017 [90] Egypt	All adults Sample size = 180 Average: age = NR, BMI = NR %Female: 0%	Bus divers	Occupational – vehicle time (> 8 h/day) Self-reported	LBP – 12-month prevalence %Prevalence: 73.9% Self-reported – NMQ	Binary logistics regression Adjusted for age, BMI, marital status, education, smoking, work duration	Positive association of vehicle time (> 8 h) with LBP OR(95%CI) = 2.93(1.45 – 5.93)	0.68

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Larsen et al. 2018 [91] Sweden	All adults Sample size = 4114 Average: age = NR, BMI = NR %Female: 25.8%	Professionals – Duty police officer	Occupational – Vehicle time (% shift time sitting: 25 – 50%, 50 – 75%, > 75%) Self-reported	Multisite MSP (pain in two or more body regions) – 3-month prevalence %Prevalence: 41.3% Self-reported – 5-point scale	Binominal logistic regression.; adjusted for age, sex, physical exercise, physical workload factors, and psychosocial factors	Vehicle time vehicles were not significantly associated with multi-site MSP among police **Shift time sitting:** *25 – 50%* OR(95%CI) = 0.97(0.74 – 1.28); *50 – 75%* OR(95%CI) = 1.11(0.84 – 1.47); *> 75%* OR(95%CI) = 1.10(0.77 – 1.57)	0.86
Lourenço et al. 2015 [92] Portugal	21-year cohorts Sample size = 1733 (Non-workers = 1083; Workers = 650) Average BMI = NR %Female: Non-workers = 51.8%; Workers = 51.2% Epidemiological Health Investigation of Teenagers in Porto (EPI-Teen)	Professionals – Student	Occupational – Workplace sitting (> 4.2 h/week); computer time (> 5.0 h/week) Self-reported	Neck, shoulders, elbows, wrists/hands, upper back, lower back, hips/thighs/buttocks, knees, and ankles/feet – 12-month prevalence Self-reported	Logistic regression Adjusted for sex, BMI, physical activity, smoking, education, and job strain (Karasek's Job Strain Model)	A positive association of workplace sitting with **LBP** [OR(95%CI) = 1.70(1.20 – 2.42)]; no association with **neck pain** [OR(95%CI) = 1.23(0.89 – 1.71)] and **extremities pain** [OR(95%CI) = 0.83(0.60 – 1.16)]	0.91
Mehrdad et al. 2012 [93] Iran	All adults Sample size = 405 Average: age = 44.6 (7.9), BMI: 23.7(2) %Female: 47%	Professionals – physicians	Occupational – Prolonged workplace sitting (> 20 min) Self-reported	Neck pain[a] – 12-month prevalence %Prevalence: 41.7% Self-reported – NMQ	Logistic regression Adjusted for both individual and work-related factors such as age, gender, BMI, shift work, type of employment, and secondary job	A positive association of prolonged workplace sitting with neck pain Coefficient(B) = 0.204, OR(95%CI) = 1.227(1.032 – 1.458), $p = 0.020$	0.86
Omokhodion et al. 2003 [94] Nigeria	All adults Sample size = 840 Average: age = NR, BMI = NR %Female: 43%	Office workers	Occupational – Workplace sitting (> 3 h) Self-reported	LBP – 12-month prevalence %Prevalence: 37.5%; Self-reported	Not reported	Workplace sitting for > 3 h associated with increased severity of LBP	0.36
Pradeepkumar et al. 2020 [95] India	24 – 55 years Sample size = 301 Average: age = 39(7.3), BMI = NR %Female: NR	Bus drivers	Occupational – Vehicle time (Prolonged sitting) Self-reported	MSP conditions – 7-day and 12-month prevalence %Prevalence: 55.8%; Self-reported – NMQ	Chi-square test	Prolonged sitting in a vehicle is positively associated with the risk of MSP conditions $\chi 2 = 5.833$, $p < 0.05$	0.55
Ratzon et al. 2000 [96] Israel	All adults Sample size = 60 Average: age = 46.0 (8.66), BMI – Sitting position = 25.14(2.18), Alternating position = 25.31(2.44) %Female: 0%	Professionals – Dentist	Occupational – Workplace sitting (≥ 80% of work time) Self-reported	General MSP, LBP – 7-days and 12-month prevalence %Prevalence; Low back pain = 55% Self-reported – NMQ	Pearson and Spearman correlations	Sitting position at work positively and significantly correlated with LBP Correlation coefficient – **MSP** = − 0.16; **LBP:** $r = 0.41$, $p < 0.01$	0.45

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Şimşek et al. 2017 [97] Turkey	All adults Sample size = 1682 Average: age = 37.9(7.46), BMI: NR %Female: 60%	Professionals – Healthcare workers	Occupational – Workplace sitting (> 4 h), computer time (> 4 h) Self-reported	LBP – 7-days, 12-month, and lifetime prevalence %Prevalence: Lifetime prevalence 53%, 12-month prevalence 39% and 7-days prevalence 29.5% Self-reported – NMQ (10-cm-long Visual Analogue Scale (VAS))	Binary logistic regression Adjusted for sex, BMI, marital status, smoking habit, physical exercise, job satisfaction, workplace stress	Positive associations of workplace sitting and computer time > 4 h with LBP **Workplace sitting time:** OR(95%CI) = 4.7(1.25 – 17.64), $p = 0.021$; **Computer time:** ORROR(95%CI) = 0.0(0.00 – 0.04), $p = 0.0001$	0.86
Spyropoulos et al. 2007 [98] Greece	All adults Sample size = 648 Average: age = 44.5, BMI = NR %Female: 75.8%	Office workers	Occupational – Workplace sitting (≥ 6 h) Self-reported	LBP – Lifetime prevalence %Prevalence: Lifetime 61.6% Self-reported – Visual Analogue Scale (VAS) and physical examination by a physiotherapist	Multiple logistic regression Adjusted for age gender, BMI, psychosocial factors	Positive association of workplace sitting time > 6 h with lifetime LBP OR(95z5CI) = 1.588(1.064 – 2.368)	0.82
Szeto & Lam, 2007 [99] Hong Kong	All adults Sample size = 481 Average: age = NR, BMI – Male = 25.24(3.42); Female = 23.60(2.74) %Female: 16%	Bus drivers	Occupational – Vehicle time (prolonged sitting) Self-reported	LBP[a] – 12-month prevalence %Prevalence: 92.7% Self-reported – NMQ	Logistic regression Adjusted for age, gender, company	Positive association of prolonged vehicle time with LBP OR(95% CI) = 3.71(2.40 – 5.74)	0.77
Temesgen et al. 2019 [100] Ethiopia	All adults Sample size = 754 Average: age = 42(9.73), BMI = NR %Female: 57.8%	Professionals – Teachers	Occupational – Workplace sitting (prolonged sitting > 4 h/day) Self-reported	Neck/shoulder pain – 12-month prevalence %Prevalence: 57.3% Self-reported – NMQ	Logistics regression Adjusted for age, marital status, salary, smoking, alcohol, physical exercise, diabetes, hypertension, respiratory diseases	Positive association of prolonged workplace sitting > 4 h with neck/shoulder pain OR(95%CI) = 1.50(1.02 – 2.23)	0.95
Tsigonia et al. 2009 [101] Greece	All adults Sample size = 102 Average: age = 38.42(10.74), BMI = 23.09(2.86) %Female: 93%	Tradespeople – Cosmetologists	Occupational – Workplace sitting (High exposure to prolonged sitting – often or always) Self-reported	Neck, shoulder, hand/wrist, low back, knee; 12-month prevalence; %Prevalence: Neck = 58%; shoulder = 35%; hand/wrist = 53%; low back = 53%; knee = 28%; Self-reported– NMQ	Logistics regression; adjusted for age and sex	Positive association of high exposure to prolonged workplace sitting with hand/wrist complaints, OR(95%CI) = 55.7(18.75-354.93) Univariate analysis indicates workplace sitting is significantly related to the occurrence of LBP, neck/shoulder pain, hand and knee pain (both acute and chronic complaints)	0.73

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
van Vuuren et al. 2005 [102] South Africa	All adults Sample size = 366 Average: age = 31.76(7.80), BMI = NR %Female: NR	Tradespeople – Steel plant workers	Occupational – Workplace sitting (sitting position half the time or more) Self-reported	LBP, LBP disability – Point, 1-month, 12-month, and lifetime prevalence %Prevalence: Point 35.8%, 1-month 41.3%, 12-month 55.7%, and lifetime 63.9%; LBP disability – ≥ 30% Self-reported – Functional Rating Index (FRI)	Multivariate logistic regression Adjusted for all risk factors including work organization, trunk posture, handling activities, body position, and environmental demands	Positive association of workplace sitting with LBP, but no significant association with LBP disability **LBP:** [OR(95%CI) = 2.33(1.01 – 5.37)]; **LBP disability:** [OR(95%CI) 1.89(0.75 – 4.78)]	0.77
Yue et al. 2012 [103] China	All adults Sample size = 893 Average: age = 32.21(10.6), BMI = 39(2.79) %Female: 67%	Professionals – Teachers	Occupational – Workplace sitting (≥ 4 h/day); Computer time (≥ 4 h/day) Self-reported	LBP, neck/shoulder pain – 12-month prevalence %Prevalence: LBP = 45.6%, NSP = 48.7% Self-reported – NMQ	Binary logistic regression Adjusted for age, gender, BMI, education, smoking, exercise, years of work, duration of work	Positive association of prolonged *workplace sitting (≥ 4 h)* with **neck/shoulder pain** [OR(95%CI) = 1.76(1.23 – 2.52)] and **LBP**[OR(95%CI) = 1.42 (1.01 – 2.02)] No significant association of *computer time (≥ 4 h)* with **neck/shoulder pain** [OR(95%CI) = 1.02 (0.63 – 1.65)] and **LBP** [OR(95%CI) = 0.71 (0.44 – 1.14)]	0.86
Non-occupational Sedentary Behaviour							
Ben-Ami et al. 2018 [104] Israel	All adults Sample size = 1026 Average: age = 27.2(6.4), BMI = NR %Female: 57.7%	Professionals – Students	Non-occupational – Leisure-time SB (at least half an hour a day) Self-reported	LBP – 6-month prevalence %Prevalence: 38.6% Self-reported	Multinominal logistic regression Adjusted for sociodemographic, lifestyle, and personal vulnerability	No significant association of total SB with LBP (backache) AOR(95%CI) = 0.96(0.78 – 1.18)	0.86
Hildebrandt et al. 2000 [56] Netherlands	All adults Sample size = 2030 Average: age = 33.7(9.6), BMI: NR %Female: 51%	Tradespeople – Industry (shipyard, metal, transport) and services (cleaners, childcare); Professionals – Healthcare(nurses); and Office workers	Non-occupational – Leisure-time SB Self-reported	LBP, neck/shoulder pain, and lower extremity pain – 12-prevalence %Prevalence: LBP = 60%, NSP = 44%, and lower extremity pain = 31% Self-reported	Logistic regression Adjusted for age, gender, education, and type of workload	Leisure-time SB is positively associated with **LBP** [OR(95%CI) = 1.46(1.18 – 1.29)]; and no associated with **neck/shoulder pain** [OR(95%CI) = 1.02(0.82 – 1.27)], and **lower extremities pain** [OR(95%CI) = 1.07(0.85 – 1.36)]	0.73

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Ibeachu et al. 2019 [105] UK	18 – 39 years Sample size = 314 Average: age = 22.0(5.2), BMI = 24.3(4.1) %Female: 43.9%	Professionals – Student	Non-occupational – Total SB (mean 5.6(2.6)hrs/day) Self-reported – IPAQ	Knee pain – 12-month prevalence %Prevalence: 31.8% Self-reported – Knee Pain Screening Tool (KNEST)	Logistic regression Adjusted for age, gender, BMI, mental distress	Total SB has a borderline non-significant association with knee pain ($p = 0.069$) Quadratic term: OR(95%CI) = 1.02(1.00 – 1.05) Linear term: OR(95%CI) = 1.04 (0.93 – 1.16)	0.82
Rodríguez-Nogueira et al. 2021 [106] Spain	All adults Sample size = 472 Average: age – Male = 48.1(10.9); Female = 45.3(11.2) %Female: 60%	Professionals – University staff	Non-occupational – Daily sitting time (Mean daily sitting time (hrs): Male = 7(2.5); Female = 6.9(2.3)) Self-reported	General MSP – 12-month prevalence Self-reported – NMQ	Logistic regression Adjusted for age, sex, anxiety, physical activity, self-perceived stress	No significant association of daily sitting with general MSP OR(95%CI) = 0.934(0.86 – 1.01), $p = 0.09$	0.86
Sklempe et al. 2019 [107] Croatia	Young adults Sample size = 517 Average: age – 20(2), BMI = 22.3(4.3) %Female: 63.8%	Professionals – Student	Non-occupational – Total SB (mean 5(3.5) hrs/day) Self-reported – IPAQ	Musculoskeletal symptoms (neck, shoulder, upper back, and lower back) – 12-month prevalence %Prevalence: 81% Self-reported – NMQ	Point-biserial correlation coefficient	No significant association between the time spent sitting and MSP score	0.73
Tavares et al. 2019 [108] Brazil	Young to middle-aged adults Sample size = 629 Average: age – median(IQR) = LBP = 22.5(21.0 – 24.0); no LBP = 23.0(21.0 – 25.0); Average BMI = NR %Female: 72.8%	Professionals – Student	Non-occupational – Total SB Self-reported	LBP – Lifetime prevalence; %Prevalence: 81.7%; Self-reported	Chi-squared test	No association of total SB with LBP	0.59

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Occupational and Non-occupational Sedentary Behaviour							
Gupta et al. 2015 [109] Denmark	All adults Sample size = 201 Average: age = 44.7(9.7), BMI = 26.4 (5.0) %Female: 41.8	Tradespeople – Construction workers, cleaners, garbage collectors, manufacturing workers, assembly workers, mobile plant operators, and workers in the health service sector	Occupational – Total workplace sitting (low: ≤ 2.0 h, moderate: 2.1 – 3.7 h, high: > 3.7 h); and non-occupational – Total full day sitting (low: ≤ 6.4 h, moderate: 6.5 – 8.3 h and high: > 8.3 h); Total leisure-time sitting (Low: < 4.4 h, moderate: 4.0 – 5.4 h, high: > 5.4 h Device-measured – ActiGraph	LBP intensity – 1-month prevalence Low intensity: ≤ 5 pain score; high intensity: > 5 pain score Self-reported – NMQ	Binary logistic regression Adjusted for age, gender, BMI, and smoking, job seniority, influence at work, and occupational lifting/carrying time at work	Positive associations of the total full day sitting time and leisure-time with LBP intensity, and marginally significant association of total workplace sitting with LBP intensity **Total full day sitting:** OR = 1.43(1.15 – 1.77), $p = 0.01$; **Workplace sitting:** OR = 1.34(0.99 – 1.82), $p = 0.06$; Leisure **sitting:** OR = 1.45(1.10 – 1.91), $p = 0.01$. **High total full day sitting:** OR = 3.31(1.18 – 9.28), $p = 0.03$; **High Workplace sitting:** OR = 3.26(0.89 – 11.98), $p = 0.08$; **High Leisure sitting:** OR = 5.31(1.57 – 17.90), p = 0.01	0.95

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Hallman et al. 2015 [110] Denmark	All adults Sample size = 202 Average: age = NR, BMI = NR %Female: 41.8% Danish PHysical ACTivity cohort with Objective measurements (DPHACTO)	Tradespeople – Construction workers, cleaners, garbage collectors, manufacturing workers, assembly workers, mobile plant operators, and workers in the health service sector	Occupational – Mean total workplace sitting = 3.0(1.4); and Non-occupational – mean total full day sitting = 7.3 (2.1), mean total leisure-time sitting = 4.8(1.7) Device-measured – ActiGraph	Neck/shoulder pain-intensity – 1-month prevalence %Prevalence: 75.2% Self-reported – NMQ (numeric rating scale (NRS))	Logistic regression Adjusting for age and gender, individual factors (i.e., BMI and smoking), work-related factors (i.e., seniority, influence at work, and lifting/carrying)	Positive associations of the total full day sitting and workplace sitting with neck/shoulder pain intensity. Low total workplace sitting is associated with reduced neck/shoulder pain intensity in men. No association of leisure-time sitting with neck/shoulder pain intensity **Total full day Sitting:** *High sitting (Overall)* OR(95%CI) = 2.97(1.25 – 7.03), $p = 0.01$; *(Male)* OR(95%CI) = 6.44(1.76 – 23.56), $p = 0.005$; *(Female)* OR(95%CI) = 1.19(0.31 – 4.51), $p = 0.44$. **Workplace sitting:** *High sitting (Overall)* OR(95%CI) = 0.92(0.41 – 2.06), $p = 0.83$; *(Male)* OR(95%CI) = 0.94(0.31 – 2.85), $p = 0.92$; *(Female)* OR(95%CI) = 1.17(0.32 – 4.33), $p = 0.82$; *Low sitting (Overall)* OR(95%CI) = 0.54(0.23 – 1.25), $p = 0.15$; *(Male)* OR(95%CI) = 0.26(0.07 – 0.96), $p = 0.04$; *(Female)* OR(95%CI) = 1.01(0.28 – 3.59), $p = 0.99$. **Leisure-time:** *High sitting (Overall)* OR(95%CI) = 1.60(0.68 – 3.74) $p = 0.28$; *(Male)* OR(95%CI) = 2.76(0.83 – 9.18), $p = 0.097$; *(Female)* OR(95%CI) = 1.02(0.28 – 3.74), $p = 0.97$	0.91

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Hallman et al. 2016 [111] Denmark	All adults Sample size = 659 Average: age = 45.0(9.9), BMI = 27.5(4.9) %Female: 44.9% DPHACTO	Tradespeople – Cleaning, manufacturing, transport	Occupational – workplace sitting pattern and absolute sitting time (brief: < 5 min, moderate: > 5 – 20 min, prolonged: > 20 min) and Non-occupational –leisure-time sitting pattern and absolute sitting time (brief: < 5 min, moderate: > 5 – 20 min, prolonged: > 20 min) Device-measured – ActiGraph	Neck/shoulder pain-intensity – 3-month prevalence %Prevalence: 74% Self-reported – NMQ [numeric rating scale (NRS)]	Binary logistic regression Adjusted for age, gender, smoking, BMI, job seniority, lifting/carrying time at work, physical activity at work, and leisure, sitting with arms above 90°	Negative association of short workplace sitting bout with neck/shoulder pain intensity and positive association with moderated workplace sitting bout with neck/shoulder pain intensity. No association of prolonged Workplace sitting bout nor leisure-time sitting bouts with neck/shoulder pain intensity **Workplace sitting bout:** *Brief* Coefficient (B) = -0.38, OR(95%) = 0.60(0.40 – 0.91), $p = 0.04$; *Moderate* B = 0.28, OR(95%CI) = 1.23(0.93 – 1.63), $p = 0.02$; *Prolonged* B = − 0.08, OR(95%CI) = 0.84(0.69 – 1.02), p = 0.33. **Leisure sitting bout:** *Brief* B = 0.23, OR(95%CI) = 1.25(0.71 – 2.21), $p = 0.44$; *Moderate* B = 0.27, OR(95%CI) = 0.76(0.52 – 1.10), $p = 0.15$; *Prolonged* B = 0.11, OR(95%CI) = 0.90(0.71 – 1.14), $p = 0.37$	0.91
Study design – prospective							
Occupational Sedentary Behaviour							
Hallman et al. 2016 [112] Denmark	All adults Duration: 12-months Sample size = 625 Average: age = 44.8(9.8), BMI = 27.5(4.9) %Female: 45% DPHACTO	Tradespeople – Cleaning, manufacturing, transport	Occupational – Total workplace sitting [2.4(1.7)hrs] Device-measured – ActiGraph	Neck/shoulder pain-intensity – 1-month prevalence (measured over 12 months) %Prevalence/incidence: 70%; mean pain score 3.1(2.7) Self-reported – Numerical rating scale (NRS)	Linear mixed models Adjusted for age, gender, and BMI; occupational sector, lifting/carrying time at work, physical activity at and leisure, working with the dominant arm elevated > 60°	Negative association of increased workplace sitting with neck/shoulder pain-intensity (i.e., reduced neck/shoulder pain-intensity) after 12-month follow-up in the Tradespeople Coefficient, B = 0.012, SE = 0.055, 95%CI = 0.000 – 0.025, $p = 0.006$	0.91

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Korshøj et al. 2018 [39] Denmark	All adults Duration: 12-months Sample size = 665 Average: age = 45.0(10.0), BMI = 27.4(4.9) %Female: 44.2% DPHACTO	Tradespeople – Cleaning, manufacturing, transport	Occupational – Total workplace sitting, sitting bout Device-measured – ActiGraph	LBP-intensity – 3- and 12-month prevalence Mean pain score 3.1(2.7) Self-reported – Numerical rating scale (NRS), which ranges from 0 ('no pain') to10 ('worst pain imaginable')	Linear mixed models Adjusted for herniated disc, occupational lifting and carrying, LBP the last 3 months from baseline, sitting time during leisure time	Negative association of both total workplace sitting and temporal patterns of sitting (sitting bout) with LBP intensity across 12-month **Total workplace sitting:** Coefficient(B) = -0.050, SE = 0.007, p < 0.001, 95%CI = -0.065 – -0.040; Brief **(bouts ≤ 5 min):** B = -0.118, SE = 0.017, *p* < 0.001, 95%CI = -0.152 – -0.084; **Moderate (bouts of > 5 – 20 min):** B = -0.117, SE = 0.017, *p* < 0.001, 95%CI = -0.151 – -0.084; **Prolonged (bouts of > 20 min):** B = -0.123, SE = 0.018, *p* < 0.001, 95%CI = -0.158 – -0.088	0.95
Yip, 2004 [113] Hong Kong	All adults Duration: 12 months Sample size = 144 Average0: age = 31.1, BMI = NR %Female: 85.5%	Professionals – Nurses	Occupational – Workplace sitting (≥ 2 h) Self-reported	LBP – 12-month incidence %Prevalence: 56% Self-reported	Chi-square test	No association of prolonged workplace sitting ≥ 2 h/day with the prevalence of LBP, *p* = 0.47	0.59
Non-occupational Sedentary Behaviour							
Santos et al. 2020 [114] Brazil	All adults Duration: 24-months Sample size = 978 at baseline Average: age – median age(IQR) Baseline = 42(34 – 49), Follow-up = 44(36 – 51); BM – median BMI(IQR) Baseline = 25.2(22.8 – 28.2), Follow-up = 25.6(23.2 – 28.6) %Female: 66.6% baseline Pro-Mestre study	Professionals – Teachers	Non-occupational – TV time Self-reported	Chronic MSP – 6-month prevalence % Prevalence – baseline = 32.3%; follow-up = 24.7% Self-reported	Generalized estimating equation (GEE) regression Adjusted for age, sex, BMI, and depression	Positive association of change in TV time (30 min/day) with chronic MSP, OR(95%CI) = 1.051(1.001 – 1.102)	0.95
Jun et al. 2020 [115] Australia, South Korea	All adults Duration: 12-month Sample size = 214 (Australia – Brisbane = 156; South Korea – Daegu = 58) Average: age = 37.3(9.9), BMI = 24.0(4.2) %Female: 55.1%	Office workers – University faculty members, research centre, management service, industrial institution	Non-occupational – Total SB [total hours sitting in weekdays = 51.9(11.8)] Self-reported – IPAQ	Neck pain – monthly prevalence for the 12-month %prevalence/incidence: 18.2% self-reported	Survival analysis Adjusted for age, gender, and BMI	Positive association of increased total SB during weekdays with increased risk of neck pain Adjusted HR(95%CI) = 1.04(1.03 – 1.06), *p* < 0.001	0.82

Table 2 (continued)

Study ID + Country	Study population + Duration + Sample size + Average age/ BMI + %Female + Study name	Nature of occupation	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + % Prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Occupational and Non-occupational Sedentary Behaviour							
Lunde et al. 2017 [57] Norway	All adults Duration: 6-month Sample size = 124 Average: age – Construction = 39.9(13.6), Health = 44.5(9.6); BMI – Construction = 25.7(3.3), Health = 25.1(3.8) %Female – Construction = 1.6%, Health = 77.8%	Tradespeople – Construction; Professionals – Healthcare workers	Occupational – Total workplace sitting (Construction = 156.8(114.2) Health = 171.6(93.8); and Non-occupational – Leisure-time sitting (Construction = 282.0(78.4); Health = 274.0(94.3)) Device-measured – ActiGraph	LBP-intensity; 1-month prevalence %Prevalence: Health – Baseline = 59%; 6-month = 55%; Construction – Baseline = 52%; 6-month = 49%; mean pain score Baseline – Construction = 0.5(0.5); Health = 0.6(0.5); 6-months – Construction = 0.7(0.9); Health = 1.0(1.0) Self-reported	Linear mixed models Adjusted for age, gender, smoking, body mass index, heavy lifting, forward bending at work, social climate, decision control, fair leadership, empowering leadership, sitting (minutes) during leisure time	*Total full day Sitting:* Association of the total full day sitting with LBP-intensity in both healthcare and construction workers at baseline and 6-months Healthcare: **Baseline** – B(95%CI) = -0.16(-0.40 – 0.08), $p = 0.183$; **6-month** – B(95%CI) = -0.17(-0.40 – 0.07), $p = 0.168$ Construction: **Baseline** B(95%CI) = -0.07(-0.31– 0.18), $p = 0.596$; **6-months** – B(95%CI) = -0.08(-0.31– 0.17), $p = 0.541$ *Workplace Sitting* Healthcare workers – a negative association of workplace sitting with LBP intensity at baseline and 6-months' follow-up **Baseline:** B(95%CI) = B(95%CI) = -0.31(-0.63 – 0.01), $p = 0.058$; **6-Month:** B(95%CI) = -0.34(-0.66 – -0.02), $p = 0.040$ Construction workers – no associations of workplace sitting with LBP intensity **Baseline:** B(95%CI) = -0.00001(-0.35 – 0.35), $p = 1.00$; **6-Month:** B(95%CI) = -0.003(-0.36 – 0.35), $p = 0.986$	0.95

[a] Measured multiple MSP conditions but presented only the MSP condition that was reported in the study result NR: Not reported, NMQ: Nordic musculoskeletal questionnaire, TV: Television-viewing,

Table 3 Characteristics of the experimental/intervention of occupational cohort studies

Study ID + Country	Study design + Time points + Sample size + Intervention	Study population + Average age/ BMI + %Female	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + Time points/% prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Randomised controlled trial – RCT							
Benzo et al. 2018 [116] USA	RCT Sample size = 15 Time points: 13 data points (minute 0, 10, 29, 60, 70, 89, 120, 130, 149, 180, 190, 209 and 240) – 4-h experiment	All adults – Office workers Average: age – 36.7(5.5), BMI = 29.6(3.1) %Female: 13.3%	Occupational – Sitting changes (sitting condition)	Physical MSP discomfort Incidence: average comfort scores 13 Self-reported – General Comfort Scale (GCS)	Linear mixed-effects (LME) regression Adjusted for age, gender, BMI, blood pressure	Positive association of 4 h of uninterrupted sitting with increased self-reported physical MSP discomfort, which was reduced with 10-min, hourly bouts of standing and pedalling	0.79
Brown et al. 2020 [117] Australia	RCT Sample size: AA = 32 (Control = 11; Intervention = 21) Time points: Baseline and 1-month follow-up Sit-stand workstations	All adults – Office workers Average: age = 43.0(1.8), BMI = 25.1 (4.0) %Female = 75%	Occupational – Usual sitting condition	MSP – Upper extremity (shoulders, elbows, hands); trunk (neck, upper back, lower back); lower extremity (hips, knees, ankles) and total body 7-days prevalence Self-reported – NMQ	Fisher's exact test to evaluate between-group differences in MSP	Sitting reduction does not increase the risk of MSP compared to usual sitting at work	0.71
Coenen et al. 2017 [118] Australia	RCT Sample size = 201 (Intervention = 118; Control = 83) Time points: Baseline, 3-month Stand Up Victoria	All adults – Office workers Average: age – All = 45.3(9.3), Intervention = 44.8(8.9), Control = 46.1(9.7); BMI: NR %Female: All = 69%, Intervention = 65%, Control = 73%	Occupational – Sitting changes (sitting bout) Device-measured – activPAL	LBP, lower extremity symptoms, and upper extremity symptoms 7-day prevalence %Prevalence: At baseline LBP 52%, lower extremity 54%, and upper extremity 69% Self-reported – NMQ	Multivariable linear regression Adjusted for smoking, height, waist circumference, work productivity, mental demands at work, and fatigue	The intervention was effective in reducing workplace sitting time and increasing standing time The intervention was significantly effective by just over half an hour/day [34.6(0.9 – 68.3), $p = 0.040$] in individuals without LBP [MD95%CI = -126.6(-151.4 – 101.7), $p < 0.001$] than those with LBP [MD95%CI = -91.9-120.7 – 63.1), $p < 0.001$] Differences in intervention effect on extremities pain symptom were smaller and not statistically significant *Lower extremity:* [3.1(-28.8 – 35.0), $p = 0.838$]; *upper extremity:* [16.2(-28.3 – 60.7), $p = 0.446$] Prolonged sitting bout negatively association with extremities pain	0.88

Table 3 (continued)

Study ID + Country	Study design + Time points + Sample size + Intervention	Study population + Average age/ BMI + %Female	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + Time points/% prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Coenen et al. 2018 [33] Australia	Cross-sectional analysis of baseline dataset of RCT Sample size = 216 Stand Up Victoria	All adults – Office workers Average: age -45.4(9.3, BMI: NR %Female: 69%	Occupational – total workplace sitting time, sitting bout Device-measured – activPAL	LBP, lower-extremities, and upper-extremities 3-month prevalence %Prevalence: LBP = 68%, lower extremities = 69%, and upper extremities = 83% Self-reported – NMQ	Multivariable probity regression Adjusted for smoking, height, waist circumference, sitting not at work, standing not at work, stepping not at work, mental demands at work, and fatigue	No association of sitting time with LBP and extremities pain **Upper tirtle sitting time:** *LBP* – B = 0.01 (95%CI = -0.18 0.20), $p > 0.999$; *Lower extremities* – B = -0.05(-0.32 – 0.22), $p = 0.934$; *Upper extremities* – B = -0.08(-0.22 – 0.05), $p = 3.28$ No association of sitting bout with LBP but a negative association with extremities pain **Upper tirtle sitting bout:** *LBP* – B = -0.10(-0.29 – 0.09), $p = 0.433$; *Lower extremities* – B = -0.17(-0.34 – 0.01), $p = 0.061$; *Upper extremities* – B = -0.18(-0.34 – -0.02), $p = 0.029$	0.91
Danquah et al. 2017 [35] Denmark and Greenland	RCT Sample size = 317 (Intervention = 173; Control = 144) Time points: Baseline, 1-month, 3-month Take a Stand!	All adults – Office workers Average: age -All = 46(10), Intervention = 47(10) Control = 46(11); BMI: All = 26(4.9), Intervention = 26(5.0), Control = 27(4.8) %Female: All = 66%, Intervention = 61%, Control = 73%	Occupational –Sitting changes (sitting bout) Device-measured – ActiGraph	Neck/shoulder pain, low back pain, extremities as well as total pain score combining the degree of pain and number of pain sites 14-days incidence %Incidence: Neck/shoulder pain 51%, LBP 41% and extremities pain 38%; Average total pain score = 1.6(1.6) Self-reported	Multilevel mixed-effects logistic regression Adjusted for workplace, gender, and age	The intervention reduced workplace sitting time Sitting reduction positively associated with reduction in **neck/shoulder pain** [OR(95% CI) = 0.52(0.30 – 0.92), $P = 0.02$], but no significant association with reduction in in **LBP** [OR(95% CI) = 0.91(0.51 – 1.63), $p = 0.74$] and e**xtremities pain** [OR(95% CI) = 1.00(0.59 – 1.69), $p = 0.99$] Also, sitting reduction was significantly associated with **general MSP** score [B(95% CI) = -0.17(-0.32 – -0.01), $p = 0.04$]	0.83

Table 3 (continued)

Study ID + Country	Study design + Time points + Sample size + Intervention	Study population + Average age/ BMI + %Female	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + Time points/% prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
E F Graves et al. 2015 [119] UK	RCT Sample size = 47 (Intervention = 26; Control = 21) Time points: At baseline, 4 weeks (mid-intervention) and 8 weeks (end-intervention) Sit-stand workstations	All adults – Office workers Average: age – All = 38.6(9.5), Intervention = 38.8(9.8), Control = 38.4(9.3); BMI – All = 24.8(4.4), Intervention = 24.9(4.4), Control = 24.7 ± 4.6 %Female: All = 79%, Intervention = 89%, Control = 67%	Occupational – Sitting changes Self-reported – Ecological Momentary Assessment (EMA) diaries	LBP, UBP, and neck/shoulder pain/discomfort Incidence at 4-weeks and 8-weeks during the intervention Self-reported – Likert scale from 0 (no discomfort) to 10 (extremely uncomfortable)	ANCOVA, Anthropometric, sociodemographic, work-related, and office-environment characteristics were potential confounders	Intervention beneficially reduced workplace sitting time The intervention did not increase musculoskeletal discomfort or pain Beneficial reductions in UBP and neck/shoulder pain/discomfort Adjusted Mean Difference(95%CI) **UBP** = -0.9 (-1.9 – 0.2); **Neck/shoulder pain/discomfort** = -0.6 (-1.5 – 0.2) No significant benefit with reduction in LBP discomfort Adjusted Mean Difference(95%CI) = -0.2 (-1.0 – 0.7)	0.79

Table 3 (continued)

Study ID + Country	Study design + Time points + Sample size + Intervention	Study population + Average age/ BMI + %Female	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + Time points/% prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Renaud et al. 2020 [120] Netherlands	RCT Sample size = 244 Time points: Baseline, 4- month and 8-month follow-up Dynamic Work intervention – adjustable sit-stand workstations	All adults – Office workers Average: age – Intervention = 43.0(10.3), Control = 41.5(10.1); BMI: NR %Female: Intervention = 57.0%, Control = 62.6%	Occupational – Sitting changes Device-measured – activPAL	Neck/shoulder pain (Neck, shoulders, or upper back); Upper limbs pain (arms, wrists or hands); LBP; Lower limb pain (hips, thighs, knees, ankles, or feet) intensity 3-month prevalence Self-reported – NMQ (visual analogue scale (VAS) score)	Linear mixed and logistic mixed regression Adjusted for age, gender, and BMI	The intervention significantly reduced workplace sitting time at 4-month and 8-month **Total sitting, h/16 h:** *Baseline – (Control)* = 10.0 (1.2), *(Intervention)* = 10.1 (1.3); *4-month – (Control)* = 10.2 (1.2), *(Intervention)* = 10.2(1.3), OR(95% CI) = 0.11(0.43 – 0.22); *8-month – (Control)* = 10.2 (1.2), *(Intervention)* = 10.2(1.4), OR(95% CI) = 0.27(0.60 – 0.06) No significant association of workplace sitting time reduction with a reduction in musculoskeletal pain symptoms (intensity) at both 4-month and 8-month follow-up **Neck/shoulder pain:** *4-month* – OR(95% CI) = 1.73(0.39 – 7.69); *8-month* – OR(95% CI) = 0.61(0.19 – 3.11). **Upper limbs:** *4-month* – OR (95% CI) = 2.13(0.50 – 8.97); *8-month* – OR(95% CI) = 1.17(0.24 – 5.65). **LBP:** *4-month* – OR(95% CI) = 0.97(0.40 – 2.38); *8-month* – OR(95% CI) = 0.53(0.19 – 1.43). **Lower limbs pain:** *4-month* – OR(95% CI) = 0.44(0.07 – 3.00); *8-month* – OR(95% CI) = 0.20(0.02 – 1.87)	0.92

Table 3 (continued)

Study ID + Country	Study design + Time points + Sample size + Intervention	Study population + Average age/ BMI + %Female	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + Time points/% prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Non-randomised controlled trial – Non-RCT							
Brakenridge et al. 2018 [121] Australia	Randomised trial without control Sample size = 153 Time points: baseline, 3-, and 12-month Stand Up Lendlease	All adults – Office workers Average: age = 38.9(8.0), BMI = 24.6(3.4) %Female: 45.8%	Occupational – Sitting changes (mean sitting time 7.4(1.0)hr/10 h workday, prolonged sitting bouts ≥ 30 min reduction at work Device-measured – activPAL	Musculoskeletal symptoms – Neck, shoulder, elbow, wrists/hands, upper back, lower back, hips/thighs/buttocks, knees and ankle/feet 1-month prevalence %Prevalence: 79.3%; Mean pain scores: Lower extremity 0.7(1.1), upper extremity 0.7(1.0), LBP 1.4(2.0), neck 1.5(2.1), and total pain 1.1(1.1) Self-reported – NMQ	Mixed model Adjusted for age, sex, BMI category (normal/underweight, overweight/obese, missing), MVPA, mental quality of life, physical quality of life, job control score, work satisfaction score, desired sitting (over half/under half), current smoker (yes/no)	An hour of workplace sitting reduction is positively associated with significant small-to-moderate reductions in LBP [Coefficient, B(95% CI) = 0.84(1.44 – 0.25), $p = 0.005$ – study completers, and B(95% CI) = 0.61(1.22 – 0.01), $p = 0.047$ – multiple imputation analyses] An hour reduction in prolonged sitting is associated with reduction in LBP [B(95% CI) = -0.39(-0.79 – 0.00), $p = 0.050$] The associations of sitting reduction were not significant with a reduction in other musculoskeletal pain symptoms **Neck pain:** *Sitting reduction* – B(95% CI) = 0.14(-0.43 – 0.72), $p = 0.626$, *an hour reduction in prolonged sitting* – B(95% CI) = 0.07(-0.31 – 0.45), $p = 0.715$; **Lower extremity:** *Sitting reduction* – B(95% CI) = 0.07(-0.21 – 0.35), $p = 0.611$, *an hour reduction in prolonged sitting* – B(95% CI) = 0.01(-0.17 – 0.20), $p = 0.873$	0.96

Table 3 (continued)

Study ID + Country	Study design + Time points + Sample size + Intervention	Study population + Average age/ BMI + %Female	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + Time points/% prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Engelen et al. 2016 [122] Australia	Non-RT pilot study Sample size = 34 Time points: Baseline; 2-month Active design office buildings designed for health promotion and connectivity	All adults – Office workers Average: age = NR, BMI = NR %Female: 73.5%	Occupational – Sitting changes Self-reported	LBP-intensity/discomfort[a] 2-month prevalence/ incidence Self-reported	Paired t-tests compared baseline and follow-up	The intervention resulted in 1.2 h/day less workplace sitting time (83 – 67%, $p < 0.01$), with sitting displaced largely by standing (9 – 21%, $p < 0.01$) A positive association of sitting reduction and reduced LBP, participants reported less LBP [t-test = -2.53, $p < 0.01$]	0.42
Foley et al. 2016 [123] Australia	Non-RT cross-over design Sample size = 88 Time points: Baseline, 4 weeks(end-intervention), and 7 weeks(follow-up) ABW environment	All adults– Office workers Average: age = 38.1, BMI = 25.7 %Female: 43%	Occupational – Sitting changes Device-measured – ActiGraph, activPAL Self-reported – Occupational Sitting and Physical Activity Questionnaire (OSPAQ)	LBP[a] 7-days discomfort at 4 week and after 7 week follow-up Self-reported – NMQ	Linear mixed model; adjusted for age and gender, as well as measurement time points and laboratory effects	The intervention significantly ($P < 0.01$) resulted in 13.8% reduced sitting time and 10.7% increased standing time among workers Intervention was not associated with an increase in musculoskeletal discomfort despite the increased standing time Participants were twice as likely to report LBP at baseline compared with during the intervention [OR(95% CI) = 1.98(1.06 – 3.67)]	0.77

Table 3 (continued)

Study ID + Country	Study design + Time points + Sample size + Intervention	Study population + Average age/ BMI + %Female	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + Time points/% prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Gao et al. 2016 [124] Finland	Non-RCT Sample size = 45 (Intervention = 24; Control = 21) Time points: Baseline; 6-month Sit-stand workstations	All adults – Office workers Average: age = All = 43.7(10.7), Intervention = 47.8(10.8), Control = 39.0(8.5); BMI = All = 24.1(3.9), Intervention = 24(3.9), Control = 23.3(3.8) %Female: All = 75.6%, Intervention = 70.8%, Control = 81.0%	Occupational – Sitting changes; and Non-occupational – leisure-time sitting Self-reported	LBP-intensity(discomfort)[a] 6-month prevalence and incidence Self-reported	ANOVA for testing the intervention effects and Spearman's correlation coefficient for assessing the strength of the correlation	The intervention significantly resulted in decreased workplace sitting time by 6.7% ($p = .048$) and increased standing time by 11.6% ($p < .001$) **Sitting change:** Intervention – Baseline = 75.5 ± 15.9; 6-month = 68.9 ± 16.2. Control – Baseline = 76.0 ± 19.9; 6-month = 81.0 ± 11.9, The sitting reduction was significantly correlated with the increased standing time ($r = -0.719$, $p < .001$) Reduction in sitting time was significantly positively correlated with increased low back comfort, thus reduced LBP ($r = 0.344$, $p = 0.024$)	0.63
Kar & Hedge 2020 [125] India	Randomised controlled cross-over Sample size = 80 Time points: Baseline and end of the experiment (65 min)	Young adults -Students Average: age = 26.04(8.61), BMI = 22.53(4.13) %Female: 50%	Occupational – Workplace sitting (7.22(2.49)hrs/day) Self-reported	Musculoskeletal discomfort Baseline and end of the experiment (65 min) Self-reported – NMQ (15-item visual analog discomfort scale – VAS)	MANOVA Adjusted for gender	Pairwise comparisons revealed that mean musculoskeletal discomfort for the "Sit-Stand-Walk work condition" was significantly lower compared to the "Sitting work condition", a statistically significant mean difference (MD95%CI) = -11.28(22.41 – 0.15) SE = 0.84, $p = 0.045$	0.79
Park & Srinivasan, 2021 [126] USA	Non-randomised experiment without control Sample size = 12 Time points: Baseline and post-exposure Sit-stand workstations	Young to middle-aged – Office workers Average: age – Male = 23.5 (3.1); Female = 3.3 (3.6) %Female = 50%	Occupational sitting – 2 h continuous sitting (prolonged sitting condition)	LBP/discomfort Pain intensity – Baseline = 6.3 (3.8)%; post-exposure = 18.8 (14.0)% Self-reported – VAS	Repeated-measure analysis of variance (RANOVA)	Prolonged sitting significantly increased LBP/discomfort ($p = 0.009$)	0.58

Table 3 (continued)

Study ID + Country	Study design + Time points + Sample size + Intervention	Study population + Average age/ BMI + %Female	Sedentary behaviour (SB) domain + measures	Musculoskeletal pain (MSP) conditions + Time points/% prevalence + Measures	Statistical analysis + Adjusted covariates	Conclusions on associations of SB with MSP conditions + Effect Size/*p*-value	Quality score
Thorp et al. 2014 [127] Australia	Randomised controlled cross-over Sample size = 23 SIT-condition and STAND-SIT condition – Over 5 consecutive workdays Sit or Stand @ Work-Study	All adults – Office workers Average: age = 48.2(8), BMI = 29.6(4.1) %Female: 26.1%	Occupational – Sitting changes Device-measured – activPAL	Musculoskeletal symptoms – Neck, shoulder, elbow, hand/wrist, upper back, lower back, hip/thigh, knee, and ankle/foot 12-month prevalence and past 5-workday of the experimental condition %Prevalence: 60.9% 12-momth prevalence self-reported – NMQ	Linear and logistic mixed models; McNemar's test to determine significant changes in the prevalence of musculoskeletal symptoms between experimental conditions Adjusted for order effects	Reducing sitting with 30 min standing break is positively associated with a reduction of LBP discomfort **LBP:** Mean difference (95% CI) = -31.8 (-62.8 – -0.9), $p = 0.03$) No significant association was reported in other body regions **Mean difference and 95%CI:** *Upper back* = +4.5(-23.5 – 32.6); *Neck* = +3.8(-17.3 – 24.9); *Shoulder* = +9.1(-7.5 – 25.6); *Elbow* = 0(− 4.5 – 4.5); *Wrist/hand* = -4.5(-17.8 – 8.7); Knee = -4.5(-24.4 – 15.3); *Hip* = -9.71(-35.1 16.9); *Ankle/feet* = -13.6(-32.5 – 5.2);	0.83
Waongenngarm et al. 2020 [128] Thailand	Non-randomised experiment without control Sample size = 40 Time points: Baseline and every 10 min until completion of the 4-h sitting period	20 – 45 years adults – Office workers Average: age = 29 (3.9), BMI = 21.1(1.7) %Female: 72.5%	Occupational – Sitting continuously for 4 h (Experimental condition)	Musculoskeletal discomfort – Neck, shoulder, elbow, wrist, upper back, low back, buttocks, hip/-thigh, knee, and ankle Baseline and every 10 min until completion of the 4-h sitting period Self-reported – Borg CR-10 scale (0 – 10 scale; 0 denotes no discomfort and 10 denotes extreme discomfort)	ANOVA to determine the effect of sitting time on perceived discomfort scores	Positive association of 4 h of continuous sitting with increased perceived musculoskeletal discomfort in all body regions. The body regions with the highest perceived discomfort were the low back, buttocks, upper back, thigh, and neck	0.64

[a] Measured multiple MSP conditions but presented only the MSP condition that was reported in the study result, NR: Not reported, NMQ: Nordic musculoskeletal questionnaire

Four studies in the experimental/intervention category, however, were based on pre-determined or usual workplace sitting conditions.

Among the studies that examined full-day SB or sitting, more than twice as many were in the general population category (15 studies) as were in the occupational category (seven studies). More studies in the occupational category examined workplace sitting (21 studies) and leisure-time sitting (seven studies) than in the general population category (workplace sitting time, two studies and leisure time, zero studies). Time spent watching television and/or other SBs were investigated in seven studies (six in the general population and one in the occupational cohort categories). Also, computer time (five studies) and vehicle time (five studies) were examined only in the occupational category. In addition to SB or sitting time, five studies examined SB/sitting bout duration, four of these studies were in the occupational category. Finally, 11 experimental/intervention studies examined changes in self-reported or device-measured sitting time.

Regarding MSP condition outcomes, 38 studies investigated a single MSP condition, 30 studies investigated multiple MSP conditions and 11 studies investigated general MSP. In general, LBP (50 studies) and neck/shoulder (28 studies) were the most frequently investigated. Except for two studies in the general population category that examined either medical record data or clinical examination data, all the studies investigated self-reported MSP conditions. In total, 22 studies investigated MSP-related pain intensity (19 studies) or MSP-related disability, and only three of these studies were in the general population category.

Regarding the population, 10 of 24 general population studies were of adults ≥ 45 years, including three studies of older adults (≥ 65 years). Also, one study in this category which was conducted in 2013 was of a 1946 birth cohort. In the occupational category, the studies were of adults ≥ 18 years; among these, five studies specifically recruited young or middle-aged adults, and one study was of a cohort of 21-year olds.

Inter-rater reliability and quality assessment

There was 83.9% agreement between the two reviewers for including or excluding studies. Decisions on seven studies were made after consultation with the three senior reviewers.

Quality assessment scores for the studies are presented in Tables 1, 2, and 3 for the general population, observational-occupational, and experimental/intervention studies, respectively. On average, the studies in each of the categories were of high quality with mean scores of 0.83, 0.80, and 0.76 for the general population, observational-occupational, and experimental/intervention studies, respectively. The lowest scores in these categories were 0.41 for Aweto et al. [58], a cross-sectional study in the general population category; 0.36 for Omokhodion et al. [94], a cross-sectional study in the observational-occupational category; and 0.42 for Engelen et al. [122], a non-RT without control design pilot study in the experimental/intervention category. The highest score among the general population category was 0.95 scored in six studies [16, 64, 66, 67, 75, 76]. In the occupational category, the highest score in observational studies was 0.95 scored by six studies [39, 57, 100, 109, 114, 129], and in experimental/intervention studies was 0.96 for one study, Brakenridge et al. [121].

The low-quality studies mostly scored low for QualSyst checklist item-11, "Some estimate of variance is reported for the main results?". Most of the experimental/intervention studies scored low on item 9, "Sample size appropriate?". In general, most of the studies scored average on item 8, "Outcome and (if applicable) exposure measure(s) well defined and robust to measurement/misclassification bias? Means of assessment reported?". Overall, based on a relatively liberal cut-off threshold of 0.55 put forward by Kmet & Lee [52], six studies scored ≤ 0.55 (general population two, observational-occupational three, and experimental/intervention occupational one); when based on a relatively conservative 0.75 cut-off threshold, 56 studies scored >0.75 (general population 18, observational occupational 28 and experimental/intervention occupational 10). Studies that scored above 0.75 were considered high-quality, and those that scored below were considered low-quality studies.

Associations of non-occupational sedentary behaviour with musculoskeletal pain conditions

Table 4 shows the key associations of non-occupational SB with MSP conditions and Table 5 summarises the findings.

Full-day sedentary behaviour or sitting time

Low back pain Fourteen studies in total (10 general population [59–61, 63, 66, 68–70, 75, 77] and four occupational [57, 108, 109, 129]) examined the association of full-day SB/sitting time with LBP [59–61, 63, 66, 68–70, 75, 77] or LBP-intensity [57, 109, 129], including two studies [69, 129] that also examined full-day SB bout. Among these studies, 11 were cross-sectional [57, 59–61, 63, 66, 68–70, 108, 109, 129] and three applied a prospective [57, 75, 77] design; one study [57] reported both cross-sectional and prospective analyses. In the cross-sectional studies, six reported a positive association [60, 66, 68–70, 109] and four reported no association [59, 61, 63, 108, 129]. Five of the positive association studies [60, 66, 69,

Table 4 Summary of key associations of sedentary behaviour with musculoskeletal pain conditions by studies quality

Sedentary Behaviour	MSP Conditions	Cross-Sectional Studies									Prospective Studies								
		Positive Association			No Association			Negative Association			Positive Association			No Association			Negative Association		
		Quality			*Quality*			*Quality*			*Quality*			*Quality*			*Quality*		
		All	**High**	***Low***	***All***	***High***	***Low***	***All***	***High***	***Low***	***All***	***High***	***Low***	***All***	***High***	***Low***	***All***	***High***	***Low***
Non-occupational sedentary behaviour[b]		***Observational studies***																	
Total SB	LBP	**5**	4	1	**4**	3	1	**1**	1		**1**		1	**1**	1				
	LBP-intensity	**1**	1											**1**	1				
	Neck/shoulder pain	**1**	1																
	Neck/shoulder pain-intensity				**1**	1													
	Knee pain	**4**	4											**1**	1				
	Arthritis	**2**	2		**1**	1													
	Hip pain	**1**	1					**1**	1										
	Extremities pain				**1**	1													
	General MSP	**2**	2		**2**	1	1				**1**		1						
Total SB bout	LBP[c]	**1**	1																
	LBP-intensity[d]	**1**	1					**1**	1										
SBs/TV time	LBP	**1**		1	**2**	1	1												
	LBP-intensity													**1**	1				
	LBP-disability[e]										**1**	1							
	Neck/shoulder pain				**2**	1	1												
	Back/neck pain				**1**	1													
	Knee pain	**1**		1															
	Extremities pain	**1**		1	**1**	1													
	General MSP	**1**	1								**1**	1							
Leisure-time SB	LBP	**1**		1	**1**	1													
	LBP-intensity	**2**	2		**1**	1													
	Neck/shoulder pain				**1**		1												
	Neck/shoulder pain-intensity	**1**	1																
	Extremities pain				**1**		1												
Occupational sedentary behaviour		***Observational studies***																	
Workplace sitting																			
Device-measured	LBP				**1**	1													
	LBP-intensity[f]				**2**	2								**1**	1		**2**	2	
	Neck/shoulder pain-intensity	**1**[g]	1		**2**	2											**1**	1	
Workplace sitting bout[a]	LBP-intensity	**1**	1					**1**	1								**1**	1	

Table 4 (continued)

Sedentary Behaviour	MSP Conditions	Cross-Sectional Studies									Prospective Studies								
		Positive Association			No Association			Negative Association			Positive Association			No Association			Negative Association		
		Quality			*Quality*			*Quality*			*Quality*			*Quality*			*Quality*		
		All	**High**	***Low***	***All***	***High***	***Low***	***All***	***High***	***Low***	***All***	***High***	***Low***	***All***	***High***	***Low***	***All***	***High***	***Low***
Self-reported	LBP	**7**	5	2	**4**	4								**1**		1			
	Neck/shoulder pain	**9**	6	3	**1**	1					**1**	1							
	Knee pain																**1**	1	
	Extremities pain	**2**	1	1	**4**	3	1	**3**	2	1									
Computer time	LBP	**1**	1					**1**	1										
	Neck/shoulder pain	**2**	1	1															
	General MSP	**1**		1	**1**	1													
Vehicle time	LBP	**2**	1	1	**1**	1													
	General MSP	**1**		1	**1**	1													
Occupational sedentary behaviour		**Experimental/intervention studies**																	
Changes in sitting time		***Randomised controlled trial***									***Non-randomised controlled trial***								
Sitting reduction	LBP/discomfort	**1**	1		**2**	2					**5**	3	2						
	Neck/shoulder pain/discomfort	**2**	2		**1**	1								**2**	2				
	Extremities pain				**4**	4								**2**	2				
	General MSP/discomfort	**2**	1	1							**1**	1							
Prolonged sitting	General MSP/discomfort	**1**	1								**1**		1						
	LBP/discomfort										**1**		1						
Prolonged sitting bout	Extremities pain							**1**	1										

Numbers in the Table represent the number of studies

LBP: Low back pain, *MSP:* Musculoskeletal pain, TV: Television-viewing, *SB(s):* Sedentary behaviour(s) including sitting watching television, video game, reading, listening to music, talking on the phone

[a] A negative association for a moderate sitting bout and a positive association for a brief bout in the cross-sectional study

[b] Included both self-reported and device-measured occupational SB

[c] A positive in association obese individuals

[d] Positive association in normal-weight individuals and a negative association in overweight/obese individuals

[e] Association in females but not in males

[f] One study reported no association in construction workers and a negative association in healthcare workers

[g] Low SB negatively associated with neck/shoulder pain-intensity in men but not women, thus high SB probably increase the risk of neck/shoulder pain-intensity in men

Table 5 Summary of findings synthesised by meta-analysis and the best-evidence synthesis

Sedentary Behaviour Domain	Meta-Analysis	Best-Evidence Synthesis
Non-occupational sedentary behaviour – observational studies		
Full-day sedentary behaviour	**LBP –** 8 Overall: • Positive association – OR = 1.19(1.03 – 1.38)* Subgroup analysis: *Self-reported SB (5 studies)* • Positive association – OR = 1.33(1.13 – 1.57 *Device-measured SB (3 studies)* • No association – OR = 1.05(0.86 – 1.29)	**LBP-intensity –** 2 • Probable evidence of association (SB bouts) moderated by BMI **Neck/shoulder pain –** 2 • Inconclusive evidence of association **Knee pain –** 4 1 • Evidence of cross-sectional association* • Insufficient evidence of a prospective association **Hip pain –** 2 • Inconsistent evidence of association **Arthritis –** 2 • Evidence of association* **Extremities pain –** 1 • Insufficient evidence of association **General MSP –** 4 1 • Evidence of cross-sectional association* • Insufficient evidence of prospective association
Time spent in sedentary behaviours –sitting watching TV (TV time), playing video games, reading, and listening to music	N/A	**LBP/UBP –** 3 1 • Inconsistent evidence of cross-sectional association • Insufficient evidence of prospective association **Neck/shoulder pain –** 2 • Insufficient evidence of association **Knee pain/Ankle pain –** 1 • Insufficient evidence of association **Limb pain –** 1 • Insufficient evidence of association **General MSP –** 1 • Insufficient evidence of association
Leisure-time sedentary behaviour/sedentary behaviour bouts	N/A	**LBP/LBP-intensity –** 3 • Insufficient evidence of association **Neck/shoulder pain or pain-intensity –** 3 • Insufficient evidence of association **Lower extremities –** 1 • Insufficient evidence of association
Occupational sedentary behaviour – observational studies		
Device-measured workplace sitting time	N/A	**LBP/LBP-intensity –** 3 2 • Inconsistent evidence of cross-sectional association • Probable protective/negative prospective association* **Neck/shoulder pain-intensity –** 2 1 • Inconsistent evidence of a cross-sectional association • A negative prospective association and a negative cross-sectional association in the same dataset indicate a probable protective association.

Table 5 (continued)

Self-reported workplace sitting time	**LBP –** 8 Overall: • Positive association – OR = 1.47(1.12 – 1.92)* Subgroup analysis: *Non-tradespeople (6 studies)* • Positive association – OR = 1.56(1.18 – 2.05)* *Tradespeople (2 studies)* • No association – OR = 1.40(0.61 – 3.20) **Neck/shoulder pain –** 9 Overall: • Positive association – OR = 1.73(1.46 – 2.03)* Subgroup analysis: Neck pain (6 studies) • Positive association – OR = 1.90(1.35 – 2.68) Shoulder pain (3 studies) • Positive association – OR = 1.71(1.31 – 2.22) Neck/shoulder pain (3 studies) • Positive association – OR = 1.62(1.34 – 1.96) **Extremities pain –** 5 Overall: • No association – OR = 1.17(0.65 – 2.11) Subgroup analysis: *Upper limbs pain (2 studies)* • No association – OR = 0.82(0.47 – 1.14) *Lower limbs pain (3 studies)* • Negative association – OR = 0.61(0.46 – 0.80)* *Hands/Wrists (2 studies)* • No association – OR = 11.07(0.53 – 232.69)	**Hip pain –** 1 • Insufficient evidence of association **LBP –** 1 • Insufficient evidence of association **Neck pain –** 1 • Insufficient evidence of association **Knee pain –** 1 • Insufficient evidence of association
Computer time	N/A	**LBP –** 2 • Insufficient evidence of association **Neck/shoulder pain –** 2 • Evidence of association* **General MSP –** 2 • Insufficient evidence of association
Vehicle time	**LBP –** 3 • Non-significant association – OR = 2.16(0.79 – 5.93)	**General MSP –** 2 • Inconsistence evidence of association
Occupational sedentary behaviour – experimental/intervention studies		
Changes in workplace sitting time	N/A	**LBP/discomfort –** 3 5 • Positive correlation of workplace sitting reduction with LBP/discomfort reduction* **Neck/shoulder pain/discomfort –** 3 2 • Positive correlation of workplace sitting reduction with neck/shoulder pain/discomfort reduction* **Extremities pain –** 4 2 • No evidence of correlation of workplace sitting reduction with extremities pain reduction **General MSP/discomfort –** 3 2 • Workplace sitting reduction correlates with reduced general MSP/discomfort* • Prolonged sitting increases general MSP/discomfort*
# Cross-sectional studies	# Prospective studies	# Case-control studies	# RCT studies	# Non-RCT studies

The numbers in the box indicate the number of studies considered in the evidence synthesis. The effect sizes in the meta-analysis indicate odds ratio with confidence intervals in brackets

LBP: Low back pain, *UBP:* Upper back pain, *MSP:* Musculoskeletal pain, *OR:* Odds ratio, *SB:* Sedentary behaviour, *RCT:* Randomised control trial, *TV:* Television-viewing, *BMI:* Body mass index, *N/A:* Not Applicable due to variations in included studies

[a] The key findings

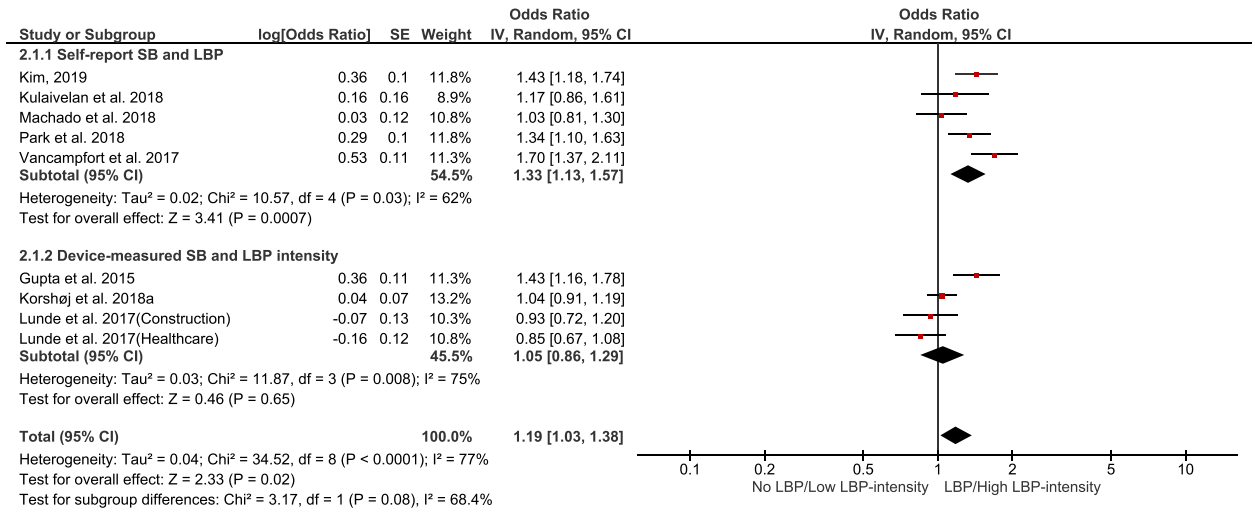

Fig. 2 A forest plot for inverse-variance meta-analysis using a random effect of cross-sectional studies that investigated non-occupational sedentary behaviour (SB) showing the pooled effect size of the association of full-day SB with low back pain (LBP); subgroup analysis by self-reported SB and LBP and device-measured SB and LBP-intensity

70, 109] and three with no associations [57, 59, 129] were of high quality. Further, one of the two high-quality cross-sectional studies that investigated full-day SB/sitting bout reported a positive association in obese individuals [69]; whereas the other study [129] reported a positive association in non-overweight individuals (BMI < 25kgm^{-2}), and a negative association in overweight/obese individuals (BMI ≥ 25kgm^{-2}). This suggests probable evidence of cross-sectional association of full-day SB/sitting bout with LBP-intensity which is moderated by BMI. Eight of these cross-sectional studies were considered in a meta-analysis, including five studies [60, 61, 63, 66, 70] that investigated self-reported full-day SB and LBP and three studies [57, 109, 129] that analysed device-measured full-day SB/sitting and LBP-intensity (Fig. 2). The overall pooled effect size indicated full-day SB is positively associated with LBP [OR = 1.19(1.03 – 1.38), $p = 0.02$], though a significantly moderate-high heterogeneity was observed ($I^2 = 77\%$, $p < 0.00001$). A subgroup analysis by self-reported and device-measured full-day SB showed a cross-sectional association of self-reported full-day SB with LBP [OR = 1.33(1.13 – 1.57), $p = 0.007$; $I^2 = 62\%$, $p = 0.03$], but no association of device-measured full-day SB/sitting with LBP-intensity in mostly tradespeople [OR = 1.05(0.86 – 1.29), $p = 0.65$; $I^2 = 75\%$, $p = 0.008$]. The robustness of the analysis was tested in a sensitivity analysis (Supplementary Figure 1A) by excluding two studies [61, 63] with low-quality; the overall and the self-reported full-day SB subgroup associations remained significant.

For the prospective studies, the evidence was inconsistent with a positive association of full-day SB with LBP reported in one low-quality study [77], and two high-quality studies reported no association of self-reported full-day SB [75] and device-measured [57] full-day sitting with LBP [75] and LBP-intensity [57] respectively.

Neck/shoulder pain There were two high-quality cross-sectional studies [64, 110] that investigated the association of device-measured full-day SB with neck/shoulder pain-intensity [110] and shoulder pain [64]. One study [110] of tradespeople reported a positive association of high full-day SB with neck/shoulder pain-intensity. The other study [64] of severely obese individuals reported no association of low full-day SB with shoulder pain, which may imply a high full-day SB could be associated with shoulder pain. Thus, there is inconclusive evidence of a cross-sectional association of full-day total SB with neck/shoulder pain.

Knee/hip pain/arthritis Four high-quality cross-sectional studies, three of adults ≥ 45 years in the general population cohorts [16, 59, 60] and one study of adults < 40 years in the occupational cohorts [105] reported a positive association of full-day SB with knee pain (osteoarthritis), including one study that reported the association only in men [59]. There was one prospective study [76] that reported no association of extensive full-day SB with knee pain. According to the best-evidence synthesis, we concluded there is strong evidence of cross-sectional association of full-day SB with knee pain in middle-aged to older adults, however, there is insufficient evidence whether the association is gender-dependent. Also, there is insufficient evidence of a prospective association of full-day SB with knee pain. Also, of

the two high-quality cross-sectional studies [60, 64], one reported a positive association of self-reported full-day SB with hip pain [60], and the other a positive association of device-measured low full-day SB with hip pain, indicating a protective association of high full-day SB with hip pain [64]. Therefore, there is insufficient evidence of a cross-sectional association of full-day SB with hip pain. Furthermore, two high-quality cross-sectional studies [62, 70] in the general population category reported a positive association of full-day SB with arthritis of adults ≥ 50 years [70] or ≥ 65 years [62] old. Another high-quality cross-sectional study [60], however, reported no association of full-day SB with osteoarthritis of adults ≥ 65 years old. Thus, there is evidence of a cross-sectional association of full-day SB with arthritis in adults ≥ 50 years.

Extremities pain One high-quality cross-sectional study in the general population cohort reported an association of wrist/hand pain with a high volume of full-day SB, but no association with a low volume of full-day SB [64]. However, evidence in one study is insufficient to conclude.

General musculoskeletal pain Four cross-sectional studies investigated full-day SB and general MSP. Two high-quality studies of the general population category reported a positive association [65, 67] and two studies (one high-quality [106] and one low-quality [107]) study of the occupational category reported no association. Based on the high-quality studies, there is strong evidence of a cross-sectional association of full-day SB with general MSP. However, the evidence of a prospective association is inconclusive with only one low-quality study in the general population category reporting a positive association [17].

Time spent in sedentary behaviours – sitting watching TV, video games, reading, listening to music

Five cross-sectional [58, 61, 72, 73, 86] and two prospective [78, 114] studies – five of general population [58, 61, 72, 73, 78], two of occupational [86, 114] – investigated time spent in SBs and MSP conditions [58, 61, 72, 73, 86] or MSP-related outcomes [78]. Three were of high-quality [72, 73, 86] and two low-quality [58, 61]. There were variations in the MSP condition outcomes, hence meta-analysis was not performed for these studies. Among the cross-sectional studies, only one study [58] (low-quality) reported positive associations of SBs > 3 h/day with LBP, UBP, knee pain, and ankle pain, and no associations with neck/shoulder pain and elbow pain. Another study [86] (high-quality) also reported a positive association of TV-viewing time (TV time) > 2 h/day with clinically diagnosed MSP condition of > 50 year old adults. Most of the cross-sectional studies reported no associations of TV time (≥ 2 or 3 h/day) with LBP [61, 72], neck/shoulder pain [73], back/neck pain [86], or limb pain [86]. Based on the best evidence, there is insufficient evidence of cross-sectional associations of SBs or TV time with MSP conditions.

For the two prospective studies, both of high quality, one reported no association of TV time > 2 h/day with LBP-intensity, but a positive association with LBP-disability only in women [78]. The other study [114], however, reported a positive association of TV time with general MSP. Herein also, prospective evidence of associations of TV time with MSP conditions and MSP-related outcomes are insufficient.

Leisure-time sedentary behaviour

Five cross-sectional studies (four high-quality [104, 109–111] and one low-quality [56]) of occupational category examined the associations of self-reported [56, 104] and device-measured leisure-time SB [109–111] or SB bout [111] with LBP [56, 104], LBP-intensity [109], neck/shoulder pain [56], neck/shoulder pain-intensity [110, 111] and lower extremities pain [56]. All these studies except one [104] were of tradespeople, and two were from a single large study – "Danish PHysical ACTivity cohort with Objective measurements (DPHACTO) [110, 111]. Three of the studies reported a positive association of leisure-time SB with LBP [56], LBP-intensity [56, 109], and neck/shoulder pain-intensity [110], whereas three studies reported no association of SB [56, 104] or SB bout [111] with LBP [104], neck/shoulder pain [56], neck/shoulder pain-intensity [111] or lower extremities pain [56]. Based on the best-evidence synthesis, there is insufficient evidence of cross-sectional associations of leisure-time SB or SB bout with LBP, LBP-intensity, neck/shoulder pain, neck/shoulder pain-intensity, or lower extremities pain.

Associations of occupational sedentary behaviour with musculoskeletal pain conditions

Table 4 (above) shows the key associations of occupational SB with MSP conditions and Table 5 summarises the findings.

Device-measured workplace sitting time

Low back pain Three high-quality cross-sectional [33, 109, 129] and two high-quality prospective [39, 57] studies investigated device-measured workplace sitting [39, 57, 109, 129] or sitting bout [129] and LBP [33] or

LBP-intensity [39, 57, 109, 129], including a study with both a baseline cross-sectional and a prospective analysis [57]. Two of these studies [39, 129] were from a single large study. One study was of office workers [33] and four studies were of tradespeople [39, 57, 109, 129], which included one study also with healthcare workers [57]. No association was reported in any of the cross-sectional studies, except one that reported a marginally significant positive association with LBP-intensity [109]. One cross-sectional study [129], nonetheless, reported a negative association of total workplace sitting or a moderate sitting bout with LBP-intensity in overweight/obese individuals ($BMI \geq 25 kgm^{-2}$), and a positive association of brief bout workplace sitting with LBP-intensity in non-overweight individuals ($BMI < 25 kgm^{-2}$). The baseline cross-sectional analysis of one prospective study [57] reported a negative association with LBP-intensity in healthcare workers but no association in construction workers (tradespeople). Meta-analysis was not feasible, hence, the best-evidence synthesis indicates there is insufficient evidence of cross-sectional associations of device-measured workplace sitting with LBP and LBP-intensity in tradespeople and non-tradespeople. For the prospective studies, there were two high-quality studies [39, 57]; the association was inconsistent in one study with a reported negative association with LBP-intensity in healthcare workers but no association in construction workers [57]. The other study of tradespeople, however, reported a negative association of both total workplace SB and SB bout with LBP-intensity [39]. There is, therefore, an indication that sitting at the workplace may have a protective effect which is dependent on occupation type.

Neck/shoulder pain Two cross-sectional studies [110, 111] and one prospective [112] study all from a single large study (all high-quality) examined the association of device-measured total workplace sitting or sitting bout with neck/shoulder pain-intensity of tradespeople. No association of high total workplace sitting with neck/shoulder pain-intensity was reported in the cross-sectional studies [110, 111]. One cross-sectional study [110], however, reported a negative association of low total workplace sitting with neck/shoulder pain-intensity in males but no association in females. Also, the other cross-sectional study [111] reported equivocal associations of workplace sitting bouts with neck/shoulder pain-intensity; a positive association for a moderate bout, and a negative association for a brief bout. A negative association was reported in the prospective study [112]. The cross-sectional association is inconsistent [110, 111], however, a negative association in a prospective analysis [112] of the same DPHACTO study dataset suggests there is a probable protective association of workplace sitting exposure with neck/shoulder pain-intensity in tradespeople.

Self-reported workplace sitting time

There were 19 cross-sectional [71, 82–89, 92–94, 96–98, 100–103], one case–control [74] and three prospective [79, 113, 115] studies that investigated self-reported workplace sitting and MSP conditions – LBP [71, 83, 87–89, 92, 94, 96–98, 102, 103, 113], neck/shoulder pain [82–85, 87, 88, 92, 93, 100, 103, 115], knee/hip pain [74, 79, 93] and extremities pain [83–86, 88, 92, 101]. All but three of these studies [71, 74, 79] were in the occupational category. The durations of the workplace sitting examined varied across the studies, included 20 min continuous [93], >4.2 h/week [92], ≥2 h/day [74, 79, 87, 88, 113], ≥3 h/day [94], ≥4 h/day [82–85, 92, 97, 100, 103], ≥6 h/day [98], 51.9(11.8)hrs per total weekdays [115], or unspecified durations (prolonged sitting) [71, 86, 89, 96, 101, 102].

For the cross-sectional studies, of the 11 studies (two of office workers, five of professionals, and three of tradespeople, as well as one general population study) that examined associations with LBP, seven reported positive associations [92, 94, 96–98, 102, 103] and four reported no association [71, 87–89]. All these studies except two [94, 96] were of high-quality. Eight studies (all high-quality) were meta-analysed with a subgroup analysis according to non-tradespeople (office workers [98], professionals [89, 92, 97, 103], and general population [71]) and tradespeople [87, 102] as indicated in Fig. 3. Overall, there is a significant cross-sectional association of workplace sitting with LBP (OR = 1.47(1.12 – 1.92), $p = 0.005$; however, there is non-significant moderate heterogeneity ($I^2 = 44\%$, $p = 0.08$). The subgroup analysis indicates the association is significant in the non-tradespeople [OR = 1.56(1.18 – 2.05), $p = 0.002$] with moderate but non-significant heterogeneity ($I^2 = 31\%$, $p = 0.20$), and non-significant association in the tradespeople [OR = 1.40(0.61 – 3.20), $p = 0.43$] with substantial non-significant heterogeneity ($I^2 = 70\%$, $p = 0.07$). Sensitivity analysis (Supplementary Figure 2A) excluded two studies [71, 102] with lower quality score and the overall association as well as the association for non-tradespeople were still significant, and zero heterogeneity in the non-tradespeople ($I^2 = 0\%$).

With neck/shoulder pain, a positive association was reported in eight studies (one of office workers [82], three of professionals [87, 88, 93, 100, 103], and four of tradespeople [84, 85]). Only one study [92] of professionals reported no association. Also, one study [83] reported a negative association only in females. Seven of these studies [84, 87, 88, 92, 93, 100, 103] were of high-quality. A meta-analysis (Fig. 4) of pooled effect sizes of nine studies

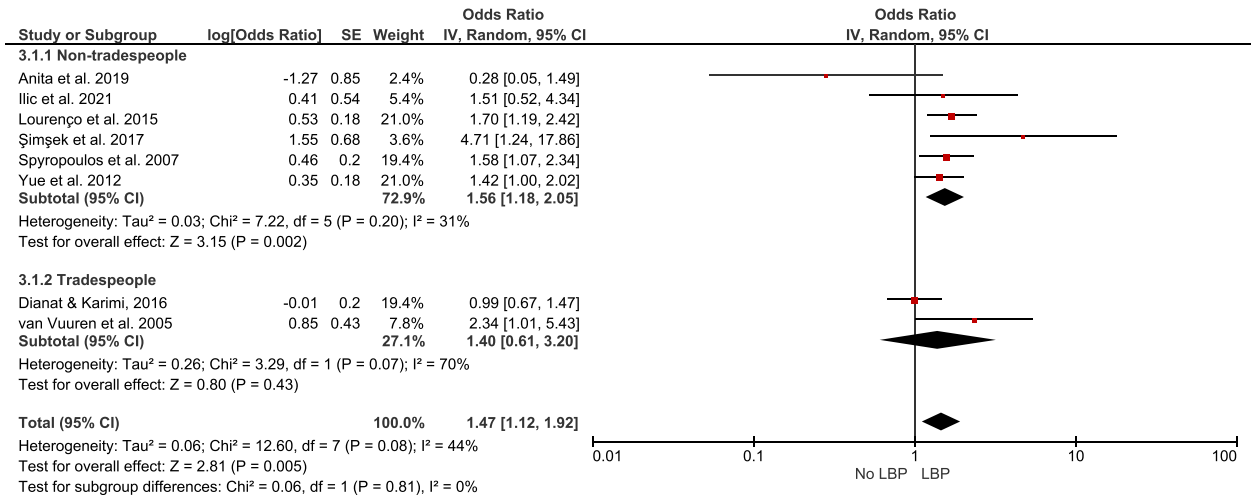

Fig. 3 A forest plot for inverse-variance meta-analysis using a random effect of cross-sectional studies that investigated occupational SB showing the pooled effect sizes for the association of self-reported workplace sitting time with LBP; subgroup analysis by non-tradespeople and tradespeople

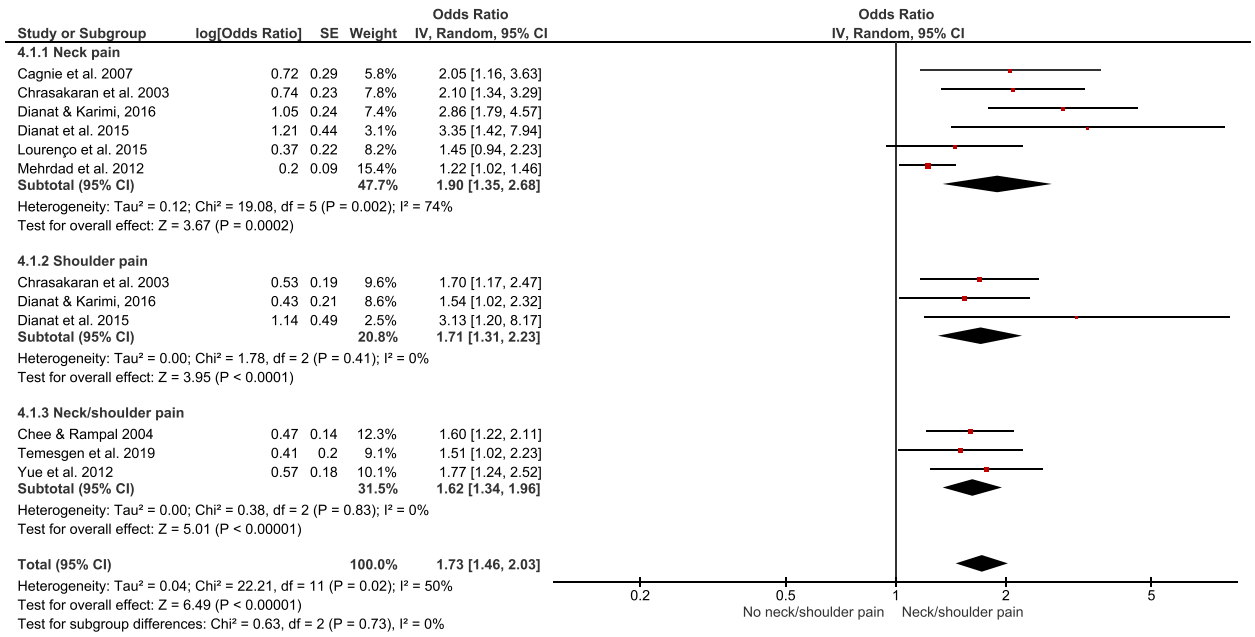

Fig. 4 A forest plot for inverse-variance meta-analysis using a random effect of cross-sectional studies that investigated occupational SB showing the pooled effect size for the association of self-reported workplace sitting time with neck/shoulder pain; subgroup analysis by studies that reported neck pain, shoulder pain, and neck/shoulder pain

[82, 84, 85, 87, 88, 92, 93, 100, 103] indicates workplace sitting is associated with increased odds of neck/shoulder pain [Overall OR = 1.73(1.46 – 2.03), $p < 0.00001$]. Subgroup analysis also shows there is increased odds of neck pain [OR = 1.90(1.35 – 2.68), $p = 0.0002$], shoulder pain [OR = 1.71(1.31 – 2.22), $p < 0.0001$] and neck/shoulder pain [OR = 1.62(1.34 – 1.96), $p < 0.00001$]. The overall heterogeneity was, however, significantly substantial ($I^2 = 51\%$, $p = 0.02$), mainly due to heterogeneity in studies on neck pain ($I^2 = 74\%$), as studies on shoulder and neck/shoulder pain were homogeneous ($I^2 = 0\%$). Sensitivity analysis (Supplementary Figure 3A) after excluding two studies [82, 85] with low-quality shows the estimate is robust and the association remained significant.

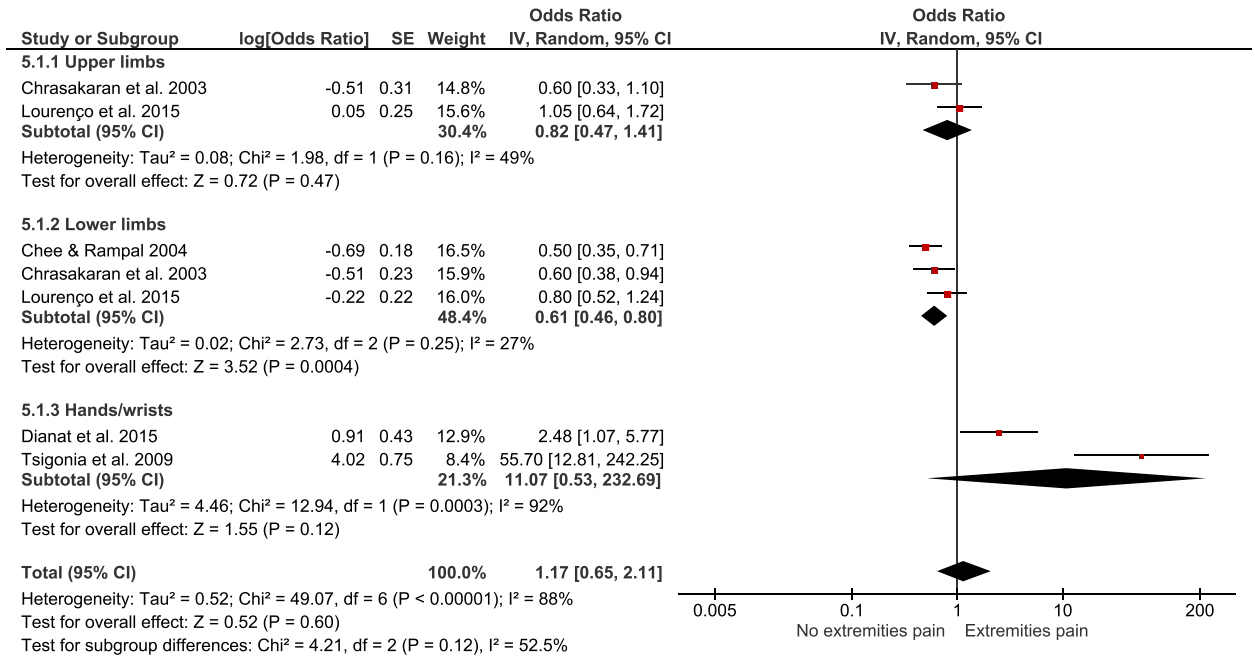

Fig. 5 A forest plot for inverse-variance meta-analysis using a random effect of cross-sectional studies that investigated occupational SB showing the pooled effect size for the association of self-reported workplace sitting time with extremities pain; subgroup analysis by upper limbs, lower limbs, and hand/wrist pains

For extremities pain, a positive association with hand/wrist pain was reported in two studies [88, 101]; three studies [83, 84, 86] reported a negative association, including one study [83] with the association only in females; and another study [86] with lower limb disability; no association was reported in four studies [85, 87, 88, 92]. Five of the studies were of high quality. A pooled analysis (Fig. 5) of five studies [84, 85, 88, 92, 101] with considerable heterogeneity ($I^2 = 88\%$, $p = 0.00001$) indicated no association of workplace sitting with extremities pain [OR = 1.17(0.65 – 2.11), $p = 0.60$]; however, a subgroup analysis of three studies [84, 85, 92] with low and non-significant heterogeneity ($I^2 = 28\%$) indicated an inverse association of workplace sitting with lower limbs pain [OR = 0.61(0.46 – 0.80), $p = 0.0004$]. Sensitivity analysis shows the overall effect size remained non-significant (Supplementary Figure 4A).

The only case–control study [74] of the general population reported a positive association of workplace sitting with hip pain, insufficient evidence of association from a single study.

For the prospective studies, one of low-quality reported no association of workplace sitting with LBP [113]; another one of high-quality reported a positive with neck pain [115]; the third study of high-quality reported a negative association with knee pain [79]. Therefore, prospective evidence of association of workplace sitting is insufficient with LBP, neck pain, and knee pain.

Computer time

Five cross-sectional studies of the occupational category (office workers [80, 82] and professionals [86, 97, 103]), including three high-quality investigated computer time and LBP [97, 103], neck/shoulder pain [82, 103] or general MSP [80, 86]. A positive association of computer time ≥ 4 h/day was reported with LBP [97], neck/shoulder pain [82, 103], and general MSP [80], and a negative association reported with LBP in another study [103]. Also, one study reported no association of computer time ≥ 2 h/day with general MSP [86]. There is moderate evidence of a cross-sectional association of computer time with neck/shoulder pain, however, the evidence is restricted to a small number of studies. The evidence with LBP and general MSP is insufficient with limited studies.

Vehicle time

Five occupational category cross-sectional studies of bus drivers [90, 95, 99] and professionals (patrol duty police officers) [81, 91] reported vehicle time and LBP [81, 90, 99] or general MSP [91, 95], including three of high-quality [81, 91, 99]. There is an inconsistent association with general MSP; of the two studies [91, 95], one reported no association [91] and the other a

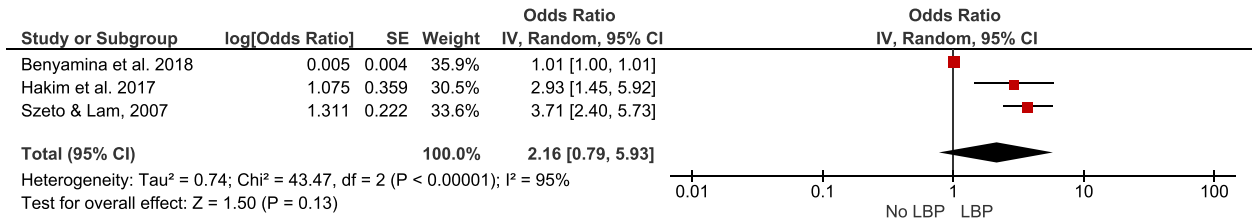

Fig. 6 A forest plot for inverse-variance meta-analysis using a random effect of cross-sectional studies that investigated occupational SB showing the pooled effect size for the association of vehicle time with LBP

positive association [95]. A similar inconsistent association was reported with LBP; two studies [90, 99] reported a positive association and one study [81] reported no association. In a meta-analysis (Fig. 6), the pooled effect size of the three studies [81, 90, 99] showed considerable heterogeneity ($I^2 = 95\%$) but increased odds of LBP with prolonged sitting in a vehicle, although this was not statistically significant [OR = 2.16(0.79 – 5.93), $p = 0.13$]. After excluding the low-quality study [90] in a sensitivity analysis the association was still non-significant (Supplementary Figure 5A).

Changes in workplace sitting time

Fourteen experimental/intervention studies investigated changes in sitting time and MSP symptoms, including LBP, neck/shoulder pain, extremities pain, and general MSP/discomfort of office workers [35, 116–124, 126–128] and students [125]. Designs included six RCTs [35, 116–120], two randomised controlled cross-over trial [125, 127], two non-randomised experiment without control [126, 128], one study each of non-RCT [124], RT without control [121], non-randomised cross-over trial [123], and non-RT pilot study.

Duration of experiments/interventions ranged from 65 min [125] to 12 months [121]. Sample sizes ranged from 12 participants [126] to 317 participants [35]. Nine of the studies were of high quality [35, 116, 118–121, 123, 125, 127] and four of low quality [117, 122, 124, 128]. Of the studies, nine measured sitting time change and reported a reduction in sitting time after the period (device-measured – ActiGraph [35, 123] and activPAL [118, 120, 121, 123, 127]; self-report [119, 122–124]) while three studies were based on fixed sitting duration (65 min [125] and 4 h [116, 128]), over 2-h continuous sitting [126] or usual work sitting condition [117].

There were methodological and analytical variations among the studies, therefore, the data were not meta-synthesised. A positive correlation of sitting reduction with a reduction in LBP was reported in six studies [118, 121–124, 127] (including four high-quality studies with one RCT [118]); reduction in neck/shoulder pain two RCT studies [35, 119] (both high-quality). No study reported a correlation or association of sitting reduction with a reduction in extremities pain. Two high-quality RCT studies [35, 120], however, reported no significant correlation with LBP; three studies [120, 121, 127] with neck/shoulder pain, all high-quality with one RCT [120]. Furthermore, of six studies, two high-quality studies [35, 125] reported sitting reduction correlates with a reduction in general MSP/discomfort; one RCT study [117] of low-quality reported reduced workplace sitting time does not increase the risk of general MSP/discomfort; and three studies [116, 126, 128], one of high-quality [116], reported a positive association of continuous uninterrupted sitting with increased general MSP/discomfort [116, 128] and LBP/discomfort [126]. Also, one high-quality study [118], however, reported a protective association of prolonged workplace sitting bout with extremities pain.

Generally, the best evidence suggests workplace sitting reduction is correlated with reduced LBP and general MSP symptoms. For neck/shoulder pain reduction, the evidence from RCT suggests there is a positive correlation with reduced workplace sitting. Also, there is moderate evidence of association of prolonged uninterrupted sitting with general MSP/discomfort. There is, nevertheless, no evidence of correlation of reduced workplace sitting with a reduction in extremities pain.

Risk of bias

Three studies had lower quality scores detected by the QualSyst checklist, one of which was a pilot study and had a potential risk of bias; however, most of the studies did not show any major risk of bias. The funnel plots (Supplementary Figures 1B, 2, 3, 4 and 5B) of the meta-synthesised studies were mostly asymmetrical; this could be because of the small number of studies available and not likely due to publication bias. Also, the significant heterogeneity observed may have risen from the studies' methodological heterogeneity in the variables measured and study sample.

Discussion

Key findings

This is the first review to examine separately the associations of occupational and non-occupational SB with MSP conditions in adults. We found in the non-occupational SB domain, strong evidence of cross-sectional associations for full-day SB with MSP conditions, including LBP, knee pain, arthritis, and general MSP. For the occupational SB domain, there is strong evidence of cross-sectional associations of self-reported workplace sitting with MSP conditions, including LBP and neck/shoulder pain. Also, we found moderate evidence of a cross-sectional association of computer time with neck/shoulder pain. Furthermore, we identified from experimental/intervention studies that reduced occupational sitting time was associated with a reduction in LBP, neck/shoulder pain, and general MSP. However, there was insufficient evidence on cross-sectional associations of leisure-time SB and TV time with MSP conditions. Likewise, the evidence on prospective associations of occupational and non-occupational SB with MSP conditions was insufficient, nonetheless, there is an indication that device-measured total workplace sitting could be negatively associated with LBP-intensity in tradespeople.

Non-occupational sedentary behaviour and musculoskeletal pain conditions

We observed in our meta-analysis of cross-sectional studies that full-day SB or sitting time is positively associated with the risk of LBP. However, subgroup analysis by self-reported and device-measured SB indicated the association exists between self-reported full-day SB and LBP, but not for device-measured full-day SB and LBP-intensity, which included studies of mostly tradespeople. This finding is, nonetheless, limited by a small number of studies. The cross-sectional design and self-reported data downgrade the quality in this evidence with the association only present in the case of self-reported SB, but not device-measured SB, with LBP. Our narrative synthesis based on the best-evidence synthesis found that there are cross-sectional associations for full-day SB with knee pain, arthritis, and general MSP, but an inconclusive association with neck/shoulder pain. We found inconsistent cross-sectional associations of full-day SB with hip and extremities pains. Also, limited by the number of studies, there was insufficient evidence of prospective associations of full-day SB with MSP conditions. Furthermore, we observed inconsistent evidence of cross-sectional and prospective associations of SBs, TV time, and leisure-time SB with MSP conditions. These findings were, however, constrained by the limited number of studies available, especially evidence from prospective studies.

Our cross-sectional findings for LBP are in contrast to a previous review of observational prospective and case–control studies by Chen and colleagues, that showed no associations of a sedentary lifestyle with the risk of LBP [19]. Unlike our review which included only adults, Chen and colleagues' review included both children and adults [19]. Another review of prospective studies has also reported some inconsistent associations of SB with LBP [20]. A meta-analysis by Alzahrani and colleagues reported no association of SB with the prevalence of LBP but reported positive associations with LBP intensity and disability [20]. Notwithstanding the methodological limitations that might be present in the above-mentioned reviews, a specifically clear distinction was not made between SB and physical inactivity in the inclusion criteria [19], the possibility of reverse causation within cross-sectional designs limits the comparability of our findings with these previous reviews of prospective studies. Adults, especially those with multimorbidities including MSP conditions may often be less active and resort to SB which may have a pain modulation effect [130]. A review, for instance, had previously found that SB is much common in people with knee osteoarthritis [131]. We found that there is a positive cross-sectional association of SB with knee pain, but of limited strength due to a small number of reviewed studies; however, causal relation cannot be inferred from a cross-sectional finding with a potential reverse causation bias.

Occupational sedentary behaviour and musculoskeletal pain conditions

Our meta-analysis of cross-sectional studies found a positive association of self-reported total workplace sitting with the risk of LBP and neck/shoulder pain. A subgroup analysis by non-tradespeople and tradespeople for the risk of LBP shows the association is significant only in the non-tradespeople. Although limited in terms of the number of studies available, our best-evidence synthesis indicates the association of device-measured workplace sitting with LBP or LBP-intensity was inconsistent in cross-sectional studies of both non-tradespeople and tradespeople but suggests a potential protective association in prospective studies which could be moderated by occupational demand. Also, there is an indication from three studies (including a prospective study) from the same dataset of a negative association of workplace sitting with neck/shoulder pain-intensity in tradespeople. Furthermore, our meta-analysis showed no association of self-reported workplace sitting with the risk of pain in extremities. Nevertheless, a subgroup analysis indicates self-reported workplace sitting may have a protective association for pain in lower limbs.

Evidence of prospective associations of self-reported workplace sitting with MSP conditions is insufficient due to a limited number of reviewed prospective studies. Additionally, we observed in a meta-analysis of three cross-sectional studies on vehicle time and LBP that excessive time spent sitting in a vehicle increases the odds of LBP, yet this cross-sectional association is non-significant.

Additionally, though limited by the number of studies, computer time was found to be cross-sectionally but not prospectively associated with neck/shoulder pain in the positive direction, and there was inconclusive evidence on the direction with LBP and general MSP. Also, from the reviewed experimental/intervention studies, we observed evidence of positive associations of reduced workplace sitting with a reduction in LBP, neck/shoulder pain, and general MSP/discomfort; nevertheless, no evidence on whether reduced workplace sitting is associated with a reduction in extremities pain.

A recent review of prospective studies has reported that device-measured workplace sitting among tradespeople to be associated with a reduced risk of LBP and neck pain [26]. Compared to our review, there are some similarities in the findings even though we were limited by the volume of studies reviewed in this context. For example, there was an indication from our reviewed prospective studies that device-measured workplace sitting could have a negative association with LBP-intensity which may be dependent on the physical demand of the occupation. Similarly, there is a likelihood of a negative cross-sectional association of device-measured workplace sitting bout with LBP-intensity which is potentially moderated by overweight/obesity in tradespeople. Additionally, our reviewed studies on device-measured workplace sitting in tradespeople suggest a probable negative association with neck/shoulder pain-intensity. A possible explanation of the observed tendency of protective associations of workplace sitting with some MSP conditions in tradespeople could be the physically intensive nature of some of these occupations compared to desk-based occupations. For instance, we also observed in our meta-analysis that self-reported workplace sitting of cross-sectional studies be positively associated with LBP in non-tradespeople but not in tradespeople, albeit in a limited number of studies. Some proponents of the "physical activity paradox" assert that sitting could be of health benefit in individuals who regularly engage in high occupational physical activity as sitting may allow some form of rest and recovery [40, 41]. These indications in our review are, however, inconclusive and warrant further investigations in diverse occupational settings to ascertain these findings.

Generally, our meta-analysis of cross-sectional studies indicated that self-reported workplace sitting significantly increases the odds of LBP by 1.47 times; and was marginally higher, by 1.56 times, in a subgroup of non-tradespeople (Fig. 3). In contrast, previous reviews have reported no evidence of association of workplace sitting with LBP [22, 23]. These previous reviews included both cross-sectional and prospective studies; in contrast, our evidence was synthesised from only cross-sectional studies, therefore, limiting any interpretation of a causal relationship of workplace sitting with LBP. The possibility of reverse causation along with bias in self-reported data in the cross-sectional studies reviewed may adversely affect the quality of evidence in the observed positive association. Similarly, this may have affected the interpretation of the association between SB and neck/shoulder pain.

Also, our best evidence synthesised indicates there is moderate cross-sectional evidence that computer time ($\geq$ 4 h/day) increases the risk of neck/shoulder pain; two previous systematic reviews of prospective studies [21, 24] and RCT studies [21], however, have reported no association of computer time with the risk of neck pain. Furthermore, there is informative evidence of a probable association between vehicle time and LBP. A pooled meta-analysis of three cross-sectional studies indicates prolonged hours of sitting in a vehicle increase the odds of LBP, but the association is not statistically significant. No published review studies, to our knowledge, have specifically investigated vehicle time and MSP conditions, nonetheless, a recent review has reported that MSP conditions are highly prevalent in vehicle drivers [132]. The cross-sectional evidence of computer and vehicle times is, however, of low quality and limited by a small volume of reviewed studies precluding the possibility of causal relationships.

Evidence on the effects of changes in workplace sitting on MSP conditions is scarce. In contrast, workplace interventions to reduce MSP conditions have provided some insight into the benefit of increased workplace physical activity on musculoskeletal health for comparison [133–136]. For instance, increased occupational physical activity is reported to be associated with reduced general MSP symptoms [133, 134, 136]. Also, a review of experimental studies has reported that device-measured continuous uninterrupted sitting is associated with the increased immediate report of LBP in adults [25]. The evidence from our review also suggests experiments/interventions that reduce total workplace sitting time or sitting bout duration potentially reduce general MSP/discomfort, especially in the lower back and the neck/shoulder. This is consistent with a review that found that workplace interventions potentially reduce LBP and neck/shoulder pain among workers [133, 134]. These findings should be treated with caution due to the

limited number and variations in the reviewed experimental/intervention studies.

This review did not specifically investigate the potential mechanisms that underpin the association of occupational and non-occupational SB with MSP conditions. Nevertheless, some previous studies have speculated the potential mechanisms of the association between SB and MSP conditions such as LBP [37, 137]. For instance, studies that have investigated biomechanical and physiological mechanisms of LBP suggest occupational sitting increases spinal load and accumulation of metabolites that accelerate degenerative changes in vertebral discs [36, 37]. The available systematic review literature on the association between SB and MSP conditions is yet to address potential biological mechanisms. Nonetheless, there is an observation in this current review that indicates the association of occupational SB with, for example, LBP may be modulated by overweight/obesity. Increasingly, higher volumes of SB are linked with adiposity [38]; adipose tissue is metabolically active, releasing pro-inflammatory cytokines and adipokines that may potentiate inflammatory changes in the musculoskeletal systems leading to pain [138]. There is, therefore, a need for further studies on the potential biological mechanisms that explain the associations.

Implications for practice and research

Despite the methodological challenges within the reviewed studies in this current systematic review, the overall observation which is supported by the evidence from experimental/intervention studies is that SB may have a detrimental association with musculoskeletal health. Theoretically, replacing a portion of time spent in SB with physical activity could beneficially impact MSP conditions. For instance, one of our reviewed studies [67] reported that substituting 30 min of a full day's total sedentary time with 30 min of moderate-to-vigorous physical activity (MVPA) may reduce general MSP by 29%. Further, evidence from some of the reviewed experimental/intervention studies also indicates that reduced workplace sitting, and increased standing or walking did not worsen general MSP symptoms [116, 121, 123]. Current WHO physical activity and sedentary behaviour guidelines, in part, recommend reducing and interrupting prolonged SB or sitting with physical activity of any intensity for improved health outcomes [139]. This practice guideline could be encouraged in adults, especially in occupational settings to minimise the risk of MSP conditions.

Our review has identified some knowledge gaps for potential further studies. For instance, inconsistent associations were observed for self-reported and device-measured SB. The evidence of positive cross-sectional associations of SB with MSP conditions was mainly based on self-reported SB. The evidence synthesised from the few studies that investigated device-measured SB was inconsistent with MSP conditions. There is evidence of disparities in device-measured and self-reported SB in adults, with increased potential of self-reported tools to either underestimate or overestimate SB [27]. Furthermore, there were some variations in the measures of MSP conditions; some studies investigated single MSP conditions and some multiple MSP conditions, which could impact the studies' quality and their comparability. Also, the review identified insufficient evidence of prospective associations of SB with MSP conditions and could not make definite conclusions regarding possible causal relationships due to the limited number of prospective studies. Hence, future attention on the application of device-measured SB will be relevant in this context to minimise bias in the probable associations, taking into consideration the outcome measure. Specifically, future research focus could explore the use of posture-based activPAL, the gold standard instrument for measuring sitting time, in prospective study designs. Additionally, some contemporary analytical approaches in the field, such as compositional data analysis could be applied to investigate SB associations relative to other 24-h movement behaviours such as physical activity and sleep with MSP conditions [140]. This review mainly examined the associations of SB with different types of MSP conditions and did not consider the underlying pathophysiology of the MSP conditions. Future studies could also examine the direction of the associations in subgroups of particular MSP conditions. For instance, the direction of association of SB with LBP secondary to lumbar disc degeneration may contrast with the association of SB with LBP due to facet joint inflammation.

This review and previous reviews have not investigated the probable interaction of chronic diseases in the association of SB with MSP conditions. Importantly, MSP conditions are highly prevalent in the presence of multi-morbidities [3, 4], and also emerging as common comorbidities in some chronic diseases, especially type 2 diabetes (T2D) [141–143]. Evidence from an observational study, for example, suggests there is a potential interaction of SB with the association of T2D with MSP conditions in adults [141]. Therefore, it will be of great interest for potential future studies, including cross-sectional, prospective, and RCTs study designs to also focus on the interaction of some chronic diseases such as obesity, T2D, cardiovascular diseases, etc. with the association of SB with MSP conditions. Research in this direction will also provide insight into the understanding of the potential biological mechanisms of SB/MSP conditions associations.

Strengths and limitations

A key strength of this review is its distinct consideration of occupational and non-occupational SB, as well as a wide range of MSP conditions. Also, the evidence synthesis was organised into SB domains and measures, likewise the type of MSP outcomes. For a better insight into the risk associations, studies conducted exclusively in clinical groups diagnosed with MSP conditions and those of autoimmune disease-related MSP conditions were not reviewed.

However, we acknowledge that there are some limitations, and caution should be applied when interpreting the findings. First, a single reviewer initially excluded irrelevant studies by title and abstract screening in stage one of two-phase screening; this might have contributed to exclusion of some relevant studies [144]; however, where there was uncertainty regarding inclusion, such studies were considered for second-stage screening by two independent reviewers. Second, most of the studies reviewed were cross-sectional in design, hence, causality cannot be inferred. Third, there were a limited number of studies, especially prospective and experimental/intervention studies, as well as high methodological and analytical variations in the reviewed studies. The limited number of experimental/intervention studies, especially RCTs, may be because we used the term "sitting" to search for "sitting reduction interventions" and "sitting experimental studies" instead of searching for specific interventions (e.g., sit-stand workstations, stand-up desk, etc.). Also, the limited number of prospective studies might be a result of publication bias as some prospective studies on risk factors for MSP conditions may have examined sitting as a risk factor or have accounted for SB as a confounder but found no association and did not report in the Abstract; therefore, these studies would not be identified by the search.

Fourth, a small number of studies were included in the meta-analyses to estimate the pooled effect sizes, resulting in moderate-to-high heterogeneity in some of the outputs. It is important, however, to note that the inverse-variance meta-analysis approach has a limitation of estimating a false high heterogeneity [145]. Therefore, the observed heterogeneity may be potentially due to variations within the studies but not bias in the results. Fifth, we did not consider the covariates adjusted for in the individual studies in our evidence synthesis. For instance, evidence synthesised from studies that accounted for physical activity might be different from those that did not control for physical activity in analyses. Similarly, studies that accounted for sitting positions assumed (e.g., leaning forward or backward) and occupational activities may influence the evidence synthesised from those that did not account for these factors. Also, specific sources of potential bias and specific limitations that were commented upon by the authors of the reviewed studies, or which potentially could be identified in the studies might impact the findings but were not considered in the evidence synthesis.

Sixth, strict selection criteria were adapted to enhance the efficiency of the review, however, this might consequently lead to studies with relevant information being excluded. Furthermore, we adapted the PICO format in constructing our search terms which included search terms for the outcome to maximise the search output. There is the possibility that the outcome may not be well described in the title and abstract of potential studies and therefore not indexed in databases with controlled vocabulary terms leading to missing potential studies [146]. Finally, only articles published in the English language were reviewed; this could bias our finding as informative evidence in studies published in other languages may have been missed. To minimise this shortcoming, however, we also searched grey literature to identify more relevant studies.

Conclusions

Our systematic review identified evidence of cross-sectional associations of SB (occupational and non-occupational) with MSP conditions. The direction of the association of occupational SB with some MSP conditions, nonetheless, may be dependent on the type and physical demand of the occupation involved. The possibility of reverse causation could not, however, be discounted from the observed cross-sectional associations. Further, evidence from intervention studies shows that reducing prolonged sitting at work reduces MSP conditions and discomforts. There was, however, limited evidence of prospective associations of SB with MSP conditions. Importantly though, the review highlighted some knowledge gaps, including a limited number of studies using device-measured SB and MSP conditions, as well as limited prospective and RCT study designs. Considering the inconsistencies of the review's findings, as well as the highlighted knowledge gaps, further research, especially prospective and RCT studies, is required to better understand the association of SB in occupational and non-occupational settings with MSP conditions. Furthermore, as studies of clinical groups with existing MSP conditions were not reviewed in this current study, future review studies could consider exclusively reviewing this study population. Such studies could also consider examining the contribution of the presence of MSP conditions to the engagement in SB. Also, there is the need for tailored studies to understand the potential interactions of chronic diseases such as obesity, T2D, and cardiovascular diseases in the association of SB with MSP conditions.

Abbreviations
SB: Sedentary behaviour; MSP: Musculoskeletal pain; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; CINAHL: Cumulative Index to Nursing and Allied Health Literature; AMED: Allied and Complementary Medicine Database; LBP: Lower back pain; OR: Odds ratio; GBD: Global Burden of Disease; METs: Metabolic equivalents; WHO: World Health Organisation; PICO: Population, Intervention, Control/Comparison, and Outcome; RCTs: Randomized controlled trials; BMI: Body mass index; QualSyst: Standard Quality Assessment Criteria for Evaluating Primary Research Papers from a Variety of Fields; N/A: Not applicable; UBP: Upper back pain; RevMan5: Review Manager version 5.4.1; USA: United States of America; UK: United Kingdom; TV: Television-viewing; DPHACTO: Danish PHysical ACTivity cohort with Objective measurements; MVPA: Moderate-to-vigorous physical activity; T2D: Type 2 diabetes.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12966-021-01191-y.

Additional file 1: Supplementary Table 1. Search key terms and strings strategy. **Supplementary Table 2.** Studies excluded after full-text screening. **Supplementary Figure 1.** Full-day SB and LBP: (A) A forest plot of sensitivity analysis after excluding two studies, Kulaivelan et al. 2018 and Machado et al. 2018 from the analysis. (B) A funnel plot showing publication bias. **Supplementary Figure 2.** Self-reported workplace sitting and LBP: (A) A forest plot of sensitivity analysis after excluding two studies of lower quality assessment score, Anita et al. 2019 and van Vuuren et al. 2005 from the analysis. (B) A funnel plot showing publication bias. **Supplementary Figure 3.** Self-report workplace sitting and neck/shoulder pain: (A) A forest plot of sensitivity analysis after excluding two studies of low-quality, Cagnie et al. 2007 and Chrasakaran et al. 2003 from the analysis. (B) A funnel plot showing publication bias. **Supplementary Figure 4.** Self-reported workplace sitting and extremities pain: (A) A forest plot of sensitivity analysis after excluding two studies of low-quality, Chrasakaran et al. 2003 and Tsigonia et al. 2009 from the analysis. (B) A funnel plot showing publication bias. **Supplementary Figure 5.** Vehicle time and LBP: (A) A forest plot of sensitivity analysis after excluding the study, Hakim et al. 2018 with low-quality from the analysis. (B) A funnel plot showing publication bias.

Acknowledgements
We would like to thank Jessica Dickson, a senior librarian at Australian Catholic University in Melbourne, for the assistance and guidance offered in the key search terms development and the conduct of the database search.

Authors' contributions
FD, AC, NO, and DD contributed substantially to the conceptualisation and development of the scope of the study. FD and CB performed the studies search, screening, and data extraction. FD, AC, NO, and DD synthesized the data and prepared the manuscript. CB, FC, and DU contributed to the revision and realisation of the final draft manuscript. The final manuscript was read and approved by the authors.

Funding
Dzakpasu and Brakenridge were supported by the Australian Government Research Training Program Scholarship. Owen was supported by the National Health and Medical Research Council (NHMRC) of Australia through a Senior Principal Research Fellowships (#1003960), an NHMRC Centre for Research Excellence (#1057608), and by the Victorian Government's Operational Infrastructure Support Program. Dunstan was supported by an NHMRC Senior Research Fellowship (1078360) and the Victorian Government's Operational Infrastructure Support Program. Urquhart was supported by an NHMRC Career Development Fellowship (Clinical Level 2; 1142809). The funding bodies played no role in the design of the systematic review nor contributed to the manuscript.

Availability of data and materials
Almost all data generated or analysed during this study are included in this published article [and its supplementary information files]. Further datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
All authors declare that they have no conflict of interest.

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Received: 3 May 2021 Accepted: 23 August 2021
Published online: 13 December 2021

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Publisher's Note

2.6.4 The evidence gaps identified from the review

This systematic review identified several evidence gaps, some of which informed the empirical studies that were conducted in this thesis. The key knowledge gaps identified included:

1. There is a paucity of prospective studies – the review identified a limited number of prospective studies on both self-reported and device-measured sedentary behaviour and MSP conditions. Therefore, insufficient evidence of prospective associations of sedentary behaviour with MSP conditions was observed.
2. Lack of a sufficient number of device-measured sedentary behaviour-based studies – the review identified a limited number of studies based on device-measured sedentary behaviour. Therefore, evidence synthesised on device-measured sedentary behaviour was inconclusive.
3. Lack of studies documenting the potential moderation of the relationships between sedentary behaviour and MSP conditions by T2D – among the studies reviewed, none specifically examined the relationships of sedentary behaviour with MSP conditions exclusively in those with T2D. Also, the identified studies did not specifically report on the potential moderation of sedentary behaviour/MSP conditions relationships by T2D.
4. Limited randomised controlled trial (RCT)-based studies – there were a limited number of RCT-based study findings. The few identified experimental or intervention studies were either short-term or acute laboratory-based trials.

Chapter 3: Methods

This chapter outlines the methods and the analytical principles utilised in the empirical studies presented in Chapters 4, 5, and 6. Descriptions of the datasets used in empirical studies, including the data collection processes as well as key variables used in the empirical studies and their measurements are provided. The descriptions of the datasets are summarised in Table 3.1. Further, the statistical analytic principles used for the various studies are also described.

3.1 The Maastricht Study

The first empirical cross-sectional study (Study 2 of Chapter 4) utilised the baseline dataset of the Maastricht Study, an ongoing observational prospective population-based cohort study of middle-aged and older adults living with and without T2D.

3.1.1 Description

The rationale and methodology of the Maastricht Study have been described in a previous publication [90]. In brief, the study focuses on the aetiology, pathophysiology, complications, and comorbidities of T2D and is characterized by an extensive phenotyping approach. Eligibility for participation was open to individuals aged between 40 and 75 years and living in the southern part of the Netherlands, including the following municipalities – Maastricht, Margraten-Eijsden, Meersen, Valkenberg, Maastricht and Heuvelland in the province of Limburg [90]. Recruitment of participants was through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. The recruitment was stratified according to known T2D status, with an oversampling of individuals living with T2D, for reasons of efficiency – to enhance the statistical power to contrast any potential differences in population according to T2D status [90].

The baseline data of the initial 3,451 participants who completed the survey between November 2010 and September 2013 were considered for this thesis. In general, the study population had slightly more women than men and was mainly Caucasian [90].

3.1.2 Ethical considerations

The Maastricht Study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG). Information on the study including an informed consent form was sent to each participant via email before

their clinic visit for assessments. All participants were given an oral explanation of the study procedure before signing the written informed consent form.

3.1.3 Data collection protocol

Standard study protocols were used to collect data from all participants by trained study personnel during their three-to-four-hour visits to the Maastricht Study research centre. Each participant was examined within a window period of approximately three months [90]. Data were entered into an electronic database in duplicate for quality assurance. Web-based questionnaires were self-completed by participants under supervision at the study centre and, if feasible, completion was continued at home. The collected data relevant to this thesis are detailed below.

3.1.3.1 General questionnaire data

Information collected included the following:

Anthropometric and demographic measures, medical history, quality of life, smoking behaviour, socioeconomic status, and alcohol consumption, as well as a lifestyle-specific questionnaire – food frequency questionnaire for dietary and alcohol intakes.

3.1.3.2 Physical activity behaviour data

A thigh-worn activPAL3 physical activity monitoring device (PAL Technologies, Glasgow, UK) was used to objectively assess participants' physical activity behaviours. The activPAL3 data collection, analytic processes, sitting time, and time spent in other physical activity behaviours calculations have been described elsewhere [242, 243]. Participants wore the device continuously for eight consecutive days. The first and the final days' data were excluded from the estimation of the activity behaviours; because participants performed physical function tests while wearing the device on the first day, and the last day data were collected for less than 14 hours of waking time. Participants' data were included in the analysis if they had at least one valid day (more than 14 hours of waking data) of device wear time.

Time spent sitting during waking hours on valid days derived from the activPAL device was used to calculate the participants' mean daily sitting time (sedentary time). MVPA time was derived from the activPAL3 data as minutes with steps frequency of more than 100 steps/min during waking hours as described elsewhere [243].

3.1.3.3 Musculoskeletal pain outcome

This was assessed by both physical examination and questionnaire. The questionnaire was adapted from the United States population-based validated Health Assessment Questionnaire used in the National Health and Nutrition Survey (NHANES) [244]. Participants undertook a physical examination and later asked whether they had at least one instance of experiencing pain in the neck, shoulder, elbow, wrist, hand, low back, hip, pelvis, knee, ankle, and foot; excluding pain as a result of trauma. Those who reported experiencing pain were further asked whether the pain had been present for more than three months, which is generally accepted as an indicator of chronic pain [245]. They were also asked to indicate whether a physician had made a diagnosis of the pain.

3.1.3.4 Glucose metabolism status

The participants' glucose metabolism status was based on self-reported history of T2D, as well as clinical assessment using a standard 2-hour oral glucose tolerance test (OGTT) [90]. Aside from those with known T2D receiving insulin therapy, all other participants' T2D status was assessed by OGTT, as described elsewhere [90]. World Health Organisation (WHO) criteria were used to categorise participants according to glucose metabolism status (GMS): normal glucose metabolism (NGM); prediabetes; and T2D [246].

3.2 The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab Study)

The second empirical study (Study 3 of Chapter 5) utilised a prospective dataset from the Australian Diabetes, Obesity, and Lifestyle Study (the AusDiab Study).

3.2.1 Description

The AusDiab Study is a nationwide longitudinal study designed to study the prevalence, incidence, and risk factors of diabetes and cardiovascular disease among community-dwelling Australian adults aged 25 years and over. There were three data assessment time points, baseline, five-year, and 12-year follow-ups. The baseline and follow-up data collection protocols have been described elsewhere [89, 247, 248]. The study commenced with the baseline data (Wave 1) collected in 1999 – 2000, whereas the follow-ups were undertaken at five years (Wave 2) in 2004 – 2005 and 12 years (Wave 3) in 2011 – 2012. The sections of the AusDiab Study methods relevant to this thesis are briefly presented below.

3.2.2 Ethical considerations

The ethical considerations of the AusDiab Study have been reported in previous publications [89]. The study involved the delivery of enveloped letters to all private dwellings in the study clusters. This contained

a brochure describing study objectives, processes of interviews and examinations, as well as confidentiality. Before biomedical examinations, invitees were provided with a brochure detailing the procedures and the risks involved to inform their decisions on participating in the study. All study respondents consented to interviews and signed a written consent form before participation. Participants' information was securely stored to ensure confidentiality [89]. The Alfred ethics committee provided approval for the study (approval no. 39/11).

3.2.3 The baseline data (Wave 1) – study design and population

The description of the study design, population, sampling, and data collection of the AusDiab Study at baseline has previously been published [89]. Briefly, from 1999 – 2000, non-institutionalised adults aged 25 years and over living in each of the six Australian states and the Northern Territory and residing in private dwellings with a permanent address for at least six months before the commencement of the survey were invited; excluded were those with either physical or intellectual disabilities. Participant inclusion utilised a stratified cluster sampling approach, with probability proportional to the size of the adult population aged 25 years or over in sampled clusters. The clustering size of about 250 participants was selected based on the Australian Bureau of Statistics geographic area unit of the Census Collector District (CCD) [89]. In total, the sampling was conducted in 42 CCDs, comprising six CCDs from each of the six Australian states and one territory.

The measurements taken included self-reported survey information and biomedical data. The survey instruments consisted of interviews at participants' houses and survey sites, as well as self-administered questionnaires. Interviews were guided by a structured interviewer-administered questionnaire. Physical examinations and biological test sampling for biomedical data took place at survey sites located in each of the sampled CCDs. All procedures for data collection were in accordance with the WHO-recommended guidelines. Tests on collected pathology samples (blood and urine) were run at selected pathology (laboratory) test centres [89].

With regard to respondents, data were provided by 11,247 participants at baseline (Wave 1), which represented a 55.3% response rate [89].

3.2.4 Follow-up data collections

Follow-up assessment protocols were modelled to replicate the baseline procedures used at each of the CCD survey sites [247, 248]. Invitations for the respective follow-ups were via letters and telephone calls to all eligible participants who completed the baseline data collection (Wave 1) [247, 248]. To maximise the respective follow-up data collection, the AusDiab Study coordinators kept up-to-date participants' contact information database.

3.2.4.1 The first follow-up (Wave 2)

The five-year follow-up (Wave 2) was conducted between 2004 and 2005. Out of the 11,247 eligible baseline participants, 8,798 participants accepted the invitation and provided data at five years. This represented an 81.6% retention rate [247]. Participants provided survey and biomedical data across 43 survey sites, one site more than the baseline sites. This was a site added in the Australian Capital Territory which was necessitated by the relocation of some of the baseline participants [247].

3.2.4.2 The second follow-up (Wave 3)

The final follow-up was at 12 years between 2011 and 2012 (Wave 3). All 11,247 participants recruited at baseline were eligible, but the total number that remained and provided data at this stage was 6,186 (59.8% retention rate) [248]. Data were collected at 46 survey sites, four more testing sites than the baseline sites to account for relocated participants [248]. In addition to the core baseline data, physical activity monitoring device data (inclinometer data) were collected from selected participants [248].

3.2.5 Data collection protocol

Similar data collection protocols were used at each of the three data time points.

3.2.5.1 Survey data

Two formats of self-reported questionnaires were used to collect survey data at the household and survey sites. These were based on the mode of administering the questionnaires: interviewer-administered and self-administered questionnaires.

i. Interviewer-administered questionnaires:

These consisted of a household questionnaire, a general questionnaire, and an existing health conditions questionnaire. Data that were collected included:

a. demographic characteristics (age, gender, ethnicity, language spoken, socioeconomic status, birthplace, and marital status)
b. medical and family history (diabetes status, family history, chronic health conditions e.g., kidney, cardiovascular etc., medication use)
c. lifestyle-related factors (alcohol intake and smoking status, physical activity)
d. health-behaviour-related factors (health knowledge, attitudes and practice data, health service utilisation patterns) [89].

ii. Self-administered questionnaire

This included:

a. Short Form 36 items (SF-36) Health Survey Questionnaire [249] (a generic tool for general health and well-being assessment) which assessed eight domains of quality of life, including:
    i. Physical functioning – 10 items
    ii. Physical role limitations – 4 items
    iii. Bodily pain – 2 items
    iv. General health perceptions – 5 items
    v. Energy/Vitality – 4 items
    vi. Social functioning – 2 items
    vii. Emotional role limitations – 3 items
    viii. Mental health – 5 items
b. Anti-Cancer Council of Victoria Dietary Questionnaire (Dietary survey) [250].

3.2.5.2 Biomedical data

Biomedical examinations were conducted at survey sites in each sampled CCD between the hours of 07:00 and 14:00 local time. Examinations included:

i. Physical examination (anthropometric measurements) – height to the nearest 0.5cm; weight to the nearest 0.1kg; waist and hip circumference to the nearest 0.5cm; body fat composition; blood pressure.
ii. Blood test – (fasting samples: according to WHO standards) fasting glucose; lipids (total cholesterol; high-density lipoprotein cholesterol (HDL-C) and triglycerides); 75g OGTT (2-hour plasma glucose); HbA1c.
iii. Urine test – albumin/microalbumin and creatinine.

3.2.5.3 Activity behaviour data

Physical activity and sedentary behaviour data were based on self-reported questionnaires across the three waves. Participants' physical activity level was measured by using the Active Australia Survey questionnaire which asked questions about leisure-time physical activities, as well as time spent walking for transport in the past week (7 days). Physical activity time was estimated by summing time spent walking for 10 minutes or more, time spent in moderate-intensity physical activity (MIPA) and time spent in vigorous-intensity physical activity (VIPA) [251]. Sedentary behaviour was estimated as time spent per week watching

television. Television-viewing (TV) time was calculated as the total reported time spent on weekdays and weekends watching television or video/DVD for the past week (7 days) [248].

Also, at Wave 3, a multi-item questionnaire was included to assess domain-specific sitting time (commuting in a car, watching television, reading, visiting friends, and working at a desk/computer) [248]. Objectively measured activity behaviour data using body-worn devices were also collected from selected participants at Wave 3 (accelerometer - Actigraph® GT3X+ and inclinometer - activPAL3®) [248].

3.3 Stand-Up Victoria Study

The third empirical study (Study 4) presented in Chapter 6 utilised data from the Stand-Up Victoria sedentary behaviour reduction 12-month cluster-randomised controlled trial.

3.3.1 Description

The "Stand Up Victoria Study" was a 12-month cluster-randomised controlled trial whose main purpose was to determine whether a multi-component three-month intervention could reduce desk-based office workers' sitting time. The trial protocol has been detailed elsewhere [55]. In brief, the protocol included three data assessment time points – at baseline, three months at the end of the intervention period, and 12 months after a nine-month maintenance period. Participants were in work teams recruited from 14 different worksites which were geographically separated at least one kilometre apart between April 2012 and October 2013. The worksites were within a single organisation, the Australian Government Department of Human Services (DHS) in the Australian state of Victoria, and had no ongoing staff physical activity intervention program [55]. The employees of the participating worksites were recruited through telephone-administered interviews.

The eligibility criteria included adults aged 18 – 65 years working at least 0.6 full-time equivalents with a designated desk with access to a telephone and internet, as well as being able to speak English, and had no intention to relocate from the worksite for at least the first three months of the intervention period. Participants were excluded if they were pregnant; had physical health limitations to standing continuously for at least 10 minutes; were non-ambulatory [55]. Worksites were the unit of randomisation of participants into an intervention group (seven worksites with 136 workers) and a control group (seven worksites with 95 workers). The detailed trial protocol and the pilot findings [55, 252], measures used and intervention development process [253], as well as findings on intervention effects [69] and the impacts on cardiometabolic biomarkers [59], have all been published. The component of the trial relevant to this thesis is briefly described.

3.3.2 Ethical considerations

The study was registered with the Australian New Zealand Clinical Trials Register number ACTRN12611000742976, and Ethical approval was granted by the Alfred Health Human Ethics Committee, Melbourne, Australia. Each participant provided written informed consent. The trial followed the standards of Consolidated Standards of Reporting Trials (CONSORT) guidelines for cluster-randomized trials [254]. Funding for the Stand-Up Victoria trial was provided by the National Health and Medical Research Council (NHMRC) Project Grant (#1002706) and the Victorian Health Promotion Foundation (VicHealth).

3.3.3 Brief overview of the intervention arm treatment

Stand Up Victoria trial consisted of a multi-component three-month intervention strategy – with organisational, environmental, and individual-level components. The intervention also had three key intervention messages ("Stand Up, Sit Less, Move More") to support the multi-component strategies [55, 253]. The behavioural target was to support participants to replace portions of their daily sitting time with standing and/or stepping postures through standing for at least an hour a day at their workstation, and other self-selected strategies that targeted standing, stepping, or both postures.

a. Organisational component – this involved three elements of support including senior managerial support through consultations with research staff, workshops for representatives' consultation by senior research staff, as well as research staff delivering information and brainstorming sessions to the participants. Also, there was ongoing organisational support through team champions sending emails containing intervention-tailored messages to team members.
b. Environmental component – this included a structural modification of the work environment by the installation of a height-adjustable dual-screen sit-stand workstation (Ergotron WorkFit-S) which included a work surface accessory to enable the participant to alternate between sitting and standing postures while working. This component lasted for the three-month intervention period and remained for the nine-month maintenance period until the 12-month data collection time point. Participant-tailored sitting and standing heights of the sit-stand workstations were configured and marked with adhesive labels. Further, participants were provided with written and verbal information on the sit-stand manufacturer's instructions on appropriate ergonomic sitting and standing postures.
c. Individual-level component – this was a three-month strategy to support the behaviour change and was delivered by trained health 'coaches'. It included face-to-face health coaching sessions and supporting three consecutive telephone calls at 2-, 4-, and 8-weeks following the participants' coaching session. The coaching enforced the key intervention message – "Stand Up, Sit Less, Move More". The coaching also involved specific ergonomic instructions on workstation usage for

participants to 'listen to their body' and regularly change their posture to ensure not sitting or standing for too long.

Control:

The control group participants were advised of the aim of the trial, and they followed the usual work practice without receiving any of the intervention components. However, they underwent the same data collection assessment as the intervention group at the three data collection time points.

Note: For the purpose of this thesis, intervention and control arm participants' data were pooled together to increase the statistical power of the analysis.

3.3.4 Data collection

Participants were assessed at three-time points – at baseline, three months after the completion of organisational and individual-level intervention components, and after the nine-month maintenance period at 12 months. The data collection protocol has been previously published [55, 253]; a brief description of the data relevant to this thesis is presented below.

3.3.4.1 Primary outcome: activity behaviours (sitting, standing, stepping)

Activity behaviour outcomes were objectively measured using activPAL3™ physical activity monitoring device (PAL Technologies Limited, Glasgow, UK; Version 6.3.0). A detailed description of this process has been reported elsewhere [69]. In brief, participants wore a waterproofed activPAL3™ device by attaching it to the anterior right thigh using hypoallergenic adhesive material (Hypafix®, BSN medical) continuously for seven days at each of the data collection time points. For the validation of the activPAL device, the participants concurrently wore an accelerometer, and the tri-axial GT3X+ Actigraph activity monitor (ActiGraph, Pensacola, Florida), over the right hip, using an elastic belt. Self-completed daily logs of participants' work hours, the site at which they worked, waking and sleep times, and, if any, times when the devices were not worn.

The data were processed by using a customised statistical software program – SAS version 9.4 (SAS Institute Inc., Cary, NC, USA) – which combined the activPAL and diary data. The sitting, standing, and stepping activity behaviours were calculated as the average valid workdays (device worn during at least 80% of work hours) or valid days (device worn during at least 80% of waking hours). The Actigraph GT3X+ data was used to estimate time spent in LIPA and MVPA.

3.3.4.2 Secondary outcomes

Other data collected were:

a. Clinically assessed data – anthropometric measures included height, weight, and body composition were collected using standard instruments. Cardiometabolic markers, including participants' glucose, lipid profile (total cholesterol, LDL, HDL, and triglycerides), and insulin were assessed from fasting blood samples. Blood pressure was measured.
b. Survey data – socio-demographic information (age, gender, ethnicity, marital status, and education level) was collected at baseline only. Physical health data, including musculoskeletal health, were also collected. An online modified Nordic Musculoskeletal Questionnaire (NMQ) through a Lime-Service tool was self-completed to assess the presence of MSP in various body regions during the past seven days and the past three months [55, 255, 256]. Participants also completed a self-report questionnaire to estimate time spent in physical activity, standing, and sitting during weekdays and weekends. Other measures include work outcomes (productivity - Health and Work Questionnaire (HWQ); presenteeism and absenteeism - Work Limitations Questionnaire (WLQ), dietary intake – Fat & Fibre Behaviour Index, quality of life - Australian Quality of Life Survey (AQoL-8D) [55].

Table 3.1: Summary of datasets used in the empirical studies.

Study	Description	Measured variables
The Maastricht Study Netherlands	Population-based epidemiological study cross-sectional dataset of adults aged 40 – 75 years. Recruitment was stratified by known T2D status, with an oversampling of individuals with T2D.	Activity behaviour data: activPAL-derived sedentary behaviour (daily sitting time) and MVPA MSP outcomes – Self-reported MSP in the neck, shoulder, elbow, wrist, hand, low back, hip, pelvis, knee, ankle, and foot (Questionnaire adapted from the United States population-based validated Health Assessment Questionnaire [244]) Glucose metabolism status – Self-reported T2D and clinically assessed by 2-hour OGTT. Categorised into – NGM, prediabetes, and T2D. Covariates – Anthropometric and demographic measures (body weight – BMI), medical history, quality of life, smoking behaviour, socioeconomic status, dietary and alcohol intake.
AusDiab Study Australia	Population-based epidemiological prospective study design. Adults aged 25 years and over were recruited nationwide from six states and one territory across Australia. Three data collection time points over 12 years: Baseline – 1999 to 2000 (11, 247) Follow-ups: at 5 years – 2004 to 2005 (8,798) at 12 years – 2011 to 2012 (6,186)	Activity behaviour data (assessed at all time points) – Sedentary behaviour was estimated as self-reported total TV time on weekdays and weekends for the past 7 days. Active Australia Survey questionnaire used for leisure-time physical activity (MVPA) [251]. Pain outcome (assessed at all time points) – Based on the SF36 bodily pain domain scale (consists of two items which assess pain intensity and pain interference on normal activities [249]). Scored on a 0 to 100 scale with lower scores (towards '0') referring to more severe pain (score '100' – no pain). T2D status (assessed at all time points) – Clinically assessed using fasting blood/plasma glucose test and 2-hour OGTT. Covariates – Time-invariant data (sex and education level) captured only at baseline. Time-variant data (assessed at all time points) participants' age, and waist circumference (body weight), self-reported household income, lifestyle behaviours (energy intake and smoking) medical history, and mental health.
Stand-Up Victoria Study Australia	Workplace-based cluster-randomised control trial (prospective) design. Recruited from adults aged 18 – 65 years who were desk-based workers in a single organisation. Total participants – 231 (Intervention = 136; Control = 95) Three assessment time points – at baseline, three-month after the intervention, and 12 months after the nine-month maintenance period.	Activity behaviour data (sitting, standing, and stepping) – activPAL3-assessed activity behaviours at each time point. MSP outcomes – NMQ-assessed ache, pain, discomfort, or numbness in the neck, shoulders, elbows, wrists, low back, hips, knees, and ankles in the last seven days (acute) and the last three months (chronic) [256]. Covariates – Self-reported anthropometric and demographic (body weight – BMI), as well as socioeconomic data.
T2D – type 2 diabetes, MVPA – moderate-to-vigorous intensity physical activity, NGM – normal glucose metabolism, SF36 – short form 36 items, OGTT – oral glucose tolerance test, NMQ – Nordic musculoskeletal pain questionnaire		

3.4 Statistical analytic approaches

An overview of the statistical modelling methods that were used in the various empirical studies is presented below.

3.4.1 Logistic regression

The first empirical study (Study 2) used a simple logistic regression modelling method to examine the associations between volumes of daily sitting time and the odds of MSP outcomes in different body regions. This modelling approach assumes a linear relationship between the exposure (daily sitting time) and the outcome (MSP) variables.

3.4.1.1 Restricted cubic splines

A sub-analysis was performed in Study 2 to examine the potential non-linear relationships of daily sitting time with the MSP outcomes using a restricted cubic spline (RCS). The RCS is a robust analytical method for modelling flexible non-linear relationships with knots placed at specific locations of the curve [257]. The number of knots and their locations largely depend on the size of the data [257, 258]. An example of RCS for estimating the non-linear relationships with different knots is shown in Figure 3.1 below – the illustration was taken from Oskarsson and colleagues [258].

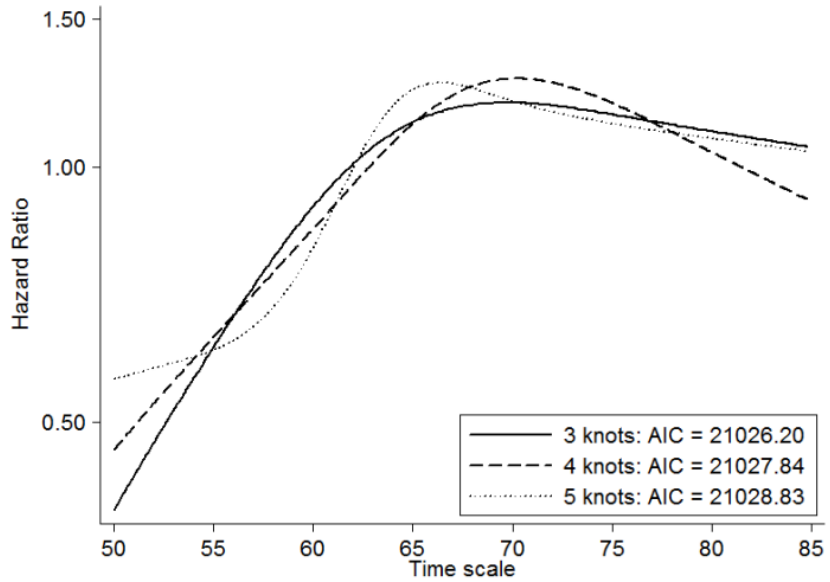

Figure 3.1: Restricted cubic splines showing a different number of knots.

3.4.2 Growth curve modelling

This analytic method was used in the second empirical study (Study 3) to examine bodily pain trajectories and their relationships with changes in sedentary behaviour (TV time). The growth curve model, which is also referred to as growth trajectory, is an analytical method used to estimate changes in outcomes of

repeated measures over several observational periods. The method uses a mixed-effects or multilevel modelling approach, and it is the ideal method recommended for longitudinally structured data with repeated measures at several observational time points [259, 260]. This approach has the advantage of accounting for differences in data distribution and variations in variables in longitudinal data. Growth curve modelling can account for missing data by treating them as missing at random (MAR), as well as irregular time points of data collection often associated with longitudinal data [259, 260]. Additionally, it is effective in concurrently handling time-variant and time-invariant covariates. Further, it can provide an estimate for participant-specific exposure effect, therefore, variabilities in longitudinal outcomes among participants can be explained. This approach provides some foundation for making future predictions of outcomes in study populations relative to the exposures of interest [259].

Longitudinally structured data are considered a type of multi-level data with repeated measures at 'level-1' nested within individual participants at 'level-2'. The measurement time points of each participant (i.e., data collection time points) are the time metric which is often treated as a 'level-1' explanatory variable. The growth curve modelling uses either random intercept or random slope models, with the latter being more robust in accounting for variations in individual trajectories [259].

3.4.2.1 Unconditional growth curve model

The unconditional model estimates the outcome as a function of the data time metric (eg., month, year, age, etc.) by fitting time as the only explanatory variable in the model. This assesses how individual variations in the growth curves are attributable to the linear changes in the time metric.

A simple three-level linear multilevel growth curve using a random slope model for 'Y'$_{(outcome)}$ individuals [i (i = 1, 2, …, N)] (level-2) nested within clusters [j (j = 1, 2, …, k)] (level-3) at observational time points [t (t = 1, 2, …, n)] (level-1) with varying intercept and slop for individuals at 'level-1' is expressed as [259]:

Level 1: Repeated Measurement within an individual

$$Y_{(Outcome)ijt} = \pi_{0ij} + \pi_{1ij} Time_{it} + \varepsilon_{ijt} \qquad [\varepsilon_{ijt} \sim N(0, \sigma_{\varepsilon}^2)]$$

Level 2: Individual nested within clusters (CCD)

$$\pi_{0ij} = \beta_{0j} + \mu_{0ij} \qquad [\mu_{0ij} \sim N(0, \sigma_{\mu_0}^2)]$$

$$\pi_{1ij} = \beta_{1j} + \mu_{1ij} \qquad [\mu_{1ij} \sim N(0, \sigma_{\mu_1}^2)]$$

Level 3: Cluster

$$\beta_{0j} = \gamma_0 + \nu_{0j} \qquad [\nu_{0j} \sim N(0, \sigma_{\nu_0}^2)]$$

Or in a composite single equation as:

$$Y_{(Outcome)ijt} = \gamma_0 + \beta_{1j}Time_{it} + [\, \nu_{0j} + \mu_{0ij} + \mu_{1ij}Time_{it}] + \varepsilon_{ijt}$$

Where,

$$\varepsilon_{ijt} \sim N(0, \sigma_\varepsilon^2)$$

$$\begin{pmatrix}\mu_{0ij} \\ \mu_{1ij}\end{pmatrix} \sim N(0, \Omega_\mu), where\ \Omega_\mu = \begin{pmatrix}\sigma_{\mu_0}^2 & \\ \sigma_{\mu_0\mu_1} & \sigma_{\mu_1}^2\end{pmatrix}\ and$$

$$\nu_{0j} \sim N(0, \sigma_{\nu_0}^2)$$

Where π_{0ij} + $\pi_{1ij}Time_{it}$ is mean Outcome for individual i in cluster j at Time t and ε_{ijt} is the difference between the observed Outcome for this individual i and the mean. β_{0j} is the mean Outcome at Time=0 across all individuals in cluster j, while μ_{0ij} measures how much the mean Outcome at Time=0 for individual i differs from their cluster-level average. Similarly, β_{1j} is the mean change in Outcome per unit Time for all individuals in cluster j, while μ_{1ij} measures how much individual i differs from their cluster-level average in terms of this parameter. Further, γ_0 is the mean Outcome at Time=0 averaged across all clusters and ν_{0j} measures how cluster j differs from this average. The variance in the Outcome attributed to the clustering of the individual is var$(\nu_{0j}) = \sigma_{\nu_0}^2$, whereas the between-individual variance in the Outcome is var$(\mu_{0ij}) = \sigma_{\mu_0}^2$, between individual variance in the slope is var$(\mu_{1ij}) = \sigma_{\mu_1}^2$, and the individuals' intercept-slope covariance is $\sigma_{\mu_0\mu_1}$. The interpretation of the covariance $(\sigma_{\mu_0\mu_1})$ follows that if a positive mean slope is estimated $(\beta_{1j} > 0)$, a positive covariance between the intercept and slope implies that those individuals with initial outcomes above the mean (above-average intercepts: $\nu_{0j} + \mu_{0ij} > 0$) will have steeper slopes $(\mu_{1ij} > 0)$, while those with initial outcomes below the mean (below-average intercept: $\nu_{0j} + \mu_{0ij} < 0$) will have flatter slopes.

3.4.2.2 Conditional growth curve

The conditional growth curve estimates the influence of exposure variables, which could be either time-variant or time-invariant variables on the growth trajectories. For instance, in Study 3, the influence of TV time (the exposure of interest) on bodily pain trajectories was investigated by adding TV time as a time-variant variable to the fitted unconditional growth curve model and further adjusted for relevant confounding variables (Covariates). This can be expressed in an equation as shown below:

$$Y_{(Outcome)ijt} = \pi_{0ij} + \pi_{1ij}Time_{it} + \pi_{2i}Exposure_i + \pi_{3i}Covariates_i + \varepsilon_{ijt}$$

3.4.3 Compositional data analysis in linear regression

Study 4 used a compositional data analysis (CoDA) method to examine the relative relationships of prospective changes in activity behaviours (sitting, standing, stepping, and the bouts of these behaviours) with MSP outcomes. The CoDA modelling approach is a novel analytical framework in the field of behavioural epidemiology that can account for the interdependency of time-use composite behaviours [261-263]. The literature on CoDA is extensive and beyond the scope of this thesis. A brief overview of CoDA relevant to the understanding of this thesis is hereby presented.

The conceptualisation of the CoDA framework considers components of time-use in different behavioural activities to be relative, which is constrained to sum up to a 24-hour full day (or 16-hour waking hours, or even 8-hour working hours) and often re-scaled to 1 (or 100% in terms of percentage) [261]. For instance, considering time used in the following 24-hour composition – sleep, sedentary behaviour (SB), light-intensity physical activity (*LIPA*), moderate-intensity physical activity (MIPA) and vigorous-intensity physical activity (VIPA) – they are inter-dependent, therefore, each component is relative to the other components. This can be expressed in an equation as shown below.

$$Sleep_{time} + SB_{time} + LIPA_{time} + MIPA_{time} + VIPA_{time} = 24_{Hours}$$

or

$$\%Sleep_{time} + \%SB_{time} + \%LIPA_{time} + \%MIPA_{time} + \%VIPA_{time} = 100\%$$

A brief overview of CoDA framework in linear regression models for activity behaviours composition and health outcomes is described here [261]. Compositional data do not occupy real space for them to be directly used in a conventional linear regression. Rather, they are considered geometrically to occupy a constrained space which is defined as simplex, hence, a change in one compositional behaviour affects the other component behaviours [261]. Compositional data, therefore, need to be log-ratio transformed (e.g., into isometric log-ratio – ilr) to map them from real space in regression models, if not, misleading inferences may be drawn from outputs [261, 264]. Consider the following waking hours' activity behaviours (X): sedentary behaviour (e.g., Sitting), LIPA (e.g., Standing) and MVPA (e.g., Stepping) as three-part compositional data. These time-use compositions can be graphically illustrated in a ternary plot, similar to a scatter plot for traditional (unconstrained) data. A ternary plot is an equilateral triangle which geometrically defines a constrained space (a simplex); thus, a change in one behaviour component affects the other components. Figure 3.2 and Figure 3.3 are examples of ternary plots.

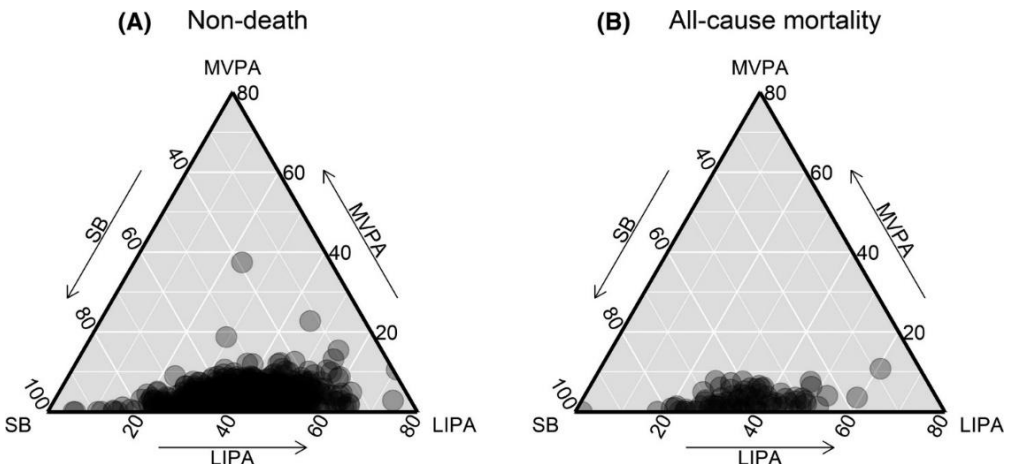

Figure 3.2: Graphical representation of compositional data in simplex space.

This ternary diagram illustrates the associations of activity behaviours with all-cause mortality using CoDA. The plot depicts the relative proportions of sedentary behaviour (SB), LIPA, and MVPA according to non-death (A) and all-cause mortality (B). Each dot (the case) represents the relative proportion of time spent in SB, LIPA, and MVPA using barycentric coordinates where the perpendicular distance from any dot to any of the bases of the triangle describes the proportion of time spent in each activity behaviour. Note: the LIPA and MVPA axes are limited to 80% for simplicity. The graph was taken from von Rosen et. al. [265]

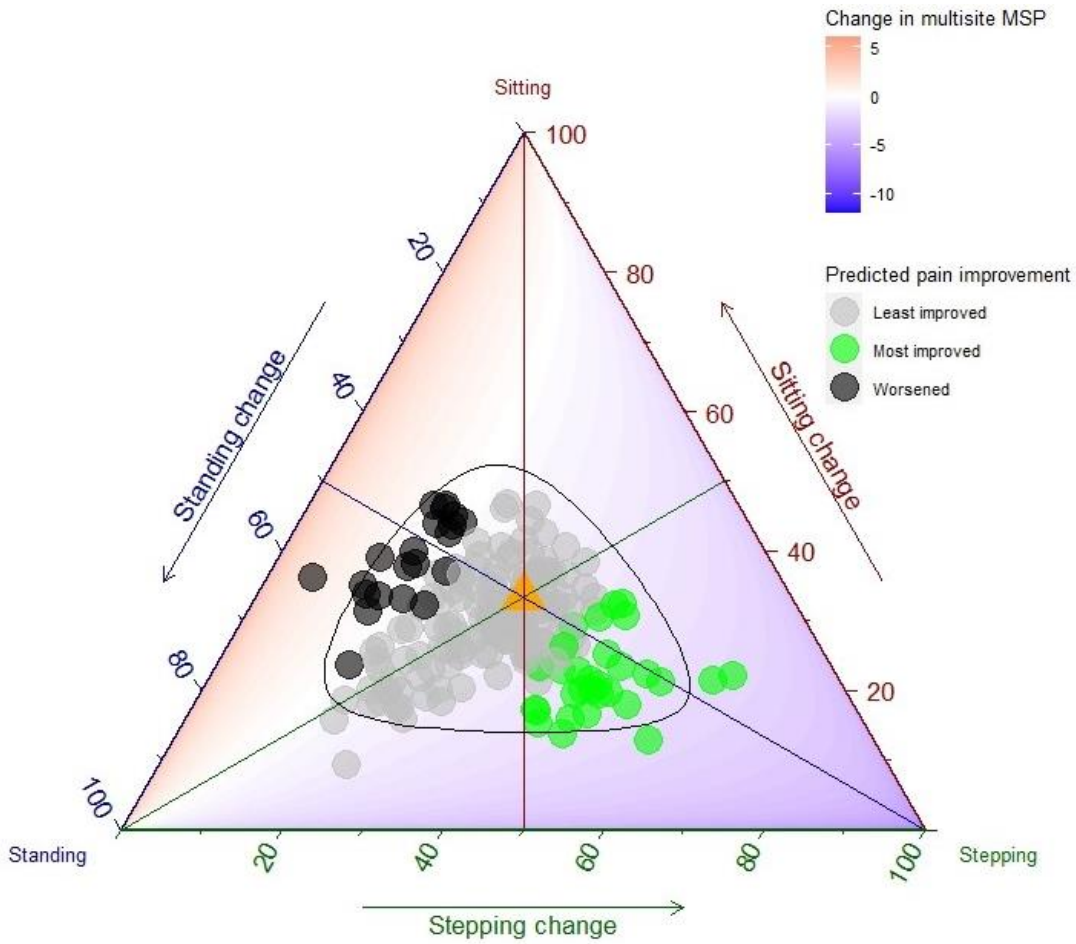

Figure 3.3: Compositional changes and predicted musculoskeletal pain outcome.

This ternary diagram illustrates compositional changes and predicted multisite MSP outcomes. The individuals' compositional changes are clustered about the centre of the triangle indicating there were not many variations in their activities at the follow-ups from the baseline. Reducing sitting and increasing stepping showed favourable changes in multisite MSP (green dots) – data from thesis Study 4.

For linear regression modelling of a health outcome on time-use data (compositional data) as an exposure variable, three-part composition (*Sitting, Standing, and Stepping*) models with covariates for subjects *(i)* are described below.

Model A:

$$Y_{(Health\ outcome)i} = \beta_0 + \beta_1 Sitting_i + \beta_2 Standing_i + \beta_3 Stepping_i + Covariates_i \ldots\ldots\ldots (C1)$$

Applying ilr transformation of a time-use composition, the d-part simplex of the compositional data coordinates is coherently structured into (d-1)-dimensional real space, with 3-parts composition being converted to 2-ilr transformed explanatory (exposure) variable vectors (or coordinates). Therefore, the regression model equation becomes:

$$Y_{(Health\ outcome)i} = \beta_0 + \beta_1 ilr_{1i} + \beta_2 ilr_{2i} + Covariates_i \ldots\ldots\ldots\ldots\ldots\ldots\ldots (C2)$$

Where,

$$ilr_i = ilr_{1i},\ ilr_{2i} \ldots, ilr_{(d-1)i}$$

$$ilr_i = \sqrt{\frac{d-n'}{d-n'+1}}\ \mathrm{In}\frac{X_{n'}}{\sqrt[d-1]{\prod_{j=n'+1}^{d} X_j}},\ n' = 1, \ldots, d-1 \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ (C3)$$

Hence,

$$ilr_{1i} = \sqrt{\frac{2}{3}}\ \mathrm{In}\frac{Sitting_i}{\sqrt[2]{Standing_i \times Stepping_i}} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (C4)$$

$$ilr_{2i} = \sqrt{\frac{1}{2}}\ \mathrm{In}\frac{Standing_i}{\sqrt[1]{Stepping_i}} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (C5)$$

The fitted model interpretation follows the same standard for a regression model, with model R^2 indicating the amount of variance explained by the behavioural activities composition and model p-value indicating how significant is the model [261, 262].

The coefficient of a behavioural activity is interpreted relative to the other behavioural activities in the model. The corresponding p-value indicates the significance of the behavioural composition in explaining the outcome but is not an indication of an independent predictor of the outcome. For output interpretations, the ilr_{1i} (in equation C3) expresses the relative relationship of one behavioural activity (denominator – *Sitting*) to the other behavioural activities (numerators – *Standing and Stepping*). Thus, the ratio of one behavioural component to the rest of the behavioural activities in the composition of the model $\left(\frac{Sitting}{Standing\ \&\ Stepping}\right)$. The coefficient β_1 (in equationC2) is, therefore, interpreted directly to indicate the relative strength of association between the compositional time spent in one behavioural activity

(*Sitting*) to time spent in the other behavioural activities (*Standing and Stepping*) and the predicted health outcome. For instance, as indicated in equation (C2), the coefficient β_1 indicate how strong the association of Sitting time relative to Standing and Stepping time is to predict $Y_{(\text{Health outcome})}$.

However, the coefficient of ilr_{2i}, cannot be meaningfully interpreted like the ilr_1 coefficient; but as the ratio of one behavioural activity to another behaviour with the other behaviour held constant at the mean $\left(\frac{Standing}{Stepping};\ excluding\ sitting\right)$. Therefore, to determine the strength of the association of the other compositional behaviours in the model, a permutation principle is used to construct multiple models. Where the other compositional behaviours are permed to follow a sequence in equivalent models with each behavioural activity intern transformed into ilr_{1i} and the associated coefficient β_1 interpreted accordingly [261]. The other sequential models will look like this:

Model B:

$$Y_{(Health\ outcome)i} = \beta_0 + \beta_1 Standing_i + \beta_2 Stepping_i + \beta_3 Sitting_i + Covariates_i \ldots\ldots (C6)$$

After ilr-transformed vector:

$$Y_{(Health\ outcome)i} = \beta_0 + \beta_1 ilr_{1i} + \beta_2 ilr_{2i} + Covariates_i \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (C7)$$

Where,

$$ilr_{1i} = \sqrt{\frac{2}{3}}\ \mathrm{In}\frac{Standing_i}{\sqrt[2]{Stepping_i \times Sitting_i}} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (C8)$$

$$ilr_{2i} = \sqrt{\frac{1}{2}}\ \mathrm{In}\frac{Stepping_i}{\sqrt[1]{Sitting_i}} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (C9)$$

Model C:

$$Y_{(Health\ outcome)i} = \beta_0 + \beta_1 Stepping_i + \beta_2 Sitting_i + \beta_3 Standing_i + Covariates_i \ldots (C10)$$

After ilr-transformed vector:

$$Y_{(Outcome)i} = \beta_0 + \beta_1 ilr_{1i} + \beta_2 ilr_{2i} + Covariates_i \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (C11)$$

Where,

$$ilr_{1i} = \sqrt{\frac{2}{3}}\ \mathrm{In}\frac{Stepping_i}{\sqrt[2]{Sitting_i \times Standing_i}} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (C12)$$

$$ilr_{2i} = \sqrt{\frac{1}{2}}\ \mathrm{In}\frac{Sitting_i}{\sqrt[1]{Standing_i}} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (C13)$$

The interpretations of Model B and Model C follow the same principle (as described for Model A), where β_1 in Model B indicates the relative strength of association of time spent in Standing to Stepping and Sitting with the predicted $Y_{(Health\ outcome)}$ and β_1 in Model C representing the strength of association of Stepping time relative to time spent in Sitting and Standing with predicted $Y_{(Health\ outcome)}$. Note, the parameters of the different fitted models, the R^2 and p-value, as well as β_0 and all covariates, are supposed to have the same output [261].

3.4.3.1 Compositional isotemporal reallocation modelling

Isotemporal substitution method is a novel statistical modelling technique used in physical activity behaviour epidemiology which was first described by Mekary and colleagues [266] in 2009. The modelling is based on fitting a multiple linear regression model with component time-use data (compositional data) as explanatory variables [264, 266]. The compositional data is treated as an absolute measure in the model. The group defined isotemporal substitution modelling as the estimation of the effect of substituting one type of behavioural activity with an equal amount of another behavioural activity on a predicted outcome. The substituted behavioural activity is taken out of the statistical model. For example, consider the time spent in each of the following behavioural activities – sedentary behaviour (e.g., Sitting), LIPA (e.g., Standing) and MVPA (e.g., Stepping), as well as the total behavioural activity (Total BA), which is all the behavioural activities time put together. Substituting time spend Sitting with Standing is done by removing Sitting from the model [266]. The regression equation for taking Sitting out from the model is expressed as:

$$Y_{(Outcome)} = \beta_0 + \beta_1 Standing + \beta_2 Stepping + \beta_3 Total\ BA + \beta_4 Covariates$$

Where,

$\beta_1 – \beta_4$ represent the respective coefficient of measured behavioural activities and the covariates adjusted for in the model. The behavioural activity eliminated, in this case, Sitting is represented by the coefficient (β_3) of Total BA in the model. The interpretation assumes that the coefficient of a given behavioural activity in the model is the result of substituting an equal amount of time for that behavioural activity instead of the eliminated behavioural activity (thus, Sitting) while holding constant the other behavioural activities remaining in the model [266, 267].

Generally, in a compositional data analysis framework, as described above, the behavioural composition coordinates that are modelled in the regression are often expressed in logarithm ratios which makes them challenging to make direct clinical interpretations of the effect sizes of the relative behavioural composition coordinates [261, 264]. With the incorporation of isotemporal substitution methods for hypothetical reallocations of the time-use compositions, they become more interpretable practically [268, 269]. The compositional isotemporal reallocation method (used in Study 4) applies the isotemporal substitution concept to interpret time-use composition regression parameters of reallocation of time

from/to one behavioural activity to/from other behavioural activity(ies) on health outcomes. The time can be reallocated by a one-to-one from one behaviour to another behaviour while holding all other behaviours in the composition constant at their mean value [268, 269]. Also, time can be reallocation from one behaviour and proportioned to the other behaviours in the composition. An example of compositional reallocation of time from sitting to other behaviours with predicted changes in pain intensity (outcome) is shown in Figure 3.4.

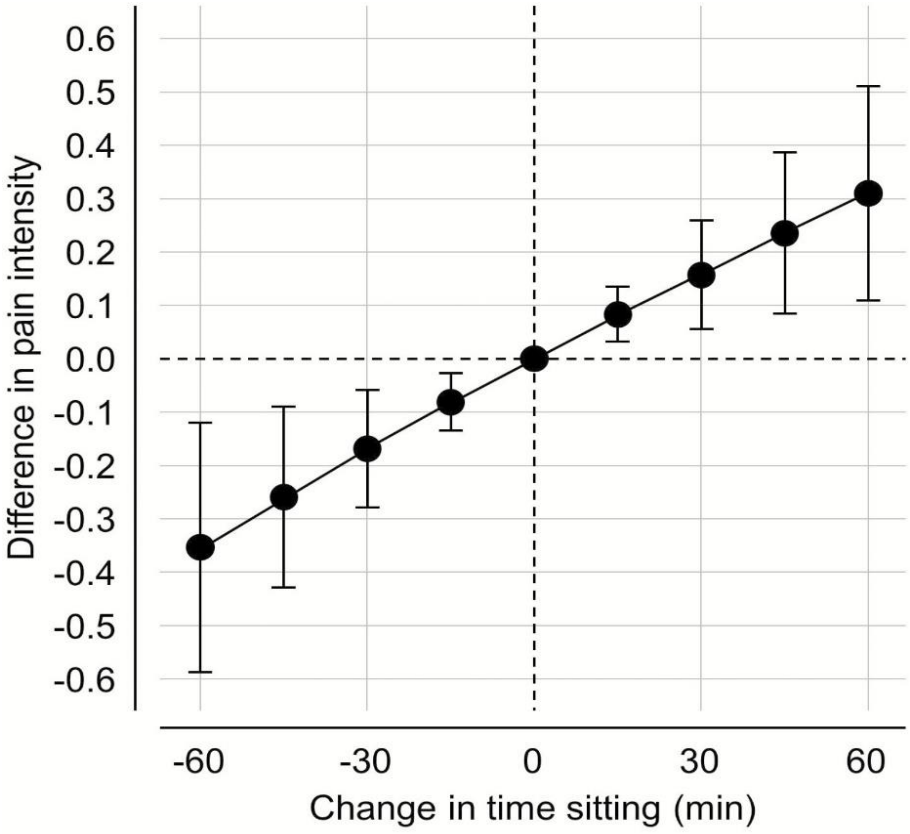

Figure 3.4: Compositional isotemporal reallocations and estimated health outcomes.

This illustrates the strength and direction of relationships of reallocating time from sitting to standing and stepping (x-axis) with low back pain intensity (y-axis). The zero on the x-axis represents the mean of the compositions and on the y-axis is the mean pain intensity. For example, the predicted pain intensity of reallocating 60 to standing and stepping from sitting is - 0.36 [95% CI (- 0.59 to - 0.12)]. The graph was taken from the publication of Gupta et al. [268]

Chapter 4: Study 2

4.1 Title:

Device-Measured Sitting Time and Musculoskeletal Pain in Adults with Normal Glucose Metabolism, Prediabetes and Type 2 Diabetes – The Maastricht Study

4.1.1 Purpose

The study used cross-sectional data to examine the associations of device-measured sitting time with MSP outcomes in adults according to glucose metabolism status (GMS) – normal glucose metabolism (NGM), prediabetes, and T2D. This study focussed on addressing some of the knowledge gaps identified in the review study [270]. The gaps included the paucity of device-measured sedentary time-based studies, as well as the lack of studies examining the association of sedentary behaviour with MSP conditions in people with T2D. Specifically, Study 2 utilised logistic regression models to examine the cross-sectional associations of device-measured daily sitting time with neck, shoulder, low back, and knee pain separately in those with NGM, prediabetes, and T2D using a large population-based observational dataset from community-dwelling middle-aged and older adults with and without T2D. Further, using the RCS modelling method, potential non-linear relationships were also examined.

4.2 The manuscript

The manuscript has been accepted and published in PLOS ONE. The contributions of the authors of this paper are provided in Appendix B1.2.

4.2.1 Citation

Dzakpasu FQS, Koster A, Owen N, de Galan BE, Carver A, Brakenridge CJ, Boonen A, Bosma H, Dagnelie PC, Eussen SJPM, Sethi P, Stehouwer CDA, Schaper NC, Dunstan DW. *Device-measured sitting time and musculoskeletal pain in adults with normal glucose metabolism, prediabetes and type 2 diabetes – The Maastricht Study.* PLoS One. 18(5): e0285276. https://doi.org/10.1371/journal.pone.0285276

4.2.2 Copy of the published manuscript – PDF

PLOS ONE

RESEARCH ARTICLE

Device-measured sitting time and musculoskeletal pain in adults with normal glucose metabolism, prediabetes and type 2 diabetes–The Maastricht Study

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Citation: Dzakpasu FQS, Koster A, Owen N, Galan BEd, Carver A, Brakenridge CJ, et al. (2023) Device-measured sitting time and musculoskeletal pain in adults with normal glucose metabolism, prediabetes and type 2 diabetes–The Maastricht Study. PLoS ONE 18(5): e0285276. https://doi.org/10.1371/journal.pone.0285276

Editor: Lex Verdijk, Maastricht University Faculty of Health, Medicine and Life Sciences: Maastricht Universitair Medisch Centrum+, NETHERLANDS

Received: October 6, 2022

Accepted: April 18, 2023

Published: May 4, 2023

Data Availability Statement: Data are unsuitable for public deposition due to ethical restriction and privacy of participant data. Data are available from The Maastricht Study for any interested researcher who meets the criteria for access to confidential data. The Maastricht Study Management Team (research.dms@mumc.nl) and the second author (co-author) A. Koster may be contacted to request data.

Abstract

Background

Detrimental associations of sedentary behaviour (time spent sitting) with musculoskeletal pain (MSP) conditions have been observed. However, findings on those with, or at risk of, type 2 diabetes (T2D) have not been reported. We examined the linear and non-linear associations of device-measured daily sitting time with MSP outcomes according to glucose metabolism status (GMS).

Methods

Cross-sectional data from 2827 participants aged 40–75 years in the Maastricht Study (1728 with normal glucose metabolism (NGM); 441 with prediabetes; 658 with T2D), for whom valid data were available on activPAL-derived daily sitting time, MSP [neck, shoulder, low back, and knee pain], and GMS. Associations were examined by logistic regression analyses, adjusted serially for relevant confounders, including moderate-to-vigorous intensity physical activity (MVPA) and body mass index (BMI). Restricted cubic splines were used to further examine non-linear relationships.

Funding: The Maastricht Study was supported by the European Regional Development Fund via OP-Zuid, the Province of Limburg, the Dutch Ministry of Economic Affairs (grant 310.041), 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 B.V. (Tilburg, the Netherlands), Novo Nordisk Farma B.V. (Alphen aan den Rijn, the Netherlands) and Sanofi-Aventis Netherlands B.V. (Gouda, the Netherlands). Dzakpasu was supported by the Australian Government Research Training Program Scholarship. Owen was supported by the National Health and Medical Research Council (NHMRC) of Australia through a Senior Principal Research Fellowships (#1003960) and by the Victorian Government's Operational Infrastructure Support Program. Dunstan was supported by an NHMRC Senior Research Fellowship (#1078360) and the Victorian Government's Operational Infrastructure Support Program. The funders played no role in the design, data analysis, and realization of this manuscript.

Competing interests: The authors have declared that no competing interests exist.

Results

The fully adjusted model (including BMI, MVPA, and history of cardiovascular disease) showed daily sitting time to be significantly associated with knee pain in the overall sample (OR = 1.07, 95%CI: 1.01–1.12) and in those with T2D (OR = 1.11, 95%CI: 1.00–1.22); this was not statistically significant in those with prediabetes (OR = 1.04, 95%CI: 0.91–1.18) or NGM (OR = 1.05, 95%CI: 0.98–1.13). There were no statistically significant associations between daily sitting time and neck, shoulder, or low back pain in any of the models. Furthermore, the non-linear relationships were statistically non-significant.

Conclusion

Among middle-aged and older adults with T2D, daily sitting time was significantly associated with higher odds of knee pain, but not with neck, shoulder, or low back pain. No significant association was observed in those without T2D for neck, shoulder, low back, or knee pain. Future studies, preferably those utilising prospective designs, could examine additional attributes of daily sitting (e.g., sitting bouts and domain-specific sitting time) and the potential relationships of knee pain with mobility limitations.

Introduction

Time spent sitting (sedentary behaviour) is associated with an increased risk of several adverse health outcomes, additional to the risks associated with insufficient levels of physical activity [1]. Specifically, there is evidence that higher volumes of daily sitting time are associated with all-cause mortality risk, along with increased risks of cardiovascular disease (CVD) and incident type 2 diabetes (T2D) [2–4].

Globally, the prevalence and burden of musculoskeletal pain (MSP)-related conditions are rising [5]. Also, there has been an increased focus on understanding the impact of MSP-related conditions as a comorbidity of T2D [6–8]. Some MSP conditions, for example, non-pyogenic tenosynovitis and stiff hand syndrome, are observed more common in those with diabetes [9]. Furthermore, neck, shoulder, low back, and knee osteoarthritic pain are well documented in those living with diabetes, particularly T2D [6–8, 10, 11]. T2D has also been linked with detrimental outcomes of some MSP conditions [7, 10]. Given that higher volumes of sitting time have been identified in those with T2D relative to those without T2D [12], sedentary behaviour could, in part, be a plausible contributor to MSP conditions in T2D [6, 13].

From a general population perspective, there is equivocal evidence on the relationships of sitting/sedentary time with MSP conditions in both cross-sectional and prospective studies [13–17]. High volumes of sitting time among some population cohorts, for instance, have been found to be associated with the increased risk of MSP conditions, such as low back pain, neck/shoulder pain, osteoarthritis, and general MSP [13, 14]. In contrast, studies have also documented either no evidence or inverse associations between sitting time and some MSP conditions [13, 15, 17]. In this context, the available evidence, most importantly those from population-based studies, has relied on self-report data on sitting time. There is limited evidence from studies using device-based measurement of sitting time, especially in large population-based samples; device-based studies have in the main utilised data from small subpopulations [13]. Also, it is unclear whether the relationships between sitting time and MSP conditions are linear or non-linear. Previous studies have mainly investigated the linear

relationships of sitting time with MSP conditions [13, 15, 17], with a paucity of studies reporting on potential non-linear relationships. Further, the associations of sitting time with MSP conditions in adults according to glucose metabolism status (GMS), and especially on unique associations in those living with T2D, are unknown. Some evidence indicates the relationship of increased time spent in sedentary behaviour with changing pain severity in adults may be more pronounced in those with T2D [18].

We examined the cross-sectional associations of device-measured total daily sitting time with MSP outcomes–neck, shoulder, low back, and knee pain–in a large population-based sample of middle-aged and older adults and then separately in stratified subgroups of those with normal glucose metabolism (NGM), prediabetes, and T2D; we further examined potential non-linear relationships.

Materials and methods

Design and participants

The data were sourced from The Maastricht Study, an observational prospective population-based cohort study. The rationale and methodology have been described previously [19]. Briefly, the study focuses on the aetiology, pathophysiology, complications, and comorbidities of T2D and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns and from the municipal registries and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known T2D status, with an oversampling of individuals with T2D, for reasons of efficiency [19].

For this cross-sectional study, 2827 participants from the full sample (N = 3451) who completed an initial survey between November 2010 and September 2013 –for whom there were data on musculoskeletal health, device-derived (activPAL) sitting time and physical activity, T2D status, and relevant covariates–were included in the analysis. The participants excluded were 126 without valid activPAL wear time, 24 with type 1 and other diabetes diagnoses, and 474 who had a missing variable of either exposure, outcome, or covariates. Little's test of missing completely at random was performed to check whether the exposure and outcome variables were missing at random, as well as the covariate-dependent missingness and ensured the assumptions were met before running the complete-case analysis [20]. Participant examinations were performed within a time window of three months. The study has been approved by the institutional medical ethical committee (NL31329.068.10) and the Minister of Health, Welfare and Sports of the Netherlands (Permit 131088-105234-PG). All participants gave written informed consent.

Measures

Outcomes–Musculoskeletal pain (MSP). Data were based on a self-reported questionnaire on musculoskeletal health (validated in a Dutch sample) [19], which was adapted from the United States population-based validated Health Assessment Questionnaire used in the National Health and Nutrition Survey (NHANES) [21]. Participants were asked whether they had at least one instance of experiencing pain (yes/no) for the past one month in the following 11 body regions–neck, shoulder, elbow, wrist, hand, low back, hip, pelvis, knee, ankle, and foot; excluding pain as a result of trauma. They were also asked to indicate whether a physician had made a diagnosis for the pain. For this analysis, a pain episode for at least one day in the past one month in the neck, shoulder, low back, and knee was considered.

Exposure–Daily sitting time. The activPAL3 physical activity monitoring device (PAL Technologies, Glasgow, UK) was used to continuously measure participants' sitting time, 24hr/day. The activPAL3 data collection, analytic processes, sitting time, and other physical activity time calculations have been described elsewhere [22]. Participants were instructed to wear the device for eight consecutive days without removing it until the final day. The first and the final days' data were excluded because participants performed physical function tests on the first day while wearing the device, and the final day's data were collected for less than 14-hours of waking time. Participants' data were eligible for inclusion in the analysis if they had at least one valid day (more than 14-hours of waking data) device wear time. Time spent sitting during wake time on valid days derived from the activPAL device was used to calculate the mean daily sitting time in hours per day.

Covariates. Self-reported history of T2D and a standard 2-hour oral glucose tolerance test (OGTT) were used to ascertain participants' GMS. Except for those with known T2D receiving insulin therapy who were captured by self-reported instrument, all other participants with unknown GMS underwent a standardised 7-time point OGTT after an overnight fast with 75g glucose ingestion, as described elsewhere [19]. World Health Organisation (WHO) criteria were used to categorise participants as NGM, prediabetes, and T2D [23]. Prediabetes was defined as impaired fasting glucose with fasting plasma glucose 6.1–6.9mmol/L and 2-hour postprandial plasma glucose less than 7.8mmol/L or impaired glucose tolerance with fasting plasma glucose less than 7.0mmol/L and 2-hour postprandial plasma glucose $\geq$7.8 and $<$11.1mmol/l. T2D was defined as fasting plasma glucose greater than 7.0mmol/L or 2-hour postprandial plasma glucose greater or equal to 11.1mmol/L [23], or known T2D and on glucose-lowering medications.

Moderate-to-vigorous intensity physical activity (MVPA) time was derived from the activPAL3 data as minutes with steps frequency more than 100 steps/min during waking hours as described elsewhere [24]. A general questionnaire was used to gather data for other covariates such as age, sex, level of education (categorised as low, medium, or high), and smoking status (never smoked, former smoker, current smoker). Participants' dietary quality score was assessed with a validated Food Frequency Questionnaire [25] from which a Dutch Healthy Diet index (DHD-index) was derived, which is based on Dutch dietary guidelines [26]. Body mass index (BMI) was calculated from the physical examination data. Mobility limitation was based on participants' self-report of any difficulty climbing one flight of stairs or walking 500 metres derived from the 36-item short-form health survey instrument. A self-reported history of CVD from the Rose questionnaire [27] was an additional confounding covariate.

Statistical analyses

The characteristics of the study population were examined by GMS categories (NGM, prediabetes, and T2D). Continuous variables were calculated and summarised as means and standard deviations with differences between the NGM, prediabetes, and T2D subgroups examined using linear regression models by regressing the continuous variables as the outcome against the GMS and significant difference tested by using testparm (post-estimation command); whereas categorical variables were summarised as proportions (percentages) and a chi-square test used to compare the groups' differences. To account for multiple-hypothesis testing in comparisons across the groups, a stringent p-value of < 0.01 was set as the significance level based on Bonferroni correction. Potential confounding variables were selected a priori based on prior literature. All statistical analyses were performed using STATA statistical software (StataCorp version 17), and the significance of associations in main analyses was considered at a p-value of ≤ 0.05 for the overall sample and those within the GMS groups.

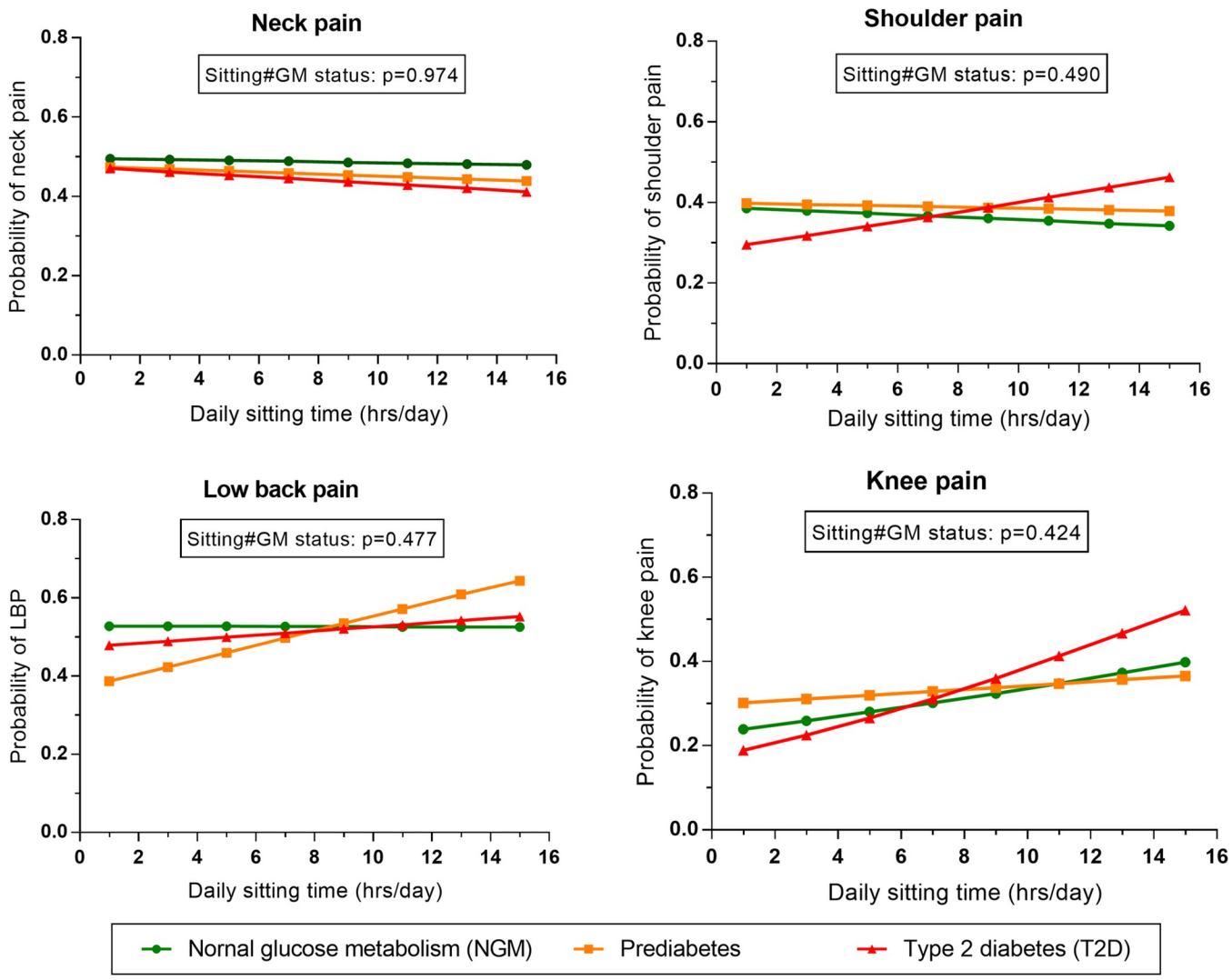

Fig 1. The predictive probability of the musculoskeletal pain outcomes with daily sitting time according to glucose metabolism status (GMS).

https://doi.org/10.1371/journal.pone.0285276.g001

First, to examine the association of total daily sitting time with the MSP outcomes (neck, shoulder, low back, and knee pain), we used logistic regression modelling and statistically checked the a priori decision to stratify the analysis by GMS. Multiplicative interaction between daily sitting time and GMS was modelled for the MSP outcomes in the overall sample, adjusting for age and sex with the margins command used to estimate the predicted probability of the MSP outcome and marginal plot (line graphs) used to interpret the potential interactions (Fig 1). For the main analysis, progressively adjusted multiple logistic regressions were modelled, regressing each of the MSP outcomes (yes-MSP/no-MSP) as the dependent (outcome) variable and daily sitting time as the independent (exposure) variable for the overall sample and separately for NGM, prediabetes, and T2D. The first model (model A) was adjusted for age and sex.

Second, the models were further adjusted for BMI and MVPA (Model B) to examine the attenuation effect on the direction of potential associations. Again, the fitted models were fully adjusted by adding some confounding variables, including socioeconomic variables (education

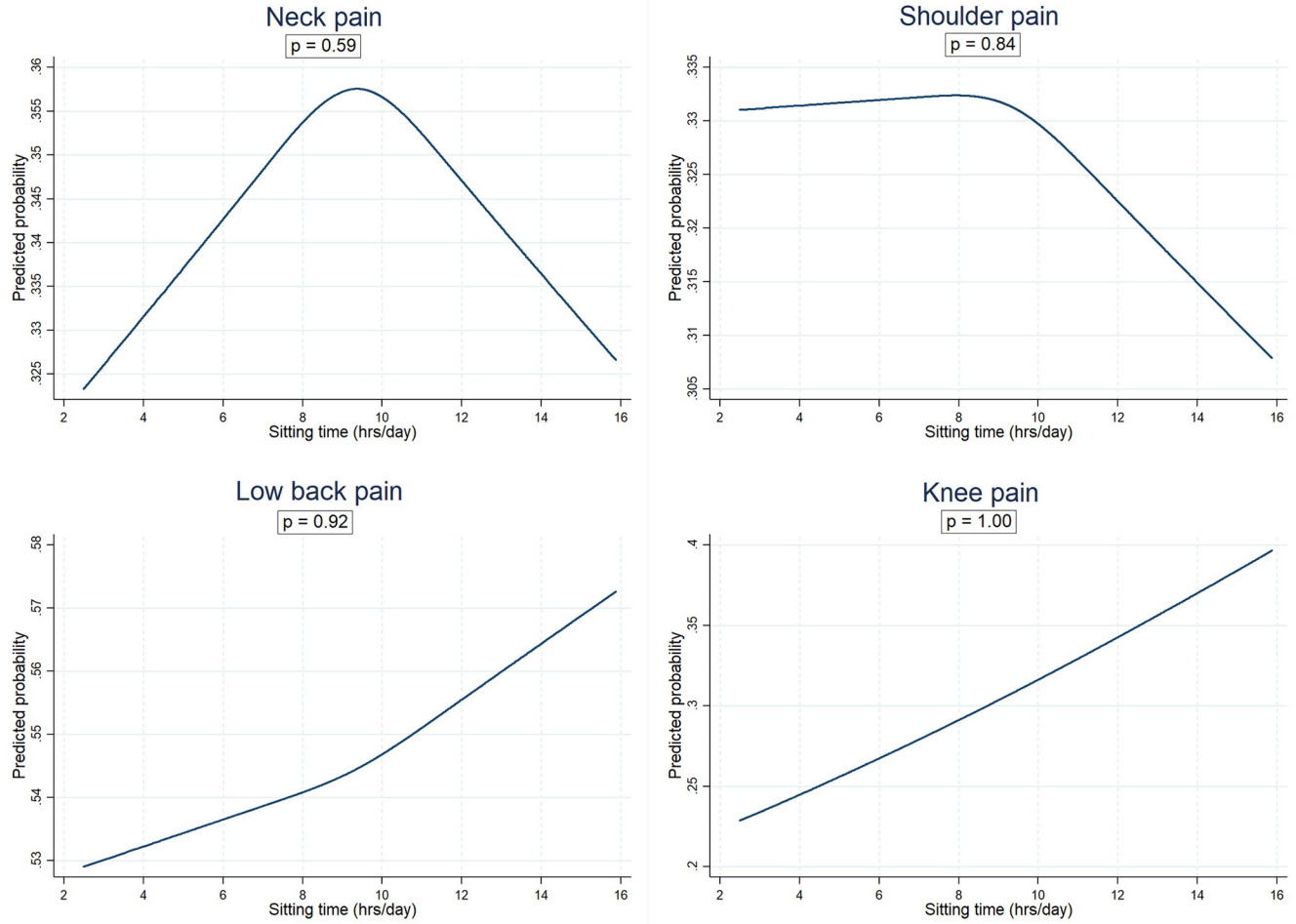

Fig 2. Non-linear relationships between daily sitting time and neck, shoulder, low back, and knee pain (overall sample with and without type 2 diabetes).

https://doi.org/10.1371/journal.pone.0285276.g002

level and employment status) and lifestyle variables (dietary quality score–DHD-index, and smoking status), as well as a history of CVD (Model C). Then, the robustness of the associations was examined by further adjusting for mobility limitation as a surrogate for other conditions that may predispose to excessive sedentary behaviour (Model D). Further, we examined the non-linear relationships of daily sitting time with the MSP outcomes using restricted cubic splines (RCS)–the most rigorous and flexible approach recommended for investigations of non-linear relationships [28, 29]. Three knots RCS (selected based on Akaike information criterion (AIC)–provided in the Supplementary file) were fitted (for the final fully adjusted models) and outputs were presented in line graphs (Fig 2 –for the overall sample and Supplementary S1 Fig in S1 File, as well as Supplementary S2a–S2d Fig in S1 File for the GMS subgroups–with scatter plots illustrations of distributions of the predicted probability of the MSP outcomes).

For sensitivity analyses, a multiplicative interaction of daily sitting time with sex was tested by modelling sitting time/sex interaction on the MSP outcomes. Also, we excluded all those with mobility limitations to check for the potential of reverse causality bias (25.9% of the total sample size) and re-ran the models.

The distributions of daily sitting with the MSP outcomes, as well as the linear and non-linear analytic models' fitness checks, are provided in the Supplementary file.

Results

Characteristics of the participants according to GMS are shown in Table 1. Those with T2D were relatively older, and on average, spent more hours sitting and fewer hours in MVPA compared to participants with pre-diabetes and NGM. Compared to those with NGM and prediabetes, those with T2D were more likely to be male, obese, have a history of CVD, and have mobility limitations.

As shown in Table 2, the body region with the highest prevalence of MSP was low back pain (52.8%) and the least prevalent was knee pain (34.2%). The prevalence of knee pain was marginally non-significantly higher ($p = 0.03$ –with the significance level set at $p < 0.01$ to account for multiple testing) in the T2D group compared to the prediabetes and NGM groups, whereas the prevalence of neck pain was significantly higher ($p < 0.001$) in those with NGM

Table 1. Characteristics of the study population.

Variables	Overall (N = 2,827)	NGM (N = 1,728)	Prediabetes (N = 441)	T2D (N = 658)	p-value
Demographic					
Age, mean (SD)	59.5 (8.6)	57.7 (8.5)	62.0 (8.1)	62.7 (7.9)	< 0.001
Sex					< 0.001
Female, n(%)	1,613 (57.1)	1,120 (64.8)	238 (54.0)	255 (38.7)	
BMI, mean. (SD), kg/m2	27.1 (4.6)	25.6 (3.8)	28.2 (4.4)	30.3 (5.0)	< 0.001
Socioeconomic status					
Education level					< 0.001
Low, n(%)	1,026 (36.3)	536 (31.0)	177 (40.1)	313 (47.6)	
Medium, n(%)	801 (28.3)	516 (29.9)	109 (24.7)	176 (26.8)	
High, n(%)	1,000 (35.4)	676 (39.1)	155 (35.2)	169 (25.7)	
Employment status					< 0.001
Unemployed, n(%)	1,579 (55.9)	848 (49.1)	275 (62.4)	456 (69.3)	
Employed, n(%)	1,186 (42.0)	842 (48.7)	155 (35.2)	189 (28.7)	
Other, n(%)	62 (2.2)	38 (2.2)	11 (2.5)	13 (2.0)	
Lifestyle					
Sitting time, mean(SD) hrs/day	9.2 (1.7)	9.0 (1.6)	9.2 (1.8)	9.9 (1.8)	< 0.001
MVPA, mean(SD) min/day	52.0 (25.4)	56.7 (25.2)	49.2 (23.3)	41.5 (23.8)	< 0.001
DHD-index score, mean(SD)	84.5 (15.1)	86.5 (14.7)	83.4 (14.8)	80.1 (15.1)	< 0.001
Smoking status					< 0.001
Never, n(%)	1,037 (36.7)	696 (40.3)	148 (33.6)	193 (29.3)	
Former, n(%)	1,433 (50.7)	825 (47.7)	245 (55.6)	363 (55.2)	
Current, n(%)	357 (12.6)	207 (12.0)	48 (10.9)	102 (15.5)	
Medical history					
CVD history					< 0.001
Yes, n(%)	493 (17.4)	240 (13.9)	69 (15.7)	184 (28.0)	
Mobility limitation					< 0.001
Yes, n(%)	732 (25.9)	318 (18.4)	136 (30.8)	278 (42.3)	

BMI: Body Mass Index | NGM: Normal Glucose Metabolism | T2D: Type 2 Diabetes | CVD: Cardiovascular Diseases | DHD-index: Dutch healthy diet index | Significance levels were set at p-value <0.01 to account for multiple-hypothesis testing across the groups.

For comparisons between the subgroups (NGM, prediabetes, and T2D)–continuous variables were examined by linear regression with post-estimation testparm; categorical variables were by chi-square test.

https://doi.org/10.1371/journal.pone.0285276.t001

Table 2. Prevalence of musculoskeletal pain outcomes according to glucose metabolism status (GMS).

MSP outcomes	Overall (N = 2,827)	NGM (N = 1,728)	Prediabetes (N = 441)	T2D (N = 658)	p-value
Neck pain	1,328 (47.0)	870 (50.4)	194 (44.0)	264 (40.1)	< 0.001
Shoulder pain	1,062 (37.6)	653 (37.8)	165 (37.4)	244 (37.1)	0.948
Low back pain	1,494 (52.8)	919 (53.2)	235 (53.3)	340 (51.7)	0.788
Knee pain	966 (34.2)	562 (32.5)	152 (34.5)	252 (38.3)	0.029

MSP: Musculoskeletal pain | NGM: Normal Glucose Metabolism | T2D: Type 2 Diabetes | Significance levels were set at p-value <0.01 to account for multiple-hypothesis testing across the groups.

Numbers indicate the frequency of MSP; numbers in brackets are percentages.

https://doi.org/10.1371/journal.pone.0285276.t002

than in the prediabetes and T2D groups. There were no statistical differences in the prevalence of shoulder or low back pain according to T2D status.

The interaction term for daily sitting time and GMS was not statistically-significant for any of the MSP outcomes. However, the plotted predicted probability shows that there may be interactions for shoulder, low back, and knee pain as the lines for NGM, prediabetes, and T2D appear to cross each other as daily sitting time increases. This seems not to be the case for neck pain which has the lines for the groups being parallel to each other. Thus, there are indications that there may be variations in the associations of daily sitting with some of the MSP outcomes by GMS (illustrated in Fig 1). Specifically for knee pain, as the volume of daily sitting time increased, the predicted probability of knee pain non-significantly increased, which was more apparent in those with T2D than in those without–prediabetes and NGM (knee pain–p for interaction = 0.424). The interaction models are provided in Supplementary S1 Table in S1 File.

Table 3 presents the progressively-adjusted logistic regression findings of the linear relationships of daily sitting time with MSP outcomes for the overall sample, and separately for those with NGM, prediabetes, and T2D. A statistically significant association of daily sitting time with MSP outcomes was observed only for knee pain. In the fully adjusted model, including demographic and socioeconomic confounders, as well as BMI, MVPA, and history of CVD, daily sitting time was positively associated with increased odds of knee pain (OR = 1.07, 95%CI: 1.01–1.12). In analyses stratified by GMS, the relationship was significant only in those with T2D (OR = 1.11, 95%CI: 1.00–1.22), but not for those with prediabetes (OR = 1.04, 95% CI: 0.91–1.18) or those with NGM (OR = 1.05, 95%CI: 0.98–1.13). The associations remained statistically-significant in the overall sample (OR = 1.06, 95%CI: 1.01–1.12) and marginally significant in the T2D group (OR = 1.10, 95%CI: 1.00–1.22) after adjusting for mobility limitation in the robustness test. A further sensitivity check showed that there was no significant interaction with sex (results not shown). The significant associations were attenuated after excluding those with mobility limitations from the analysis to check for reverse causation, but there were few changes in the trend of the associations (results provided in Supplementary S2 Table in S1 File).

There were no statistically significant associations in the overall sample or in the specific GMS groups between the daily sitting time and neck, shoulder, or low back pain in any of the models, as well as in the sensitivity tests and no significant sex interaction.

The non-linear relationships (in the overall sample with the p for non-linearity) are presented in Fig 2. Non-significant curvilinear relationships were observed for the association of daily sitting time with neck, shoulder, and low back pain, whereas the sitting time/ knee pain relationship was observed to be linear. For the subgroup analysis by GMS [results provided in Supplementary S2a–S2d Fig in S1 File], curvilinear relationships were observed in the NGM,

Table 3. Association of daily sitting time (hours/day) with musculoskeletal pain outcomes in the overall sample and separately in those with normal glucose metabolism, prediabetes, and type 2 diabetes.

MSP outcomes	N	Model A	Model B	Model C	Model D
		OR (95%CI)	OR (95%CI)	OR (95%CI)	OR (95%CI)
Neck pain					
Overall	2,827	0.98 (0.94–1.03)	0.99 (0.94–1.04)	1.00 (0.95–1.05)	1.00 (0.95–1.05)
NGM	1,728	0.99 (0.93–1.06)	1.00 (0.93–1.07)	1.01 (0.95–1.09)	1.02 (0.95–1.09)
Prediabetes	441	1.00 (0.89–1.11)	1.00 (0.89–1.13)	1.01 (0.89–1.14)	1.00 (0.89–1.14)
T2D	658	0.98 (0.89–1.07)	0.97 (0.88–1.08)	0.98 (0.89–1.08)	0.98 (0.88–1.08)
Shoulder pain					
Overall	2,827	1.01 (0.97–1.06)	0.99 (0.94–1.04)	0.99 (0.94–1.05)	0.99 (0.94–1.05)
NGM	1,728	0.99 (0.93–1.06)	0.98 (0.91–1.05)	0.99 (0.92–1.06)	0.98 (0.92–1.06)
Prediabetes	441	0.99 (0.89–1.11)	0.95 (0.84–1.08)	0.95 (0.84–1.07)	0.95 (0.84–1.07)
T2D	658	1.05 (0.96–1.15)	1.03 (0.93–1.13)	1.01 (0.92–1.12)	1.01 (0.91–1.12)
Low back pain					
Overall	2,827	1.02 (0.97–1.07)	1.01 (0.96–1.06)	1.02 (0.97–1.07)	1.01 (0.96–1.07)
NGM	1,728	0.99 (0.93–1.05)	0.99 (0.93–1.07)	1.00 (0.93–1.07)	0.99 (0.93–1.07)
Prediabetes	441	1.09 (0.97–1.21)	1.08 (0.96–1.22)	1.09 (0.97–1.23)	1.09 (0.97–1.24)
T2D	658	1.04 (0.95–1.13)	0.99 (0.90–1.09)	1.00 (0.90–1.10)	0.99 (0.90–1.09)
Knee pain					
Overall	2,827	**1.08 (1.02–1.13)**	**1.06 (1.01–1.12)**	**1.07 (1.01–1.12)**	**1.06 (1.01–1.12)**
NGM	1,728	1.06 (0.99–1.14)	1.05 (0.98–1.13)	1.05 (0.98–1.13)	1.05 (0.97–1.13)
Prediabetes	441	1.01 (0.90–1.13)	1.03 (0.91–1.17)	1.04 (0.91–1.18)	1.05 (0.92–1.19)
T2D	658	**1.11 (1.01–1.22)**	**1.10 (1.00–1.22)**	**1.11 (1.00–1.22)**	***1.10 (1.00–1.22)***[$]

Note: Complete-case analysis | The significant associations are shown in boldface ($p \leq 0.05$) | [$] $p = 0.055$ | MSP: Musculoskeletal pain | N: Sample size | NGM: Normal Glucose Metabolism | T2D: Type 2 Diabetes | OR: Odds ratio | CI: Confidence Interval.

Model A: Adjusting for age and sex. **Model B:** Adjusting for covariates in Model A + BMI and MVPA. **Model C:** Adjusting for covariates in Model B + Education level, employment status, smoking status, DHD-index, and history of cardiovascular disease. **Model D:** Adjusting for covariates in Model C + mobility limitations.

https://doi.org/10.1371/journal.pone.0285276.t003

prediabetes and T2D groups for all the MSP outcomes but were statistically non-significant, except for knee pain in the prediabetes group which showed a marginally significant non-linear relationship (p for non-linearity = 0.05).

Discussion

This study uniquely examined the cross-sectional associations of device-derived daily sitting time with MSP in different body regions, including neck, shoulder, low back, and knee pain in middle-aged and older adults, according to their GMS. We found evidence of a significant association of longer hours of daily sitting with higher odds of knee pain in a linear function after adjusting for relevant confounders including BMI, MVPA, and CVD; this remained after accounting for mobility limitations. The association was statistically significant only in those with T2D and not in the prediabetes or NGM groups. No significant associations were observed between daily sitting time and neck, shoulder, or low back pain in the overall sample or the analysis according to GMS–the NGM, prediabetes, or T2D group, as well as statistically non-significant non-linear relationships.

There is the potential for reverse causality bias within the type of cross-sectional analyses undertaken in our study. In this context, MSP could adversely impact physical function and mobility, especially in older adults [30, 31]. Chronic pain syndromes, for instance, are associated with several psychosocial factors which are often characterised by fear about using

affected joints [31]. This may result in progressive loss of physical functioning, impaired mobility, limited physical activity behaviours and excessive leisure-time sitting. Alternatively, MSP in older adults, especially in those with T2D, may contribute, in part, to high volumes of daily sitting time [12, 32]. For example, low back or knee pain that is secondary to T2D complications may plausibly lead to mobility limitations and subsequently, more time spent sitting. After excluding those participants with self-reported mobility limitation (about 25.9% of the total analysed sample; see Supplementary S2 Table in S1 File) from our analysis, the observed associations between daily sitting time and knee pain became non-significant, possibly reflecting loss of power, yet the observed trend remained unchanged. Furthermore, the prevalence of large amounts of time spent sitting is high in older adults, particularly so in those with chronic diseases, implying the potential for reverse causation [2, 12, 32]. There is evidence that suggests probable bidirectional associations between pain-related chronic conditions and higher volumes of sitting time [33].

This is one of the first studies to separately report on the associations of daily sitting time with MSP in those with and without T2D. Among the MSP outcomes investigated, we observed a higher prevalence of knee pain in the T2D group than in the prediabetes and NGM groups. Interestingly, a statistically-significant positive association with daily sitting time was observed only in those with T2D, which is assumed to be linearly related. While this finding may be biologically plausible, the statistically non-significant interaction of daily sitting with GMS in our analysis (Fig 1) limits the interpretation of this finding as indicating a significant difference in the association of daily sitting time with knee pain between those with T2D and prediabetes or NGM. The lack of a significant interaction may be due to several factors, including the wide variations in the sample sizes of the NGM, prediabetes, and T2D groups. Nevertheless, we observed that sitting time and knee pain may be non-linearly related in the prediabetes group (Supplementary S2d Fig in S1 File). The evidence on the association between T2D and MSP-related conditions such as knee osteoarthritis has been documented [7, 10]. For example, evidence from a meta-analysis indicates that the odds of incidence and progression of osteoarthritis (mostly of the knee) are higher in those with T2D [7]. This evidence is supported by the findings in the placebo arm of a randomised controlled trial in patients with osteoarthritis, in which the presence of T2D increased the risk of progressive knee joint narrowing [10]. To date, no study has documented the association between sitting time and knee pain in those with T2D. Nevertheless, a population-based study of Korean adults over 50 years has documented a positive cross-sectional association of self-reported daily sedentary behaviour (sitting time) above 10hrs/day with knee pain [34].

The mechanisms underlying MSP conditions in T2D are not well understood; however, they likely involve a complex set of factors associated with T2D, including older age, obesity, and the systemic effect of persistent hyperglycaemia [35, 36]. For instance, mechanisms of knee osteoarthritis in T2D [36] may include biomechanical joint load and systemic inflammatory pathways related to older age and obesity along with those related to hyperglycaemia, including advanced glycation end products (AGEs) and their receptor (RAGE) interaction pathway, as well as reactive oxygen species (ROS) pathway which enhances secretion of pro-inflammatory factors. Collectively, these may contribute to oxidative stress and inflammation processes that promote vascular endothelial dysfunction and joint cartilage degradation [36–38]. In this context, it is relevant to note that our statistical models controlled for BMI. Behavioural factors, including sedentary behaviour may in part contribute to, or augment, some of these potential mechanisms through some of the known cardiometabolic consequences of time spent sitting [39, 40].

There is some supporting evidence from acute experimental studies [39, 41] and observational studies [40, 42] that sedentary time may be unfavourably associated with cardiometabolic biomarkers such as dyslipidaemia, hyperglycaemia, insulin resistance, and vascular

endothelial dysfunctions in T2D. Also, an association between higher volumes of sedentary time and unfavourable levels of systemic inflammatory biomarkers in adults living with T2D has been observed [43, 44]. Thus, sedentary behaviour may potentially have some links to the plausible biological pathways of T2D/MSP associations. This may be possible through the influence of sedentary behaviour on insulin resistance, hyperglycaemia, and dyslipidaemia mediating inflammatory changes and impaired blood flow in joints leading to articular surface cartilage degradation [36–38]. In support of this, an epidemiological cross-sectional study observed that an increased prevalence of low back pain in people with T2D was also associated with self-reported sedentary behaviour [6]. Furthermore, there is evidence from a prospective study that higher volumes of sedentary behaviour are associated with increased severity of bodily pain, which is significantly more apparent in people living with T2D [18]. Our observed cross-sectional association of daily sitting time with knee pain in those with T2D after accounting for the confounding bias of BMI, MVPA, and CVD may also support the notion that cardiometabolic and systemic inflammatory effects of sedentary behaviour, which is more pronounced in people with T2D [45, 46], may, in part, play some role in the pathogenesis of knee pain in T2D. However, with our relatively small effect size cross-sectional finding, potential residual confounding effects and reverse causation could be also likely.

We did not observe significant associations between daily sitting time and neck, shoulder, or low back pain in any of the GMS groups. There is an indication that the relationship between sitting time and neck, shoulder, or low back pain may not necessarily be linear but rather curvilinear; however, the observed curvilinear relationships in our study were statistically non-significant (Fig 2). Studies are yet to specifically investigate the associations of daily sitting time/ sedentary behaviour with MSP separately in people with T2D, prediabetes, or NGM, making direct comparison challenging. Previous evidence on these associations, mostly from heterogeneous populations and for diverse sedentary behaviour domains, has been inconsistent [15, 16, 47]. Studies have documented inconsistent evidence on associations of sitting time/ sedentary behaviour with MSP-related outcomes, including neck/shoulder, or low back pain [48–51]. Our findings are consistent with those of a prospective analysis of the Danish Health Examination Survey Cohort 2007–2008 data that showed that self-reported daily sitting time of 10hrs/day or more was not associated with low back pain [51]. In contrast, some Danish studies of tradespeople have reported positive cross-sectional associations of Actigraph-derived daily sedentary time with low back pain [48] and neck/shoulder pain intensity [50]. Similarly, a study of Korean adults aged over 50 years found cross-sectional evidence that self-reported daily sitting time of more than 7hrs/day was associated with low back pain [49].

Several factors may account for the differences between our findings and those of others. Notably, differences in the instruments used to estimate daily sitting/ sedentary time are evident. Body-worn devices provide greater accuracy for estimating sitting time, specifically, the thigh-worn activPAL device used in our study is known to have higher accuracy than the Actigraph device (which primarily detects sitting time) [52, 53]. Self-report measurement instruments, on the other hand, are based on subjective estimates of sitting time or sedentary behaviours and are prone to higher levels of bias [52–54]. The inconsistencies in the evidence may also reflect that the mechanisms that underpin MSP may be complex and differ with respect to the body part involved. Also, heterogeneity in the MSP assessment (acute or chronic pain) among these studies may partly explain the differences.

Strengths and limitations

The strengths of our study include using the activPAL device to measure daily sitting time, the gold standard research instrument for accurately assessing sitting or lying postures [52, 54],

and the large sample size with a substantial number of participants with T2D, which allowed stratified analyses according to GMS. Further, we examined the association in different MSP outcomes, providing the opportunity to compare the associations of daily sitting time with different MSP outcomes by GMS in the same dataset.

Study limitations include the cross-sectional design which precludes causal inference, and as previously referred to, there is also the potential for reverse causation among the observed associations. Furthermore, the participants' mean daily sitting time was derived from one-week wear of the activPAL data, and participants were included in the analysis if there was at least one valid day of device-wear time. This may not reflect the studied participants' true habitual daily sitting behaviour. In addition, aside from the confounders for which we adjusted, there may be other unmeasured confounders, such as occupational physical activity behaviours which were not accounted for in the analyses. Also, there is no universally accepted measure of musculoskeletal pain for epidemiological studies. The MSP assessment tool used in our study has limitations inherent to self-report instruments, including that the inclusion of data from some "high reporters" of pain may bias the findings [55, 56]. Also, the assessment of acute MSP (at least one instance of experiencing pain for the past one month) might be too sensitive, with lower specificity to effectively discriminate MSP among the participants, thereby masking the potential associations.

Implications for research and practice

Our findings may provide new insights for future research and clinical implications. The primary focus of this study was to better understand the associations of total volumes of daily sitting time with MSP; however, it is well recognised that sitting time is accumulated across multiple domains (at home, work, leisure, or commuting in a vehicle) which could be of public health interest [57]. For instance, recent evidence suggests that the associations of domain-specific sitting time (e.g., time spent sitting in a car or at a workstation desk) with adverse health outcomes may be more important than just the total volume of sitting/ sedentary time accumulated during the whole day [58, 59]. Moreover, there is evidence that indicates that the association between sitting time and MSP may be influenced by factors of occupational environment structures [13]. For example, high sitting time in tradespeople who engage in labour-intensive work may be inversely associated with neck and low back pain [15], whereas it may be associated with more neck/shoulder and low back pain in office-based workers [13]. Studies have also reported differences in the associations of leisure-time and occupational sitting time with MSP, as well as the pattern of accumulation of the sitting time with MSP [17, 48].

Future studies, preferably utilising prospective designs could focus on investigating the associations of domain-specific sitting time and the pattern of sitting (sitting bouts) with MSP according to GMS in different occupational groups. The association of daily sitting time with knee pain could be explored by examining the association of sitting bout duration with knee pain to better understand sitting patterns that are more likely to be adversely associated with knee pain, especially in those living with T2D. Also, the composition of daily sitting time relative to time spent stepping and standing in relation to MSP-related conditions, particularly with knee pain according to GMS and potential associated mobility limitations could be examined in future studies. Furthermore, studies could examine MSP-related conditions as exposures that may influence sitting behaviour outcomes, as well as the potential interaction role of GMS in such relationships.

Notwithstanding the potential for reverse causality, these findings suggest that some MSP conditions, specifically knee pain, may also be added to the numerous adverse health outcomes that have been shown to be detrimentally associated with higher volumes of sitting time [2, 60].

Accumulated evidence indicates that interrupting prolonged sitting time with, at least, light-intensity physical activity breaks such as standing or light-walking may induce health benefits [61, 62]. This has prompted new recommendations to replace sedentary time with physical activity of any intensity within the 2020 World Health Organisation physical activity and sedentary behaviour guidelines [63], and within the American Diabetes Association guidelines to specifically improve glycaemic management in people with T2D and prevent T2D in those at risk [64]. Our findings suggest that there may be further benefits for people living with T2D, especially middle-aged and older adults with coexisting MSP-related conditions [65, 66].

Conclusion

In this study, we observed that device-assessed daily sitting time was associated with higher odds of knee pain in middle-aged and older adults with the association being most evident in those with T2D. There were no significant associations with neck, shoulder, or low back pain. The non-linear relationships of sitting time with the MSP outcomes were statistically non-significant. Further studies, using prospective study designs, should focus on examining the potential associations (linear and non-linear) of domain-specific sitting time (including leisure time, work, and transport) and of sitting bout patterns with knee pain and other MSP-related conditions according to GMS. This will help better understand whether particular thresholds of daily sitting time are associated with an increased risk of future knee pain, as a basis for future intervention trials to reduce time spent sitting, particularly in the context of mobility limitations for those with T2D.

Supporting information

S1 File.
(PDF)

Author Contributions

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4.3 Summary and implications of the findings in the thesis

The findings indicate those with T2D accumulated higher volumes of daily sitting time than those without. A higher volume of activPAL-derived daily sitting time was observed to be associated with increased odds of knee pain; a statistically-significant association in only those with T2D, but not in those with prediabetes or NGM. There were no statistically significant associations observed for neck, shoulder, or low back pain in the overall sample nor by the glucose metabolism status (GMS). In the overall study sample, while the relationship of daily sitting time with knee pain appears to be in a linear function, it was observed to be statistically non-significant curvilinear for neck, shoulder, and low back pain. The non-linear relationships according to GMS were observed to be curvilinear for the MSP outcomes (neck, shoulder, low back, and knee pain) in NGM, prediabetes, and T2D; however, these relationships were statistically non-significant, except for knee pain in those with prediabetes which was observed to be marginally significant ($p = 0.05$).

This study is among the first to examine the associations of sedentary behaviour (device-measured daily sitting time volumes) with MSP outcomes separately in those with T2D, prediabetes and NGM, providing some implications for research and practice. Daily sitting volumes are often accumulated in different domains and understanding the relationships of domain-specific sitting time with MSP outcomes could provide insights relevant to potential intervention targets. Also, sitting is often accumulated in sporadic short bouts as well as prolonged static bouts. The differences in the accumulation of sitting-bout patterns could be of interest in the context of understanding MSP outcomes; therefore, a potential research area for future exploits. Additionally, the potential biological mechanisms and the mediators of the association between sitting time and knee pain in T2D could be explored in future studies, preferably using prospective study designs. Furthermore, despite the potential for reverse causality bias of the cross-sectional design, the observed adverse association with knee pain of high volumes of daily sitting time is an important contribution to the growing evidence on detrimental associations between sedentary behaviour and health outcomes, especially in those with cardiometabolic disorders such as T2D [37, 198, 271]. Therefore, there is an indication from the findings that public health strategies that ensure adherence to physical activity and sedentary behaviour guidelines may be of further benefit to people living with T2D, especially in middle-aged and older adults with coexisting T2D and MSP conditions [272-274].

The main contribution of this study to the thesis is the evidence of cross-sectional associations between device-measured daily sitting time and MSP outcomes in those with and without T2D. The cross-sectional design being a key limitation, the next two empirical studies build on this study by analysing longitudinal data to examine the evidence of prospective relationships of sedentary behaviour with outcomes of MSP conditions. Chapter 5 presents Study 3 which examined the prospective relationships of sedentary behaviour (self-reported TV time) with MSP conditions-related outcomes (bodily pain) in middle-aged and older adults with and without T2D.

Chapter 5: Study 3

5.1 Title:

Television-Viewing Time and Bodily Pain in Australian Adults with and without Type 2 Diabetes: 12-Year Prospective Relationships

5.1.1 Purpose

This empirical study addresses some of the knowledge gaps identified from the systematic review [270], as well as further extends the findings from Study 2 [275] by presenting prospective data on adults with and without T2D. Specifically, it focussed on addressing the paucity of prospective studies and the potential T2D moderation of the relationships of sedentary behaviour with MSP conditions by examining the prospective evidence of relationships between sedentary behaviour (TV time) and bodily pain trajectories (pain-related to MSP conditions) in adults with and without T2D using longitudinal data over a 12-year period. The study utilised the robust multilevel growth curve statistical method to analyse a large nationwide population-based longitudinal dataset from community-based middle-aged and older adults with and without T2D (the AusDiab Study). The study adds to this thesis original evidence of prospective associations of increasing a common leisure-time sedentary behaviour in home settings – time spent sitting watching television – with the severity of MSP-related pain outcome (bodily pain); further, it provides an insight into the potential moderation effect of the presence of T2D on such relationships.

5.2 The manuscript

The manuscript has been published in BMC Public Health. The authors' contributions to this manuscript are provided in Appendix B1.3.

5.2.1 Citation

Dzakpasu FQS, Owen N, Carver A, Sethi P, Brakenridge CJ, Salim A, Urquhart DM, Cicuttini F, Dunstan DW. *Television-viewing time and bodily pain in Australian adults with and without type 2 diabetes: 12-year prospective relationships.* BMC Public Health. 2022 Nov 29;22(1):2218. https://doi.org/10.1186/s12889-022-14566-y

5.2.2 Copy of the published manuscript – PDF

BMC Public Health

RESEARCH

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Television-viewing time and bodily pain in Australian adults with and without type 2 diabetes: 12-year prospective relationships

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Abstract

Background: Bodily pain is a common presentation in several chronic diseases, yet the influence of sedentary behaviour, common in ageing adults, is unclear. Television-viewing (TV) time is a ubiquitous leisure-time sedentary behaviour, with a potential contribution to the development of bodily pain. We examined bodily pain trajectories and the longitudinal relationships of TV time with the bodily pain severity; and further, the potential moderation of the relationships by type 2 diabetes (T2D) status.

Method: Data were from 4099 participants (aged 35 to 65 years at baseline) in the Australian Diabetes, Obesity and Lifestyle Study (AusDiab), who took part in the follow-ups at 5 years, 12 years, or both. Bodily pain (from SF36 questionnaire: a 0 to 100 scale, where lower scores indicate more-severe pain), TV time, and T2D status [normal glucose metabolism (NGM), prediabetes, and T2D] were assessed at all three time points. Multilevel growth curve modelling used age (centred at 50 years) as the time metric, adjusting for potential confounders, including physical activity and waist circumference.

Results: Mean TV time increased, and bodily pain worsened (i.e., mean bodily pain score decreased) across the three time points. Those with T2D had higher TV time and more-severe bodily pain than those without T2D at all time points. In a fully adjusted model, the mean bodily pain score for those aged 50 years at baseline was 76.9(SE: 2.2) and worsened (i.e., bodily pain score decreased) significantly by 0.3(SE: 0.03) units every additional year (p <0.001). Those with initially more-severe pain had a higher rate of increase in pain severity. At any given time point, a one-hour increase in daily TV time was significantly associated with an increase in pain severity [bodily pain score decreased by 0.69 (SE: 0.17) units each additional hour; p <0.001], accounting for the growth factor (age) and confounders' effects. The association was more-pronounced in those with T2D than in those without (prediabetes or NGM), with the effect of T2D on bodily pain severity becoming more apparent as TV time increases, significantly so when TV time increased above 2.5 hours per day.

Conclusion: Bodily pain severity increased with age in middle-aged and older Australian adults over a 12-year period, and increments in TV time predicted increased bodily pain severity at any given period, which was more pronounced in those with T2D. While increasing physical activity is a mainstay of the prevention and management of chronic health problems, these new findings highlight the potential of reducing sedentary behaviours in this context.

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Keywords: Bodily pain trajectory, Chronic pain, Growth curve model, Prediabetes, Sedentary behaviour, TV time, Type 2 diabetes

Background

Bodily pain increases with age and can be of somatic, visceral, or neurogenic origin [1, 2]. Among Australian adults aged 45-years and over, it has been estimated that 20% experience persistent chronic pain [3]. The challenges to clinical management and public health implications of chronic pain are substantial and often associated with multimorbidity, including diabetes and cardiovascular disease (CVD). Furthermore, those with diabetes can be more likely to be hospitalized for musculoskeletal pain-related conditions [4]. Chronic pain impacts adversely on daily physical activity and quality of life; can be associated with physical and mental health problems; and, substantially contributes to healthcare costs and the economic burden of lost productivity [5].

The prevalence and burden of chronic pain both increase with advancing age and as physical activity participation declines [6]. Chronic pain can be associated with older adults being physically inactive and large amounts of time sitting. While changes in physical activity with advancing age have been studied extensively [7, 8], recent research attention has been directed at increases in sedentary behaviour (which is distinct from physical inactivity, and defined as time spent in a sitting or reclining posture with energy expenditure less than 1.5METs) [9]. Higher volumes of sedentary time can be associated with increased risk of all-cause mortality, incident CVD, type 2 diabetes (T2D), and some cancers [10–13]. Specifically, one of the most common leisure-time sedentary behaviours – television-viewing (TV) time – has been consistently shown to be associated with multiple adverse chronic health outcomes [12–16], providing a simple, self-report indicator of a common domain-specific sedentary behaviour in community-based adults in the home settings [17].

There is evidence of detrimental associations of higher volumes of TV time with the risk of developing chronic diseases such as CVD, T2D, musculoskeletal disorders, and some cancers which is important in this context [10, 13, 15], as well as an adverse impact on physical activity levels in ageing adults [18]. However, there is limited evidence on the influence of prospective changes in TV time on bodily pain trajectories with ageing.

In epidemiological studies of sedentary behaviour and pain, the 36-Item Short-Form Health Survey (SF-36) questionnaire [19] has been commonly used, with mixed evidence on associations with bodily pain scale scores [20, 21]. To date, only a few prospective studies, typically in small subgroups of adults, have investigated longitudinal associations between TV time and pain, with inconsistent findings [21, 22]. Large cohort studies are yet to examine prospective relationships of changes in TV time with bodily pain trajectories. Further, the effects of sedentary behaviour can be more pronounced in those with metabolic disorders, particularly in T2D which is a major risk factor of CVD [23–25]. For example, a review of experimental and intervention-trial evidence has shown that reducing sedentary behaviour can beneficially impact cardiometabolic and inflammatory biomarkers associated with T2D [25]. Also, T2D has been shown to be associated with heightened chronic pain conditions, especially neuropathic pain [26–28]. Since studies have also shown that sedentary time is more pronounced in those with T2D compared to those without [29], there is a need to better understand the convergence of high sedentary time with T2D on trajectories of bodily pain. Specifically, it is unknown whether the potential influence of TV time on prospective changes in bodily pain differs according to the presence or absence of T2D.

We examined the longitudinal relationships of concurrent changes in TV time with bodily pain at three observation points over 12 years in Australian adults who were middle-aged and older at baseline; and, whether such potential relationships may be moderated by T2D status. We hypothesized that bodily pain severity would increase with age. Also, increasing TV time would be associated with increased severity of bodily pain at any given time point, and the strength of the association would differ between those with T2D and those without T2D.

Methods

Study sample and participant selection

The Australian Diabetes, Obesity, and Lifestyle Study (AusDiab), a general population-based study of community-dwelling Australian adults aged ≥25 years to describe diabetes prevalence and cardiometabolic risk markers, was initiated in 1999/2000 (baseline – Wave 1), with two subsequent follow-ups in 2004/05 (Wave 2) and 2011/12 (Wave 3). Description of the study design and participants has been published elsewhere [30]. Initially, baseline data (n = 11,247) were collected from adults residing in 42 Australian Bureau of Statistics Census Collector District (CCD) across all States and the Northern Territory. Those with physical or intellectual disabilities were not included [30]. The first follow-up at five years (n = 8798), was undertaken in 2004/05; and the second

follow-up at 12 years (n = 6,186), in 2011/12 as detailed elsewhere [31, 32]. At each respective time point, interviewer and self-administered questionnaire data, as well as biomedical data, including physical examination, urine and blood samples were collected at a local testing site [30–32]. The study was approved by the International Diabetes Institute (now Baker Heart and Diabetes Institute) Ethics Committee and the Alfred Ethics Committee, project approval no. 39/11.

For this analysis, we considered the middle-aged and older participants aged 35 to 65 years with and without T2D at baseline. This was based on recent findings reported by the Australian Institute of Health and Welfare suggesting that one in five Australian adults aged 45 years and over live with chronic pain with physical inactivity, smoking, overweight, and obesity as the likely associated behavioural risk factors [3]. Those with type 1 diabetes, a history of current bone fracture, and women who were pregnant were excluded from the analyses. Initially, the 4099 participants who were considered for inclusion in these analyses had complete data for the outcome, exposure, and all relevant covariates variables at baseline and at least one instance of follow-up data for SF-36 bodily pain, TV time, leisure-time physical activity, and T2D status. Among these participants, a total of 223 participants were categorised as having T2D based on self-reported T2D status (101) and a newly clinically determined T2D status (122) based on a fasting blood glucose test or 2-hour oral glucose tolerance test (OGTT); 691 as prediabetes [impaired fasting glucose (IFG) or impaired glucose tolerance (IGT)]; and 3,185 as normal glucose metabolism (NGM). The total number of participants included in the analysis based on our selection criteria and those excluded at baseline, as well as the number remaining and those loss-to-follow-up at the 5-year and 12-year time points are illustrated in a flowchart in Fig. 1.

Variables

Outcome: bodily pain

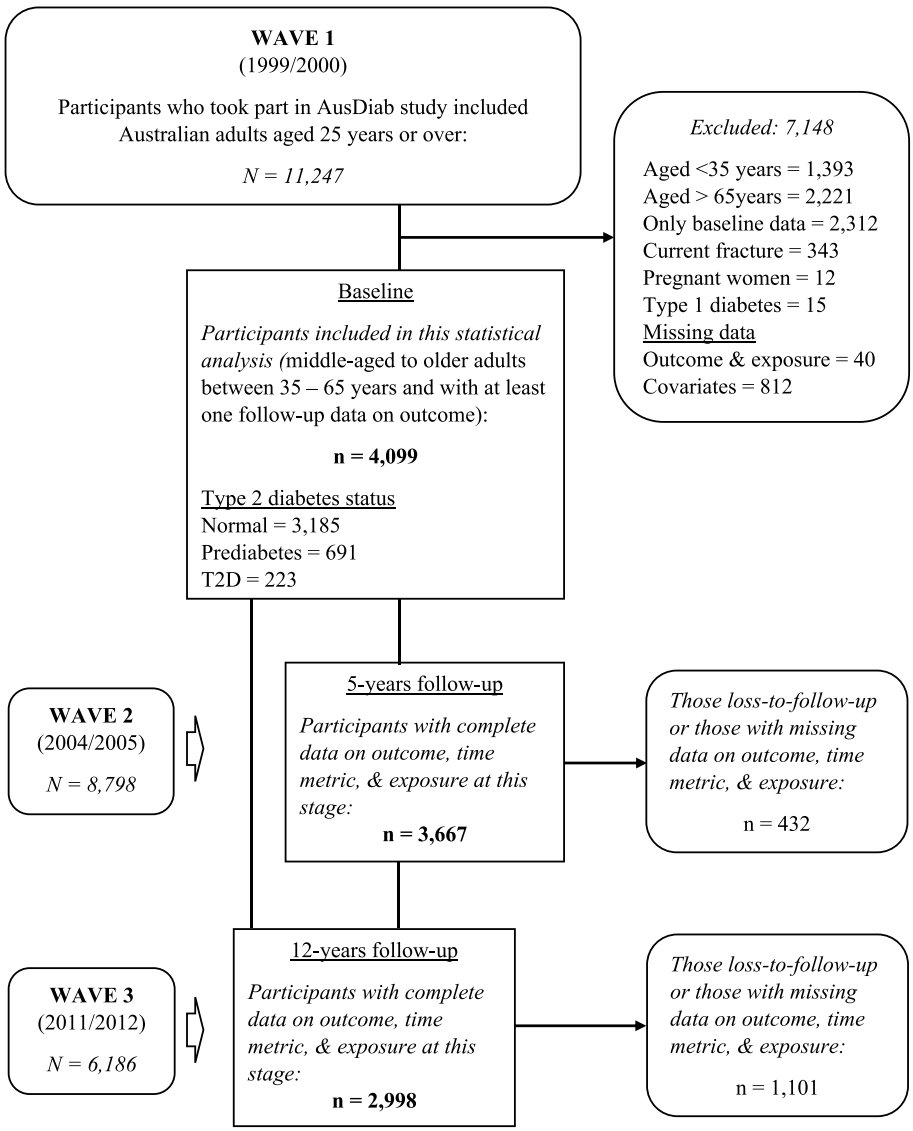
The bodily pain scores were derived at all data time-points from the validated 36-item Short Form (SF-36) self-report survey instrument for assessing health-related quality of life (HRQoL) [19, 33]. Two of the SF-36 items (items 7 and 8) measure bodily pain dimensions - the intensity and the extent of interference with daily activity (based on a standard SF-36 questionnaire 4-week recall of chronic/persistent pain) [19, 34]. Item 7 asked: "How much bodily pain have you had during the past 4 weeks?" with the response options: "1 = None; 2 = Very mild; 3 = Mild; 4 = Moderate; 5 = Severe; 6 = Very severe". Item 8 asked: "During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?", and the options were: "1 = Not at all; 2 = A little bit; 3 = Moderately; 4 = Quite a bit; 5 = Extremely". A validated scoring algorithm was used to transform the two items' responses into a single bodily pain score on a 0 to 100 scale [19], whereby the lowest possible score of "0" indicates severe bodily pain and the highest possible score of "100" indicates no bodily pain [33]. The accuracy of the SF-36 instrument to estimate HRQoL is high, with acceptable psychometric properties across all the measured dimensions in different demographic, health-related behaviour risk factors, and socioeconomic population groups in Australia [35]. A validation study in Australia indicated the 2-item bodily pain dimension has a high homogeneity (item-correction = 0.95) and internal consistency (Cronbach alpha = 0.90) [35].

Exposure: television-viewing time

The main explanatory variable (time spent watching television – TV time) was assessed at each time point. Participants self-reported total time spent on each weekday and weekend day watching television or video/DVD for the past week, excluding times when the television was switched on, but other leisure-time activities were being concurrently undertaken [12]. The total daily TV time was estimated by averaging the duration of TV time across seven days (the five weekdays and two weekend days) in hours. Psychometric studies indicate that this measure of TV time has acceptable properties in adults, with moderate-to-high validity and reliability, with a test-retest reliability intraclass correlation coefficient (ICC) of 0.66 (95% CI = 0.50 – 0.83) [17] and a Spearman correlation of 0.3 for a 3-day behavioural log criterion validity [36].

Moderator: type 2 diabetes status

T2D status was ascertained from self-reported data at baseline for known diabetes and by clinical diagnosis based on the standard recommended World Health Organisation (WHO) fasting blood/plasma glucose (FBG) test and 2-hour OGTT at each data time-point [37]. The T2D status variable was grouped into four categories (NGM, prediabetes, new T2D, and known T2D). The newly diagnosed T2D at each wave became known T2D at the subsequent wave. T2D was defined as FBG greater than 7.0 mmol/L or 2-hour OGTT greater than 11.1mmol/L. Prediabetes was defined according to the American Diabetes Association (ADA) criteria as IFG if FBG was in the range of 5.6 – 6.9 mmol/L or IGT if 2-hour OGTT fell in the range of 7.8 –11.0 mmol/L; NGM was defined as FBG less than 5.6 mmol/L and 2-hour OGTT less than 7.8 mmol/L [37]. If there were missing data on any one of the assessment methods



Note: Participants were not excluded at follow-ups if they had missing variable data. Those missing data were treated as missing at random by the growth curve analytic model.

Fig. 1 A flowchart diagram of participants at baseline and consecutive follow-ups

(either FBG or 2-hour OGTT), the classification of NGM was based on the non-missing data.

Covariates

Potential confounding time-invariant variables (attributes that varied between participants but remained unchanged at the data time-points) included sex and education level were captured only at baseline. Additionally, time-variant confounders which differed between participants, and also changed within participants at the data time points were considered. These included participants' age, and waist circumference measured in centimetres (cm). Further, leisure-time physical activity time was assessed using the Active Australia Survey (AAS) instrument [38] to capture participants' time spent in moderate-to-vigorous intensity physical activity (MVPA) at the three-time points. The AAS predominantly measures leisure-time physical activity according to the domain in which it took place and includes time spent walking for transport and leisure; moderate-intensity physical activity; and vigorous-intensity physical activity in the past week. The total physical activity time

was estimated as the sum of time spent walking continuously for 10 or more minutes for transport or recreation plus time spent in moderate-intensity physical activity plus twice the time spent in vigorous-intensity physical activity. The calculation also accounts for higher energy expenditure associated with vigorous-intensity physical activity per unit time [38, 39]. The AAS instrument has an acceptable psychometric test-retest reliability ICC = 0.64; CI = 0.57 – 0.70) [40], and also acceptable validity against accelerometer-estimated physical activity (Spearman correlation = 0.61; CI = 0.43 – 0.75) [41].

Other time-varying confounders were participants' self-reported household income, and some relevant lifestyle behaviours including total energy intake, and smoking (three categories - never smoked, ex-smoker, and current smoker). Also, confounders related to the medical status included self-reported SF-36 mental component score, clinically assessed chronic kidney disease (CKD) based on estimated glomerular filtration rate (yes/no), history of cancer (yes/no: note that data was available at baseline and was treated as a time-invariant variable), and history of CVD which included angina, coronary heart disease, heart attack, or stroke (yes/ no).

Statistical analysis

All analyses were performed using STATA statistical software (version 14.2; StataCorp LLC) and the findings were deemed statistically significant at $p \leq 0.05$. Participants' characteristics were described across the three data time points in summary statistics. Continuous variables were presented as mean values with standard deviations; categorical variables were in proportion. We used Box plots to illustrate the differences in the bodily pain score and TV time variables according to T2D status at the various data time points. Also, mixed-effects regression was used to examine the differences in the mean bodily pain score and mean TV time across the data time points in the overall sample and according to T2D status – NGM, prediabetes and T2D (newly diagnosed and known T2D combined). Confounders were selected based on prior literature; the outcome variable (bodily pain score) was regressed with all potential covariates, and multicollinearity was tested by Variance Inflation Factor (VIF $\geq$ 10).

The bodily pain trajectory with age was examined by a multilevel linear growth curve model, an ideal approach for longitudinally structured data [42, 43], considering the continuous nature of the repeated measured bodily pain score. The bodily pain trajectory was modelled using participants' age at the three data time points as the time metric. Progressively adjusted models were fitted, starting with an unconditional growth (bodily pain) trajectory (Model 1) by regressing bodily pain score as a function of age (centred at age 50 years, about the mean age at baseline) using a random slope model, a more flexible growth curve modelling which estimates both intercept variance and slope variance, as well as intercept-slope covariance. The model selection and equations for the unconditional growth curve are provided in the Supplementary File.

First, the relationship between TV time and the bodily pain trajectory was examined by conditioning the bodily pain trajectory on TV time – a continuous variable in hours/day – as an exposure variable was fitted as a time-varying variable (Model 2). To understand whether the effect of TV time on bodily pain trajectory changed with age, a TV time/age interaction term was added to the fitted model, but the interaction term was statistically non-significant. A linear-additive model was therefore fitted, excluding the interaction term. The fitted model was fully adjusted for other covariates: sex, waist circumference, education level, income, energy intake, leisure-time physical activity, smoking status, T2D status, CKD, SF-36 mental component score, history of CVD, and history of cancer (Model 3).

Second, to examine the potential moderation of the relationship between TV time and bodily pain trajectory by T2D status, a multiplicative interaction between TV time and T2D status was modelled. Three categories of T2D status [NGM, pre-diabetes, and T2D (new T2D and known T2D combined)] were used in the regression models for ease of interpretation. A full interaction of TV time with T2D status was added to the fitted unconditional model (Model 1); predictive margins and marginal effects (the impact T2D status has on the changes in bodily pain severity $\left[\frac{\partial bodily\ pain\ score}{\partial T2D\ status}\right]$ when TV time is held constant at different points or thresholds) with standard errors estimated and outputs illustrated in a line graph (Model 4) [44]. Finally, the fitted model was fully adjusted for sex, waist circumference, education level, income, energy intake, leisure-time physical activity, smoking status, CKD, SF-36 mental component score, history of CVD, and history of cancer; predictive margins as well as marginal effects and standard errors were estimated, and results illustrated in a line graph (Model 5).

Sensitivity analysis

Two sensitivity analyses were performed to check the robustness of our analysis. First, we performed a sensitivity analysis by excluding data for those who reported a history of cancer. Data on participants' history of cancer was only available at a one-time point (baseline) with the assumption made that it was a time-invariant covariate in the analysis. Secondly, many of those with a history of cancer may be more likely to self-report experiencing more pain. Therefore, the sensitivity analytic sample comprised the remaining 3827 participants with complete data

at baseline. A second sensitivity analysis was performed using data from only those participants who provided data at baseline and both of the respective follow-ups. A total of 2727 participants' data were modelled in this sensitivity analysis, adjusting for all covariates described for the main analysis, including the history of cancer variable.

Results

Participant characteristics are presented in both Tables 1 and 2. The mean age at baseline was 49.4 ± 8.0 years, and the average bodily pain score decreased (i.e., bodily pain worsened) from baseline through 5-year follow-up to the 12-year follow-up (p <0.001). Mean TV time increased

Table 1 Participants' characteristics across the data time-points

Variables	Baseline		5-year Follow-up		12-year Follow-up	
	N	Mean (SD) or %	N[b]	Mean (SD) or %	N[b]	Mean (SD) or %
Time metric						
Age, years	4099	49.42 (7.99)	3693	54.58 (8.02)	3085	60.96 (7.86)
Outcome						
SF36 bodily pain score	4099	75.51 (21.75)	3694	74.49 (22.36)	3124	72.91 (22.08)
Exposure variable						
TV time, hrs/day	4099	1.69 (1.24)	3674	1.86 (1.29)	3010	1.92 (1.32)
Moderator: T2D Status						
NGM	3185	77.7%	2952	78.6%	2634	72.4%
Prediabetes	691	16.9%	454	12.1%	522	14.4%
New T2D	122	3.0%	80	2.1%	62	1.7%
Known T2D	101	2.5%	272	7.2%	418	11.5%
Covariates						
Sex[a]						
Female	2227	54.3%	2007	54.4%	1709	54.7%
Male	1872	45.7%	1685	45.6%	1415	45.3%
Waist circumference, cm	4099	90.22 (13.77)	3689	92.47 (13.97)	3082	95.13 (14.24)
MVPA, min/week	4099	282.27 (334.06)	3673	299.93 (325.50)	3477	337.96 (357.77)
Education level[a]						
At least college	1439	35.1%	1294	35.0%	1178	37.7%
Below college	2660	64.9%	2400	65.0%	1946	62.3%
House income						
High	2934	71.6%	2697	74.0%	2255	74.9%
Low	1127	27.5%	909	24.9%	510	16.9%
Not provided	38	0.9%	39	1.1%	246	8.2%
Energy intake, kcal	4099	8119.38 (3281.22)	3641	7639.79 (3070.71)	2992	7139.74 (2827.59)
Smoking status						
Current smoker	486	11.9%	335	9.4%	204	6.0%
Ex-smoker	1226	29.9%	1135	32.0%	1232	36.0%
Non-smoker	2387	58.2%	2078	58.6%	1984	58.0%
SF36 MCS	4099	49.15 (9.41)	3693	49.66 (9.62)	3102	57.53 (12.02)
Chronic kidney disease						
No	3927	95.8%	3531	95.2%	3086	97.8%
Yes	172	4.2%	179	4.8%	71	2.3%
History of CVD						
No	3953	96.4%	3790	95.3%	3279	92.0%
Yes	146	3.6%	188	4.7%	284	8.0%
History of cancer[a]						
No	3827	93.4%	3457	93.6%	2914	93.3%
Yes	272	6.6%	237	6.4%	210	6.7%

[a] Time invariant variable, *N* Total number of participants, *SD* Standard deviation, *TV* Television-viewing, *NGM* Normal glucose metabolism, *T2D* Type 2 diabetes, *MVPA* Moderate-to-vigorous intensity physical activity (leisure-time physical activity), *CS* Mental Component Score, *CVD* Cardiovascular diseases

[b] Participants with non-missing data for any of the variables at follow-ups were included in the data presented in this descriptive table

Table 2 Mean bodily pain score and TV time across the data time-points

Parameters	Baseline	5-year Follow-up	12-year Follow-up	*P*-value
Bodily pain score, *mean (SD)*				
Overall sample	75.51 (21.75)	74.49 (22.36)	72.91 (22.08)	<0.001
NGM	76.12 (21.15)	75.85 (21.61)	74.29 (20.03)	<0.001
Prediabetes	74.24 (23.47)	71.35 (23.19)	72.27 (23.46)	0.078
T2D	70.87 (24.05)	67.17 (25.46)	65.54 (25.17)	<0.001
TV time (hrs/day), *mean (SD)*				
Overall sample	1.69 (1.24)	1.86 (1.29)	1.92 (1.32)	<0.001
NGM	1.62 (1.20)	1.80 (1.27)	1.83 (1.28)	<0.001
Prediabetes	1.84 (1.36)	2.02 (1.36)	2.13 (1.39)	<0.001
T2D	2.18 (1.30)	2.21 (1.38)	2.26 (1.39)	0.112

NGM Normal glucose metabolism, *T2D* Type 2 diabetes (included new T2D and known T2D), *SD* Standard deviation, *TV* Television-viewing

significantly across the three time points (p <0.001). The proportion of participants with T2D (newly diagnosed and known T2D) increased from 5.5% at baseline to 9.3% and 13.2% at 5-year and 12-year follow-ups, respectively.

As illustrated in the box plots in Figs. 2 and 3, those with T2D, particularly those with known T2D had relatively more severe pain. The known T2D group had relatively higher mean TV time at each data time point than the other groups, but these were not statistically-significant differences.

As shown in Table 2, the increase in the severity of bodily pain across the three-time points was statistically significant among those with NGM and T2D (p <0.001), but marginally non-significant in the prediabetes group (p <0.078). The differences in the mean TV time at the three data time points were statistically-significant in only those participants with NGM and prediabetes (p <0.001).

Unconditional growth (bodily pain) trajectory

The unconditional growth curve model output is shown in Table 3. The average estimated mean bodily pain score for participants aged 50 years at baseline was 75.6 (SE: 0.5), which significantly decreased (i.e., pain severity worsened) at a rate of 0.28 (SE: 0.02) unit points every additional year. There were, however, significant variations in the bodily pain scores of participants aged 50 years at baseline after accounting for the clustering of participants. The significant estimate of a positive intercept-slope covariance and negative slope for age 50 (the time metric) implies that those with higher baseline bodily pain scores (less pain) tend to have a below-average rate of decline in their bodily pain score with increasing age. Conversely, those with severe pain (low bodily pain score) at baseline tended to experience increasing pain severity (higher rate of decrease in bodily pain score) with increasing age.

Relationship of TV time with the bodily pain trajectory at a given time point

The conditional growth trajectory models are also presented in Table 3. A one-unit (one-hour) increase in TV time per day significantly predicted a 1.15 (SE: 0.17) point decrease in bodily pain score (thus, increase in bodily pain severity) at any given time point (e.g., at age 50 years), after accounting for the linear change in age — the growth factor (Model 2). Compared to the unconditional model (Model 1), conditioning on (i.e., adjusting for) TV time in Model 2 increased the mean baseline bodily pain score [77.5 (SE: 0.5)] at age 50 years; also, the slope variance for age 50 increased by 7.1%.

The fully-adjusted model showed that the estimated mean bodily pain score at baseline for those aged 50 years was 76.9 (SE: 2.2) (Model 3). With all other covariates held constant, the rate of increasing bodily pain severity with age (the yearly increase) was significantly estimated as 0.30 (SE: 0.03), a slight increase compared to 0.28 (SE: 0.02) of the unconditional growth model (Model 1). The slope variance for age, however, decreased by 50.0% compared to the unconditional growth model. The linear-additive marginal effect of TV time on bodily pain severity at any given time point reduced from 1.15 (SE: 0.17) in Model 2 to 0.69 (SE: 0.17) in Model 3 but remained statistically significant (p <0.001). The intercept-slope covariance was positive and remained statistically significant, meaning that those with initial more-severe pain at baseline have a significantly higher rate of increasing bodily pain severity with advancing age.

Moderation of the relationship between TV time and bodily pain severity by T2D status

Models 4 and 5 in Table 3, as well as Fig. 4, show the relationships of the multiplicative interaction between TV time and T2D status with bodily pain trajectory. For those with NGM, the marginal effect of prediabetes

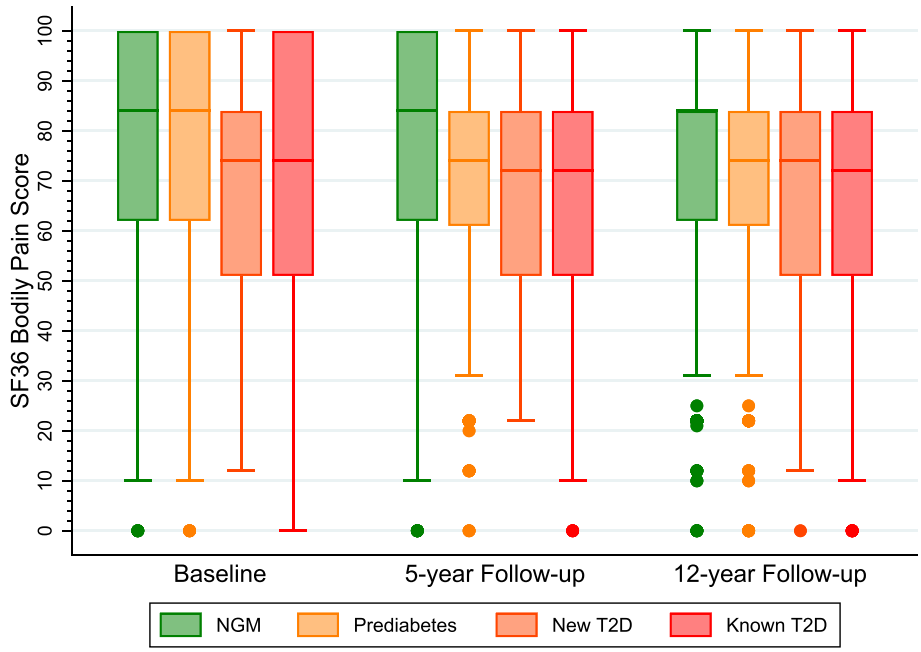


Fig. 2 Shows box plots comparing the mean bodily pain score according to type 2 diabetes (T2D) status [normal glucose metabolism (NGM), prediabetes, new T2D, and known T2D] at the three time points. **Note:** Higher score means less pain and a lower score indicates severe pain. The dots indicate outliers.

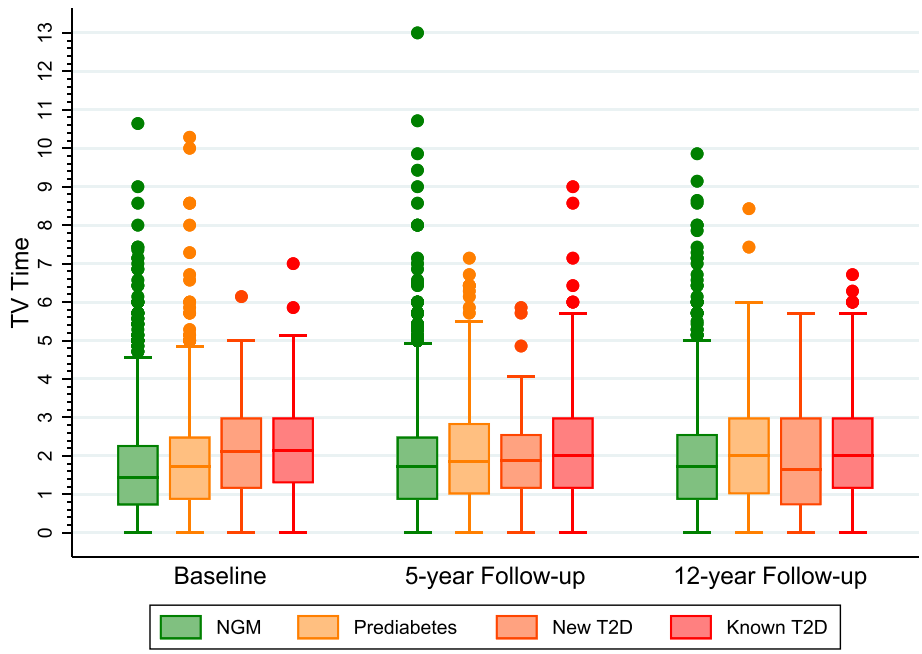


Fig. 3 Shows box plots comparing the mean television-viewing (TV) time according to T2D status (NGM, prediabetes, new T2D, and known T2D) at the data time points. Note: The dots indicate outliers.

Table 3 Unconditional and conditional linear growth curve models for bodily pain

	Unconditional model	**Conditional models**			
	Model 1: (Function of age)	**Model 2: Model 1 + TV time**	**Model 3: Fully adjusted linear-additive model**	**Model 4: Model 2 + TV time # T2D status**	**Model 5: Fully adjusted with TV time#T2D status**
	Coefficient (S.E)	***Coefficient (S.E)***	***Coefficient (S.E)***	***Coefficient (S.E)***	***Coefficient (S.E)***
Fixed effect					
Intercept	75.55 (0.45)***	77.53 (0.52)***	76.92 (2.20)***	77.83 (0.54)***	76.71 (2.20)***
Slopes					
Age (Centred at 50 years)	- 0.28 (0.02)***	- 0.24 (0.02)***	- 0.30 (0.03)***	- 0.21 (0.03)***	- 0.30 (0.03)***
TV time		- 1.15 (0.17)***	- 0.69 (0.17)***	- 1.03 (0.19)***	- 0.56 (0.19)**
T2D status					
NGM (Reference)				0	0
Prediabetes				- 0.97 (0.96)	0.91 (0.96)
T2D				- 4.07 (1.50)**	0.53 (1.48)
TV time#T2D status					
NGM (Reference)				0	0
Pre-diabetes				- 0.10 (0.40)	- 0.22 (0.40)
T2D				- 0.63 (0.56)	- 0.97 (0.55)$^{\$}$
Random effect					
Intercept variance					
Cluster[a]	4.85 (1.92)**	4.09 (1.75)**	1.05 (0.87)	3.49 (1.59)**	1.03 (0.87)
Participants	192.89 (7.48)***	191.05 (7.46)***	145.05 (6.05)***	188.80 (7.42)***	145.05 (6.05)***
Slope variance	0.014 (0.006)**	0.015 (0.006)**	0.007 (0.001)**	0.015 (0.006)**	0.008 (0.001)**
Intercept-Slope covariance	1.65 (0.34)**	1.69 (0.34)**	1.04 (0.06)***	1.66 (0.34)**	1.04 (0.06)***
Within-individual variance	266.03 (4.58)***	265.65 (4.61)***	263.06 (4.75)***	265.56 (4.61)***	262.94 (4.74)***
Goodness-of-fit					
AIC	95971.21	95117.23	90691.72	95024.25	90692.51
BIC	96022.25	95175.50	90858.33	95111.64	90873.61
Log-likelihood	- 47978.61	- 47550.62	- 45322.86	- 47500.12	- 45321.26
No of parameters	7	8	23	12	25

Statistically significant: *** $p < 0.001$, ** $p < 0.01$, * $p < 0.05$, $^{\$}$ $p = 0.076$

TV time#T2D Status Interaction between TV time and T2D status, *TV* Television-viewing, *S.E* Standard error, *NGM* Normal glucose metabolism, *T2D* Type 2 diabetes (included newly diagnosed and known T2D)

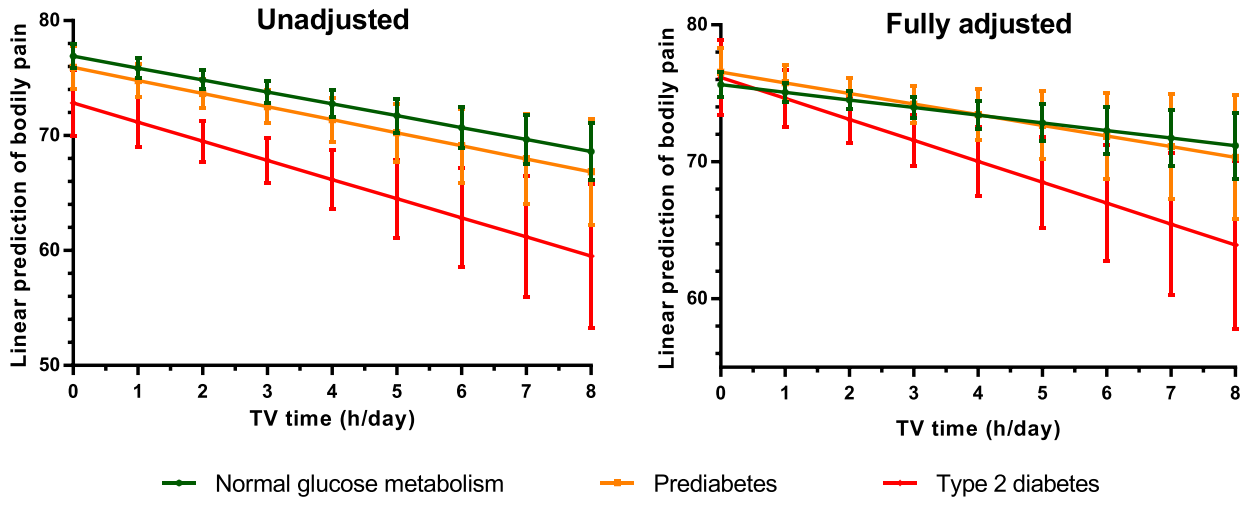
The fully adjusted linear additive model 3 included model 2 + sex, education level, household income, smoking status, leisure-time physical activity, waist circumference, energy intake, T2D status, SF36 mental component score, presence of chronic kidney disease, history of cardiovascular disease (CVD), and cancer.

The fully adjusted model 5 with TV time#T2D status included model 4 + sex, education level, household income, smoking status, leisure-time physical activity, waist circumference, energy intake, SF36 mental component score, presence of chronic kidney disease, history of cardiovascular disease (CVD), and cancer.

[a] This represents the intercept variance that is attributable to the level 3 clustering of individuals (individuals nested in clusters); thus, describes the variance component of cluster-to-cluster variability.

(See figure on next page.)

Fig. 4 This shows the relationships of TV time with bodily pain severity and potential moderation of T2D status. (**A**) The bodily pain prediction margins of T2D status with 95% confidence intervals for the unadjusted and fully adjusted models. (**B**) The marginal effects of prediabetes and T2D (in reference to NGM) on bodily pain severity at different TV time thresholds for the unadjusted and fully adjusted models. The solid lines indicate the marginal effects of changes in bodily pain severity with changing TV time. The dotted lines are the confidence intervals around the lines, which determine the threshold of TV time that has a statistically significant effect on bodily pain severity in those with prediabetes (ORANGE) and T2D (RED). They are statistically significant whenever the lower and upper limits of the confidence intervals are both below or above the zero (0 - BLUE) lines. Note: NGM was set as the reference point in the regression model.



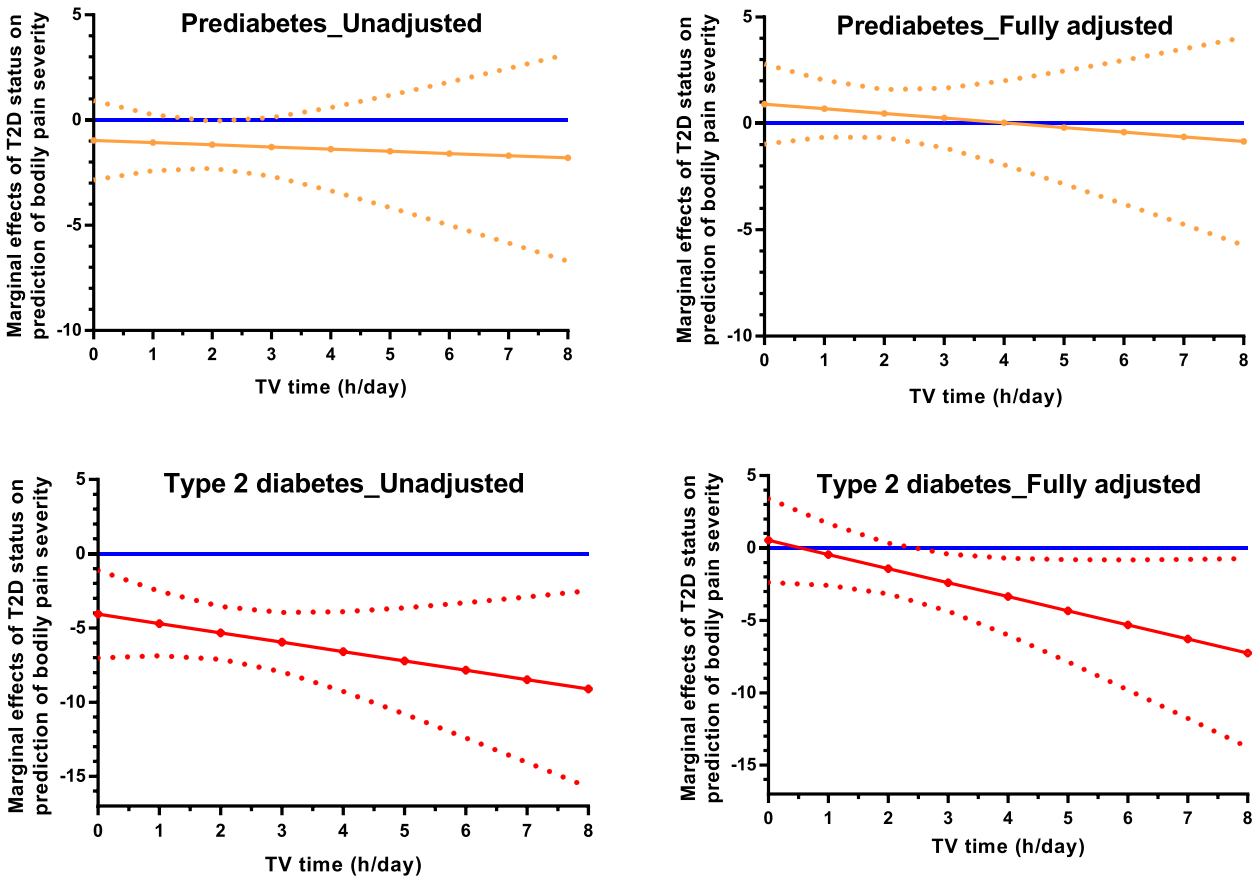


Fig. 4 (See legend on previous page.)

and T2D were negative in the unadjusted Model 4 but positive in the fully adjusted Model 5. These indicate that when TV time was zero (0) in Model 4 bodily pain severity was significantly higher in the T2D but non-significant for prediabetes compared to NGM (negative coefficients – increased bodily pain severity); however, after accounting for the confounding effects of other covariates in Model 5, changes in bodily pain severity were non-significant (positive coefficients – less bodily pain severity) in both prediabetes and T2D when TV time was equal to zero (0). The interaction terms in Model 4 were non-significantly negative for both prediabetes and T2D, and in Model 5, the interaction terms remained negative but marginally non-significant for T2D [- 0.97 (SE: 0.55); $p = 0.076$] and non-significant for prediabetes. Thus, the severity of bodily pain with increasing TV time in the NGM, prediabetes, and T2D groups was different and more pronounced in the T2D group as illustrated in Fig. 4A. Furthermore, compared to the NGM, the effect of T2D and prediabetes on bodily pain severity (decreasing bodily pain score) increased as TV time increases. This was observed to be statistically significant for T2D but not prediabetes when the volume of TV time increased more than 2.5 hours per day (Fig. 4B – the fully adjusted model).

Sensitivity analysis

For the first sensitivity analysis, after excluding participants with a history of cancer (due to the increased potential to self-report pain) from the analysis, similar results were observed with only slight changes in the effect sizes (results provided in Supplementary file, Table S1). However, the marginal non-significant TV time and T2D interaction term in the fully-adjusted model 5 was attenuated, but the trend of the bodily pain severity with increasing TV time for the different T2D status groups, as well as the effect of T2D on bodily pain severity with increasing TV time remained (results provided in Supplementary file, Figure S1).

Similar results were observed in the second sensitivity analysis performed on those participants with data at baseline and both of the follow-ups. There were only slight changes in the effect sizes, but the trends remained (Supplementary file, Table S2). The main difference observed was the statistically significant interaction of TV time with T2D in model 5 for the sensitivity analysis (Supplementary file, Table S2, $p < 0.05$) but marginally non-significant in the main analysis (Table 3, $p = 0.076$). Also, in this second sensitivity analysis, the effect of T2D on bodily pain severity was significantly pronounced when the threshold of TV time increased above 3 hours per day (Supplementary file, Figure S2).

Discussion

This study examined the relationships of concurrent changes in TV time with bodily pain in a large cohort study of Australian middle-aged to older adults with and without T2D over a 12-year period. We found that bodily pain severity increased with age, and that increasing TV time at a given time point was significantly associated with increased severity of the bodily pain which persisted after adjustment for relevant confounders, including leisure-time physical activity and waist circumference. The relationships of increasing TV time with bodily pain severity at a given time point on the bodily pain trajectories were more pronounced in those with T2D than in those without T2D (prediabetes or NGM). The effect of T2D on bodily pain severity was more apparent when the threshold of TV time increased above 2.5 hours per day.

The findings corroborate some previous evidence, as well as providing novel insights into the prospective associations of sedentary behaviour with pain conditions [20, 22]. A previous epidemiological study of community-dwelling older adults, for example, identified a prospective association of self-reported higher sitting time with worse bodily pain [20]. Similarly, a prospective study of Brazilian schoolteachers found an association between increased TV time and musculoskeletal pain [22]. Although our findings are consistent with those of previous studies, we report the first evidence of an increase in severity of bodily pain with advancing age in middle-aged and older adults with increasing hours per day spent watching television at any given period. Also, we identified the moderation of this relationship by T2D status, which has not previously been reported. Our findings suggest that the magnitude of the detrimental relationships of higher volumes of TV time with bodily pain severity at any given time point is different in those with and without T2D. These findings may have potentially-different clinical and public health implications in these populations. For example, those with T2D may have a raised possible risk of a "vicious cycle", especially in those with comorbid chronic pain; this could result in higher volumes of sedentary behaviours (including more time sitting watching television), which could worsen the severity of both T2D and pain.

In contrast, a previous study has also reported no evidence of a prospective association between sedentary behaviour, specifically, TV time and SF36 questionnaire-assessed bodily pain, albeit in a disease-specific population of cancer survivors [21]. Compared to our study, aside from the differences in the studied population, this previous prospective study [21] used a "changed analysis" approach to examine data from two time-points over 10 years, whereas our analysis was based on the multilevel growth curve approach to analyse three time-points data

over 12-years. The differences in the analytical approach and study populations make comparisons between these findings a challenge. Nonetheless, the multilevel growth curve approach is more robust and recommended for longitudinally structured data [42].

Taken together, there is equivocal evidence on the potential relationships between sedentary behaviour and bodily pain. However, our finding from a large cohort of community-based middle-aged and older adults does corroborate some of the existing evidence on detrimental associations; specifically, our finding that time spent sitting and watching television predicts the severity of bodily pain at a given time point of pain trajectory supports the growing public health concerns of excessive sedentary behaviour.

The mechanisms that may underpin the reporting of pain severity are likely to be complex, potentially involving the interplay of biological and multiple psychosocial factors [45, 46]. There is, however, evidence that suggests some behavioural attributes can modulate pain [47–49]. The potential pain modulation role of sedentary behaviour has been understudied compared to physical activity [47]. For instance, there is evidence indicating that higher levels of physical activity are associated with pain inhibition and reduced pain facilitation [47–49]. Nevertheless, evidence supporting a negative relationship between sedentary behaviour and pain modulation has also been reported [48].

The link between sedentary behaviour and adiposity may be a probable pathway that could explain the association of sedentary behaviour with bodily pain [50]. Adipose tissue is metabolically active, releasing pro-inflammatory cytokines and adipokines that may potentiate inflammatory changes in tissues leading to noxious pain stimuli [51]. Also, sedentary behaviour may directly or indirectly, through its association with obesity, lead to a reduction in physical activity levels [18] and modulate the biomechanical loading pathway of some bodily pain, such as somatic joint pain related to older age [52, 53]. In the context of this study, it is important to note that our analysis accounted for the potential confounding bias of adiposity (waist circumference) and physical activity. The observed associations of TV time (sedentary behaviour) with bodily pain, therefore, provide informative evidence on the potential role of sedentary behaviour in the pathogenesis of bodily pain. This may be mediated through some of the known sedentary behaviour associations, for example, with systemic inflammation and vascular endothelial dysfunction, especially in those with metabolic disorders such as T2D [54, 55]; and, plausibly through unknown mechanisms related to a negative modulation influence of sedentary behaviour on pain perception [48].

We observed that those with T2D, especially known T2D (and more likely longer diabetes duration) experienced relatively higher pain severity (Fig. 2) and had slightly higher TV time than those without T2D (Fig. 3). Generally, however, there were only small variations in the bodily pain scores and/or TV time across the three data time-point analysed. These limited variations may have contributed to the observed statistically non-significant or marginally non-significant TV time/T2D status interaction terms. Nevertheless, our findings have shown that compared to those with NGM, the association of increasing TV time with the severity of bodily pain at any given time point is more pronounced in those with T2D than with prediabetes. These observations support the evidence that people with T2D, especially those with long-standing cases, are predisposed to heightened pain due to systemic inflammatory response and vascular complications associated with peripheral neuropathy in T2D [26, 27]. Moreover, compared to those without T2D, people with T2D tend to spend more time in sedentary behaviour [29]. In line with our findings, the higher TV time in those with T2D could partly account for the severe bodily pain observed in this group, as demonstrated in this study. This is consistent with the existing evidence of adverse associations of high TV time with chronic health outcomes, including chronic pain [12–16].

The findings may have some implications in light of the public health and clinical challenges of chronic pain [5]. Aside from the challenges of pharmacologic management of chronic pain, many adults who experience chronic pain are physically inactive [7, 8]. There are some clinical instances where some people who present with bodily pain may be counselled to take regular rest breaks; however, evidence suggests increased activities level improve bodily pain in most people. Though clinical guidelines for chronic pain management have not specifically referred to limiting sedentary behaviour, the importance of physical therapy (which can include exercise prescriptions) has been widely acknowledged, for example, in the American Society of Anaesthesiologists Task Force on Chronic Pain Management guideline [56]. Thus, advocating for strategies with realistic goals that encourage and support people, especially older adults to move more and break up prolonged sitting (sedentary) behaviours can be of benefit to those with chronic pain, as well as other chronic conditions.

There is sufficient evidence on the pain modulation effect of increased physical activity and reduced sedentary behaviour in adults [47–49]. Also, some evidence indicates that reduced sedentary behaviour is associated with reduced musculoskeletal pain conditions [57, 58]. As demonstrated by our findings, leisure-time sedentary behaviour (TV time) can be detrimentally associated

with increasing pain severity with advancing age. These findings could help inform future intervention trials in clinical populations to examine the effect of reducing sedentary behaviour on bodily pain trajectory. Also, further study could explore the effects of the balance or interaction of physical activity and sedentary behaviour on the prediction of bodily pain severity. Taken together, findings from these studies would provide insights relevant to the prescription of sedentary behaviour reduction as a non-pharmacologic intervention and adjuvant therapy in chronic pain management, as well as support for public health initiatives to address sedentary behaviour in addition to physical inactivity in ageing adults. Such future studies may consider using device-measured sedentary behaviour and disease-specific pain instrument to minimise measurement bias.

A key strength of this study is the prospective design, using data collected at three-time points over 12 years, allowing some inferences to be made about causality. Though this study is a posthoc analysis, the bodily pain (outcome) and the TV time (exposure) were measured at all three time points. Another strength is a cohort consisting of a large sample of Australian adults; thus, the findings could be reasonably generalised across middle-aged and older adults. Furthermore, the multilevel growth curve statistical approach is an additional strength of this study. The multilevel growth curve method provides numerous advantages, including the ability to handle missing data as missing at random (MAR), the estimation of the mean baseline bodily pain severity and the rate at which the severity increases with age, the between- and within-individual variations as well as the covariance of the intercept and slope variance, and the ability to make predictions relative to exposure effect (in this case, TV time) [42, 43]. This approach, treating all missing data as MAR should have minimised the impact of loss-to-follow-up on the findings. We replicated our analysis in a sensitivity analysis on only those baseline participants who provided data at both follow-ups and observed similar results with only minor changes in effect sizes, but the trends remained the same (Supplementary file, Table S2 and Figure S2). A further strength is the wide range of data on time-invariant and time-variant covariates which were adjusted for as potential confounders in the analysis.

There are several limitations, and the findings should be interpreted in the context of the following: firstly, this is a secondary analysis in that AusDiab was not primarily designed to specifically address the aims of this study. The bodily pain scores were taken from the SF36 questionnaire, a generic instrument for the quality-of-life assessment of populations and are quite different from other instruments used to measure pain in disease-specific studies. Nevertheless, the SF36 bodily pain scale being self-report with an inherent recall bias of underestimating or overestimating pain has been shown to have acceptable psychometric properties; able to detect changes in pain over time; and has widely been used in population-based research to make comparisons across diverse populations [34]. In clinical populations, however, other disease-specific pain instruments may facilitate enhanced pain severity discrimination compared with the SF36 bodily pain scale [34]. Importantly, it must be acknowledged that bodily pain is heterogeneous, and there might be some pain-related conditions that benefit from sedentary behaviour while others are aggravated by excessive sedentary behaviours. Secondly, the exposure variable (TV time) was self-reported and represented a particular subset of leisure-time sedentary behaviour. Time spent on the internet and social media are examples of other components of overall leisure-time sedentary behaviour, that were not captured. It is important to note here that not accounting for the other leisure-time sedentary behaviour have may potentially led to underestimation or overestimation of the magnitude of TV time associations with the bodily pain severity.

Thirdly, data on some potential time-variant confounders such as a history of cancer and bone fracture were available at only one-time point and assumptions were made to either treat those variables as time-invariant variables if it was measured at only baseline (history of cancer) or exclude those participants (bone fracture) in the analysis to account for potential reverse causation bias. Finally, there could well be other unmeasured confounders, therefore, not accounted for in the analysis. For instance, there are some chronic conditions such as pain disorders of the musculoskeletal system which could influence both sedentary behaviour and pain outcome, but data were not available and hence not accounted for in our analysis. Also, the duration of T2D may have had an impact on the findings but this was not assessed in the study. However, cardiovascular conditions and chronic kidney diseases which are often associated with complications of T2D were accounted for. Future studies could consider examining sedentary behaviour/pain associations exclusively in those with T2D and the potential interactions of the relationships with T2D duration and mobility limitations.

Conclusions

In this cohort of middle-aged to older Australian adults, we showed that bodily pain increases in severity with ageing; and increasing TV time at any given time point was found to be significantly associated with increased severity of bodily pain. Those with T2D tended to report higher pain levels than those without T2D, and the association of TV

time with bodily pain severity at any particular time point was more pronounced in those with T2D than those without T2D. Specifically, compared to those with NGM, the effect of T2D on the severity of bodily pain with increasing TV time was significantly pronounced when the TV time threshold increased above 2.5 hours per day, but that of prediabetes was statistically non-significant. Considering the available evidence on the pain modulation effect of physical activity, our findings align with the WHO's physical activity and sedentary behaviour recommendation guidelines [59] of increasing levels of moderate-to-vigorous intensity physical activity and also reducing time spent in sedentary behaviours. Controlled intervention trials in disease-specific clinical populations to examine the effect of reducing prolonged sedentary behaviour on bodily pain in the long term will provide stronger support for clinical and public health initiatives to reduce sedentary time, as well as some evidence on non-pharmacologic benefits of sedentary behaviour reduction and a potential adjuvant pain modulation therapy for chronic pain management guidelines.

Abbreviations

CVD : Cardiovascular disease; METs: Metabolic equivalents; T2D: Type 2 diabetes; TV: Television-viewing; SF-36: 36-Item Short-Form Health Survey questionnaire; AusDiab: Australian Diabetes, Obesity, and Lifestyle Study; CCD : Census Collector District; OGTT: Oral glucose tolerance test; IFG: Impaired fasting glucose; IGT: Impaired glucose tolerance; NGM : Normal glucose metabolism; HRQoL: Health-related quality of life; DVD: Digital Video Disc; ICC: Intraclass (correlation) coefficient; WHO: World Health Organisation; FBG : Fasting blood glucose; ADA: American Diabetes Association; AAS: Active Australia Survey; MVPA : Moderate-to-vigorous physical activity; CKD : Chronic kidney disease; VIF: Variance Inflation Factor; SE: Standard error; MAR: Missing at random.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-022-14566-y.

Additional file 1.

Acknowledgements

The authors would like to acknowledge the support and assistance given by: K. Anstey, B. Atkins, B. Balkau, E. Barr, A. Cameron, S. Chadban, M. de Courten, A. Kavanagh, D. Magliano, S. Murray, K. Polkinghorne, J. Shaw, T. Welborn, and P. Zimmet, as well as thank all the participants and research staff that were involved in the AusDiab. Our sincere gratitude to A. Muhammad and M. Chandrabose for offering statistical analysis advice.

Authors' contributions

FD, CB, AC, NO, and DD contributed to the conceptualisation and design of the study. FD and PS contributed to the statistical analytic design. FD performed the data analysis and interpreted the results. PS, CB, and AS advised on the statistical analysis and interpretation of the results. FD, AC, NO, and DD prepared the manuscript. FC and DU contributed to the revision and realisation of the final draft manuscript. The final manuscript has been read and approved by all the authors.

Funding

The AusDiab which was co-coordinated by the Baker Heart and Diabetes Institute was sponsored by National Health and Medical Research Council (NHMRC grants 233200 and 1007544); 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; Marian & 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. Dzakpasu and Brakenridge were supported by the Australian Government Research Training Program Scholarship. Owen was supported by the National Health and Medical Research Council (NHMRC) of Australia through a Senior Principal Research Fellowships (#1003960) and by the Victorian Government's Operational Infrastructure Support Program. Dunstan was supported by an NHMRC Senior Research Fellowship (1078360) and the Victorian Government's Operational Infrastructure Support Program. Urquhart was supported by an NHMRC Career Development Fellowship (Clinical Level 2; 1142809). Cicuttini was supported by an NHMRC Investigator Grant (APP1194829).
None of the funders had a role in the design, data analysis, or interpretation of the results presented in this manuscript.

Availability of data and materials

The data that support the findings of this study are available from the AusDiab Steering Committee, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are, however, available upon reasonable request by written applications to the AusDiab Steering Committee (Dianna.Magliano@baker.edu.au).

Declarations

Ethics approval and consent to participate

The AusDiab study protocols were in accordance with the Declaration of Helsinki and were approved by the International Diabetes Institute (now Baker Heart and Diabetes Institute) Ethics Committee and the Alfred Health Ethics Committee (approval no. 39/11). All the participants in the study provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no conflict of interest.

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Received: 13 May 2022 Accepted: 7 November 2022
Published online: 29 November 2022

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Publisher's Note

5.3 Summary and implications of the findings in the thesis

The key observations from this study are that those with T2D were more likely to spend more time watching television (leisure-time sedentary behaviour) than those with non-T2D and they tended to report more severe pain. The findings indicate that the severity of bodily pain increases with age, and increasing TV time at any given time point was significantly associated with increases in bodily pain severity over the 12-year period. Those individuals with initially more severe pain tend to have a higher rate of increases in the severity of the pain trajectory. The observed association was more pronounced in those with T2D than those without T2D (prediabetes and NGM). Relative to those with NGM, the effect of T2D and prediabetes on bodily pain severity with increasing TV time was more pronounced in those with T2D, significantly so when the TV time threshold exceeds 2.5 hours/day.

The prospective design of this study provides unique insights into the relationships of increasing sedentary behaviour with changing severity of pain outcomes. This could have both clinical and public health implications for pain management. Chronic pain management is challenging and insight into the potential influence of sedentary behaviour on the outcome of pain could inform clinical guidelines. Knowing that increasing physical activity levels can have enormous health benefits, reducing and breaking up prolonged sedentary time could have additional benefits, including pain modulation. What is most relevant from this study is that the findings can inform future trials to investigate the potential effects of reducing sedentary behaviour and increasing physically active behaviours on pain trajectories, especially in clinical populations. Findings from such future studies on the impacts of displacing portions of time spent in sedentary behaviour with physically active behaviours such as standing, light-walking, or MVPA on pain outcomes may also provide some insights relevant to help understand the minimum changes in activity behaviours that will be acceptable among vulnerable populations for desirable pain outcomes. Also, prospective relationships between physical activity/sedentary behaviour interactions and pain outcomes could be explored in future studies. Taken together, these future studies' findings may provide stronger evidence for the prescription of sedentary behaviour reduction strategies for chronic pain management protocols in clinical populations.

The exposure variable (TV time), however, was based on self-reported data and may limit the strength of the evidence observed. Also, this study and Study 2 mainly focussed on the volume of accumulated sedentary behaviour but did not examine the patterns in which it is accumulated. Study 4 which is presented in the next chapter, therefore, addressed these limitations by using device-measured activity behaviours to examine the prospective relationships of changes in activity behaviours and their bout patterns with changes in MSP outcomes.

Chapter 6: Study 4

6.1 Title:

Changes in Desk-Based Workers' Sitting, Standing and Stepping Time: Short- and Longer-Term Impacts on Musculoskeletal Pain

6.1.1 Purpose

The main focus of this study was to use the compositional data analysis framework which can account for the co-dependence of time-use data, as well as the compositional isotemporal substitution method to explore the balance of activity behaviours and their impacts on MSP outcomes. This provided insights into behaviours that could displace portions of sedentary behaviour for favourable MSP outcomes. Desk-based workers can accumulate high volumes of sitting time, which can increase their occupational health risks. It has been shown that favourable changes in sitting, standing, and stepping among desk-based workers can lead to modest changes in cardiometabolic risk markers. However, the prospective relationships of changing these behaviours and the bouts in which they are accumulated with changes in MSP outcomes have been under-explored. This study, therefore, utilised pooled data from intervention and control participants of the Stand-Up Victoria trial in mixed-effects modelling to examine prospective relationships with changes in multisite MSP of three- and 12-month changes in activPAL-assessed time-use compositions that included short-bout and long-bout sitting, standing, or stepping.

6.2 The manuscript

The manuscript has been accepted for publication in Medicine & Science in Sports & Exercise (MSSE). The authors' contributions to this manuscript are provided in Appendix B2.1.

6.2.1 Citation

Dzakpasu FQS, Owen N, Carver A, Brakenridge CJ, Eakin EG, Healy GN, LaMontagne AD, Moodie M, Coenen P, Straker L, Dunstan DW. *Changes in desk-based workers' sitting, standing and stepping time: short- and longer-term impacts on musculoskeletal pain.* Med Sci Sports Exerc. (Accepted on 22 June 2023 – scheduled to be published in print in December 2023)

6.2.2 Copy of the accepted manuscript

6.3 Summary and implications of the findings in the thesis

A key finding from this study was that the interdependency of changes in volumes of time spent sitting, standing, and stepping may be the determinant of MSP outcomes. It was observed that in the short-term, increased volume of standing relative to changes in volumes of stepping and sitting time significantly increased multisite MSP; in contrast, increased volume of stepping relative to changes in volumes of sitting and standing resulted in decreases in multisite MSP outcomes. In the longer term (12 months) there were no statistically-significant relationships observed with multisite MSP changes for the relative changes in these behaviours. Importantly, increased standing volume relative to changes in the other behavioural compositions was not significantly associated with changes in multisite MSP outcomes in the longer term. Furthermore, no statistically significant relationships were observed for the relative changes in short and long bouts of these behaviours with the changes in multisite MSP outcomes; thus, notwithstanding limitations of bouts cut-offs used in this study, changes in the volumes of these behaviours may be more important than the bout patterns in which the changes may occur.

With the growing evidence of favourable cardiometabolic risk benefits of reducing desk-based workers sitting [59-61, 290], these findings of Study 4 have relevant occupational and public health implications. Strategies targeting desk-based workers' sedentary behaviour reductions may also have potential benefits on MSP outcomes. The findings suggest initial increases in standing among desk-based workers may lead to some undesirable changes in MSP outcomes; however, health promotion messages that encourage at least modest increases in stepping in addition to increasing standing can beneficially ameliorate MSP or discomforts. In the longer term, increments in standing alone resulting from reducing sitting time may not worsen MSP outcomes, even when the volume of stepping time reduces. Furthermore, there are possible indications that reallocating portions of sitting time to standing or stepping while holding constant time spent in the other behaviour can have favourable impacts on MSP outcomes, especially in the longer term. Similarly, reallocating proportions of time spent in long-sitting bouts to short-sitting bouts, as well as from short-standing bouts and short-stepping bouts to long-standing bouts and long-stepping bouts respectively may not adversely worsen MSP symptoms, but could have plausible beneficial impacts on MSP outcomes, especially in the long term.

This study's findings add to this thesis, original evidence on prospective relationships of the balance of changing device-measured sitting, standing, and stepping time among desk-based workers with changes in acute and chronic MSP outcomes. These findings together with those of the other studies (Study 1, 2, and 3) are discussed and synthesised in the next chapter.

Chapter 7: Overall Discussion

7.1 General overview

The overarching aim of this thesis was to understand the relationships of sedentary behaviour with MSP conditions in adults, and whether such potential relationships may be different in those with and without T2D. This aim was addressed through four separate studies, including a comprehensive systematic review with meta-analysis and three empirical studies. The findings of each of these studies have been discussed in their respective manuscripts and inserted in the chapters they form. This section, therefore, highlights and synthesises the findings of these studies:

1. Study 1: *"Musculoskeletal pain and sedentary behaviour in occupational and non-occupational settings: a systematic review with meta-analysis".* The manuscript is presented as part of the literature review in Chapter 2.
2. Study 2: *"Device-measured sitting time and musculoskeletal pain in adults with normal glucose metabolism, prediabetes and type 2 diabetes – The Maastricht Study".* This is the first empirical study which is presented in Chapter 4
3. Study 3: *"Television-viewing time and bodily pain in Australian adults with and without type 2 diabetes: 12-year prospective relationships".* The second empirical study is presented in Chapter 5.
4. Study 4: *"Changes in desk-based workers' sitting, standing and stepping time: short- and longer-term impacts on musculoskeletal pain".* The third empirical study is presented in Chapter 6.

Furthermore, the strengths and limitations of the thesis are discussed, as well as the implications of the findings for practice and further research. Finally, the Conclusion section summarises the key findings of this thesis.

7.2 Key findings of this thesis

7.2.1 Evidence from Study 1: Systematic review on sedentary behaviour and MSP conditions

My comprehensive systematic review synthesised evidence on associations of occupational and non-occupational sedentary behaviour with MSP conditions in adults using both narrative and meta-analysis (quantitative) approaches. For the non-occupational sedentary behaviour domain, the review found cross-sectional evidence of high volumes of total daily sedentary behaviour to be associated with MSP conditions, including low back pain, neck/shoulder, knee pain, general MSP,

and arthritis/osteoarthritis. However, these findings are mainly based on subjective self-reported sedentary behaviour. Evidence synthesised from device-measured sedentary behaviour was insufficient as the review identified a limited number of studies based on device-measured sedentary behaviour. Likewise, evidence on prospective associations between non-occupational sedentary behaviour and MSP conditions was insufficient due to a limited number of reviewed prospective studies.

Evidence synthesised on occupational sedentary behaviour from observational studies indicates that self-reported workplace sitting time is cross-sectionally associated with low back pain and neck/shoulder pain in desk-based (office) workers. Whereas, there was a probable indication that sedentary behaviour in tradespeople who engage in labour-intensive occupations may have potential protective associations. In general, my systematic review showed that prospective observational studies were limited in number, therefore, evidence synthesised in this context was inconclusive. For evidence synthesised from intervention-based studies, it was found that reduced workplace sitting time was associated with reduced MSP or discomfort in the neck, shoulder, and lower back, as well as reduced general MSP or discomforts.

In addition to the above findings, the systematic review also identified important knowledge gaps which assisted in the development of the empirical studies conducted in this thesis. Specifically, the review noted that there was a paucity of studies based on device-measured sedentary behaviour. Also, a limited number of prospective studies were reviewed, hence, there was inconclusive evidence on prospective associations of sedentary behaviour with MSP outcomes. Furthermore, intervention- or experimental-based evidence was mainly synthesised from short-term non-randomised controlled interventions or acute experimental studies with a limited number of long-term RCT-based studies. Noteworthy, none of the reviewed studies specifically examined the associations between sedentary behaviour and MSP conditions exclusively in adults living with T2D, nor the moderation of associations by the presence of T2D.

7.2.2 Evidence from Study 2: Sitting time and MSP outcomes in adults by glucose metabolism status

The first empirical study's main intent was to address the lack of studies based on device-measured sedentary behaviour identified in the systematic review, as well as the lack of evidence exclusively in those with and without T2D. The findings suggest a higher volume of activPAL-derived daily sitting time was cross-sectionally associated with increased odds of knee pain and was statistically significant in those with T2D, but not in those without T2D. The associations with neck, shoulder, or low back pain were observed to be statistically non-significant in the overall sample, as well as in the

stratified analyses according to GMS. While the relationship in the overall sample was observed to be in a linear function for knee pain, that of the neck, shoulder, and low back pain appeared to be statistically non-significant curvilinear relationships. The non-linear relationships in those with NGM, prediabetes, or T2D were observed to be curvilinear for the MSP outcomes (neck, shoulder, low back, and knee pain); however, these were statistically non-significant except for knee pain in those with prediabetes which showed a marginally significant curvilinear relationship.

7.2.3 Evidence from Study 3: Changes in TV time and bodily pain in adults with and without T2D

This study builds on the previous two studies by using a large nationwide population-based prospective dataset to examine the relationships of concurrent changes in TV time with bodily pain severity in middle-aged and older adults, and the potential moderation of the relationships by T2D. It was observed that those with T2D are more likely than those with non-T2D to spend more time watching television (the most common leisure-time sedentary behaviour in home settings), and they reported more severe pain at all the assessment time points. The bodily pain severity increased with age, and those with initial more severe pain had a higher rate of increases in the severity of the bodily pain trajectories.

Increments in TV time at any given occasion of the bodily pain trajectory were found to be significantly associated with increased pain severity. Those with T2D showed a more pronounced relationship than those without (those with prediabetes or NGM). The effect of T2D on bodily pain severity with increasing TV time was observed to be significantly pronounced when the TV time threshold exceeds 2.5 hours per day, but no significant effect was observed for prediabetes referencing those with NGM.

7.2.4 Evidence from Study 4: Relationships of changing sitting, standing, and stepping time with MSP outcomes

The fourth study utilised device-assessed activity behaviours data to examine the relative prospective relationships with changes in multisite MSP outcomes with compositional changes in desk-based workers sitting, standing, stepping, and the short and long bouts of these behaviours in the short-term (three months) and longer-term (12 months). Importantly, this study highlights the interdependency of these activity behaviours and MSP outcomes. The findings indicate that changing desk-based workers' activity behaviours by reducing sitting time would be unlikely to have adverse impacts on MSP outcomes when standing and stepping are concurrently increased in the short term. Thus, focusing on increasing stepping relative to increasing standing within efforts to

reduce sitting may potentially have favourable impacts on MSP outcomes, both acute and chronic pain. In the longer term, increasing standing only as a result of reducing sitting time may not worsen MSP outcomes even when stepping reduces. Also, there is a probable indication, albeit the limitation of the bouts cut-offs used in this study, that changing the volume of time spent in activity behaviours may be more important for MSP outcomes than the duration of bouts in which the changes occur.

Furthermore, among desk-based workers who are frequently exposed to high volumes of sedentary behaviour, hypothetical reallocation of time from sitting at baseline to standing or stepping at follow-ups while holding constant the usual time spent in the other behaviour was found not to worsen MSP outcomes and could have potential beneficial impacts, especially in the longer term. Similarly, it was observed that reallocating portions of time spent in long-sitting bouts to short-sitting bouts at follow-ups, as well as from short-standing bouts or short-stepping bouts to long-standing bouts or long-stepping bouts respectively at follow-ups may unlikely be detrimental for MSP outcomes. Further, these reallocations may be beneficial for MSP outcomes, particularly in the longer term.

7.3 Evidence synthesis

The current World Health Organisation (WHO) physical activity and sedentary behaviour guidelines recommend a reduction in volumes of daily accumulated sedentary behaviour and intermittent breaking of prolonged sedentary behaviour, in addition to adequate levels of physical activity for beneficial health outcomes [272]. The presence of some chronic conditions, however, could be a barrier to meeting the guidelines and consequently lead to excessive volumes of and/or prolonged sedentary behaviour [308, 309]. Individuals living with chronic conditions such as cardiometabolic conditions and chronic pain are more likely to reduce their physical activity participation and engage in more sedentary behaviours [308-310]. Some evidence suggests sedentary behaviour could have bidirectional relationships with MSP-related conditions [311]. This thesis provides new evidence on the associations of sedentary behaviour with MSP conditions and the potential moderation of such relationships by T2D, which is rising globally and a major risk factor for cardiovascular diseases [61, 98, 276, 312].

Despite the observed inconsistencies in the findings concerning self-reported and device-measured sedentary behaviour, the findings from the four studies collectively indicate that high volumes of sedentary behaviour could be detrimentally associated with MSP conditions or MSP-

related pain outcomes. The adverse associations may be influenced by some factors, including occupational activity and the presence of co-morbidities such as T2D. People living with T2D are more likely to accumulate higher volumes of sedentary behaviour [7] and are also most likely to experience worse detrimental associations with MSP-related outcomes. Furthermore, initiatives that reduce excessive sedentary behaviour, especially in desk-based workers may beneficially reduce MSP conditions or discomforts, particularly when portions of time spent sitting are reallocated to more physically active behaviours of varied intensities like standing and stepping. The detailed evidence synthesised from the studies undertaken in this thesis and the relations to the existing literature are discussed below.

7.3.1 Sedentary behaviour and MSP conditions

This thesis has provided some new evidence on associations between sedentary behaviour and MSP conditions in adults. The associations may, however, be dependent on factors such as the nature of occupational activity exposures. High volumes of daily sedentary behaviour accumulated in non-occupational settings, irrespective of the measure, were observed to be cross-sectionally associated with MSP conditions, including low back pain, knee pain, arthritis, and general MSP. However, some inconsistencies were observed in the associations with respect to the sedentary behaviour assessment instrument. In my systematic review (Study 1), the findings suggest significant cross-sectional associations of self-reported daily time spent in sedentary (sitting) behaviour with low back pain. However, no significant association was observed between device-measured daily sedentary behaviour and low back pain. Study 2 also observed that there is no significant association of device-measured daily sitting time (sedentary behaviour) with low back pain.

Furthermore, the systematic review (Study 1) found inconclusive evidence of a cross-sectional association of device-measured daily sitting time with neck/shoulder pain. Likewise, in Study 2, there was no evidence of significant cross-sectional associations between device-measured daily sitting time and neck/shoulder pain. However, evidence of a cross-sectional association with knee pain of a self-reported daily sedentary behaviour was observed in Study 1 and of device-measured daily sitting time in Study 2. Also, Study 1 provided evidence of cross-sectional associations of self-reported daily sedentary behaviour with arthritis and general MSP. Nevertheless, the evidence observed in Study 1 on associations of daily sedentary behaviour with hip and extremities pain was inconclusive.

For evidence on leisure-time sedentary behaviour (non-occupational), there was inconclusive evidence of cross-sectional associations of both self-reported and device-measured

leisure-time sedentary behaviour with low back, neck/shoulder, and lower extremities pain in Study 1. Similarly, inconclusive evidence was observed in Study 1 on cross-sectional associations of time spent in sedentary behaviours including video gaming, reading, and listening to music, as well as time spent in the common leisure-time sedentary behaviour at home settings, TV time with low back, neck/shoulder, and extremities pain.

Generally, evidence synthesised on prospective associations in Study 1 was inconclusive. For example, insufficient evidence of prospective associations was observed for both self-reported and device-measured daily sedentary behaviour with MSP conditions. However, there was a probable indication in Study 1 that TV time was prospectively associated with general MSP or pain-related outcomes. In Study 3, however, strong evidence of a prospective association of increased volume of TV time at any given time of bodily pain trajectory was observed with increased pain severity.

Most working adults accumulate large proportions of their daily sedentary behaviour in occupational settings [44, 49]. Broadly, the findings in this context suggest there is evidence of associations of occupational sedentary behaviour with MSP conditions, but mainly from cross-sectionally designed studies. The direction of the associations though may be dependent on some occupational factors. Observed inconsistencies in the associations mainly relate to the instrument used to assess sedentary behaviour. My systematic review (Study 1), for instance, suggests that device-measured occupational sedentary behaviour may have protective (negative) associations with MSP conditions including low back pain and neck/shoulder pain in tradespeople who engage in more labour-intensive occupations. This observation may be supportive of the "physical activity paradox" concept which suggests sedentary time among labour-intensive tradespeople allows them some time to rest and recover which is considered to be protective of MSP conditions [52, 53].

While a previous systematic review has documented evidence of a negative association of device-measured sedentary behaviour in tradespeople with low back and neck pain [313], others have indicated no evidence of workplace sitting in non-tradespeople with low back pain [314, 315]. In contrast, evidence of self-reported workplace sitting time among office-based workers (i.e., non-tradespeople) was observed to be cross-sectionally associated with low back and neck/shoulder pain (Study 1). There was, however, an indication in Study 1 of a probable negative cross-sectional association of workplace sitting with lower limb pain in office-based workers. Evidence on prospective associations of workplace sitting with MSP conditions was found to be inconclusive from Study 1. Furthermore, in contrast to some previous evidence [316, 317], the findings of Study 1 suggest that time spent sitting in front of a computer screen (computer time) is cross-sectionally associated with neck/shoulder pain, but there is inconclusive evidence on associations with low back

pain and general MSP. Additionally, vehicle time (time spent sitting in a vehicle or car) was observed in Study 1 to be non-significantly associated with increased odds of low back pain.

7.3.2 Type 2 diabetes as a moderator of the relationship between sedentary behaviour and MSP

Observations from Study 2 and Study 3 indicate that time spent in sedentary behaviour is relatively higher in those with T2D than those without, which supports the suggestion that sedentary behaviour is more pronounced in those with metabolic disorders, such as T2D [7]. Furthermore, it was observed in Study 2 and Study 3 that those with T2D were more likely to report a higher prevalence of MSP or more severe bodily pain. In Study 2, for instance, mean activPAL-derived daily sitting time was observed to be higher in those with T2D who also reported a higher prevalence of knee pain than those with NGM or prediabetes. Similarly, in Study 3, self-reported TV time was observed to be higher in those with T2D as was bodily pain severity than in those without T2D at each of the measurement time points.

My first and second empirical studies (i.e., the Thesis's Study 2 and Study 3) are among the first to examine the associations of sedentary behaviour with MSP conditions or related outcomes separately in those with and without T2D (Study 2) or the potential moderation of the relationships by T2D (Study 3). Though the findings may require further confirmation, there are some informative insights into the potential relationships in this context. The findings from Study 2 show that the observed significant cross-sectional association of daily sitting time with knee pain was driven by the presence of T2D, with the significant association observed only in those with T2D. Furthermore, in Study 3, the observed detrimental association of increased TV time at any given time of bodily pain trajectory with increased pain severity was more pronounced in those with T2D than those with prediabetes or NGM. Compared to those with NGM, the moderation effects of T2D and prediabetes on bodily pain severity with increasing time spent sitting watching television per day were observed to be more pronounced in those with T2D than individuals with prediabetes, and significantly so when the threshold of TV time increased above 2.5 hours per day.

While previous studies have not specifically documented the potential moderation of sedentary behaviour/MSP conditions relationships by T2D, there is an informative body of evidence that T2D is associated with increased risk of some MSP conditions such as knee pain or osteoarthritis [80, 87, 88, 239]. Also, there are some indications from epidemiological studies that suggest sedentary behaviour could have some role in the mechanisms of MSP conditions in those living with T2D [75, 318-320].

7.3.3. Potential mechanisms for the associations of sedentary behaviour with MSP conditions

Although no mechanistic study was undertaken in this thesis to investigate any potential biological mechanisms, the epidemiological findings could assist in developing a better understanding of the plausible roles of sedentary behaviour in the pathophysiology of MSP conditions. MSP conditions are heterogenous and so would be the potential underlying mechanisms which may likely involve the interplay of biological and psychosocial components [321-323]. Notwithstanding some evidence that suggests that sedentary behaviour associations with MSP conditions could potentially be bidirectional [18, 19], higher body weight could in part contribute to the probable mechanisms that underpin these relationships. The mechanical stress of overweight and obesity on some joints, especially weight-bearing joints, as well as local and systemic inflammatory changes may be more devastating in sedentary individuals, leading to structural changes in joints and, consequently, MSP conditions, such as knee and low back pain [324, 325]. Consequently, this could induce a 'downward spiral' effect with the MSP conditions limiting physical activity participation with excessive volumes of sedentary behaviour accumulation. In turn, this may result in further increases in body weight which could worsen and even complicate the MSP conditions.

The underlying mechanisms of MSP conditions in T2D may likely involve a complex set of factors associated with T2D. These include factors such as older age, obesity, and the systemic effect of persistent hyperglycaemia [22, 81, 87], as well as moderating and mediating factors which are likely to involve behavioural and environmental factors. For example, the pathophysiological pathways that could explain knee (pain) osteoarthritis in T2D may include biomechanical joint load and systemic inflammatory pathways [87]. There are some individual-level factors (such as older age and obesity) which are often associated with systemic inflammatory pathways, along with factors related to hyperglycaemia, including advanced glycation end products (AGEs) and receptor of AGE (RAGE) interaction pathway, and reactive oxygen species (ROS) pathway which enhances secretion of pro-inflammatory factors [87, 326, 327]. Collectively, these may contribute to oxidative stress and inflammation processes that promote vascular endothelial dysfunction and joint cartilage degradation leading to joint movement limitations and pain [87, 326, 327]. Figure 7.1 below illustrates the complexity of possible pathways of MSP conditions in T2D with the potential roles that sedentary behaviour may play in these biological mechanisms.

There is evidence suggesting that physical activity could have a protective role in relation to the mechanisms of MSP conditions [321-323]; however, there is a paucity of evidence of the potential role of sedentary behaviour in this regard. There is compelling evidence of associations between sedentary behaviour and adiposity [328] which could be implicated in the associations of sedentary behaviour with MSP conditions, especially in those with T2D. Adipose tissue is

metabolically active, releasing pro-inflammatory cytokines and adipokines that may potentiate systemic inflammatory changes in several organs and tissues [329]. Also, excessive sedentary behaviour is associated with an elevated risk of obesity and increased physical inactivity [330] which can modulate the biomechanical loading pathway of MSP conditions involving weight-bearing joints in older adults [87, 306, 331].

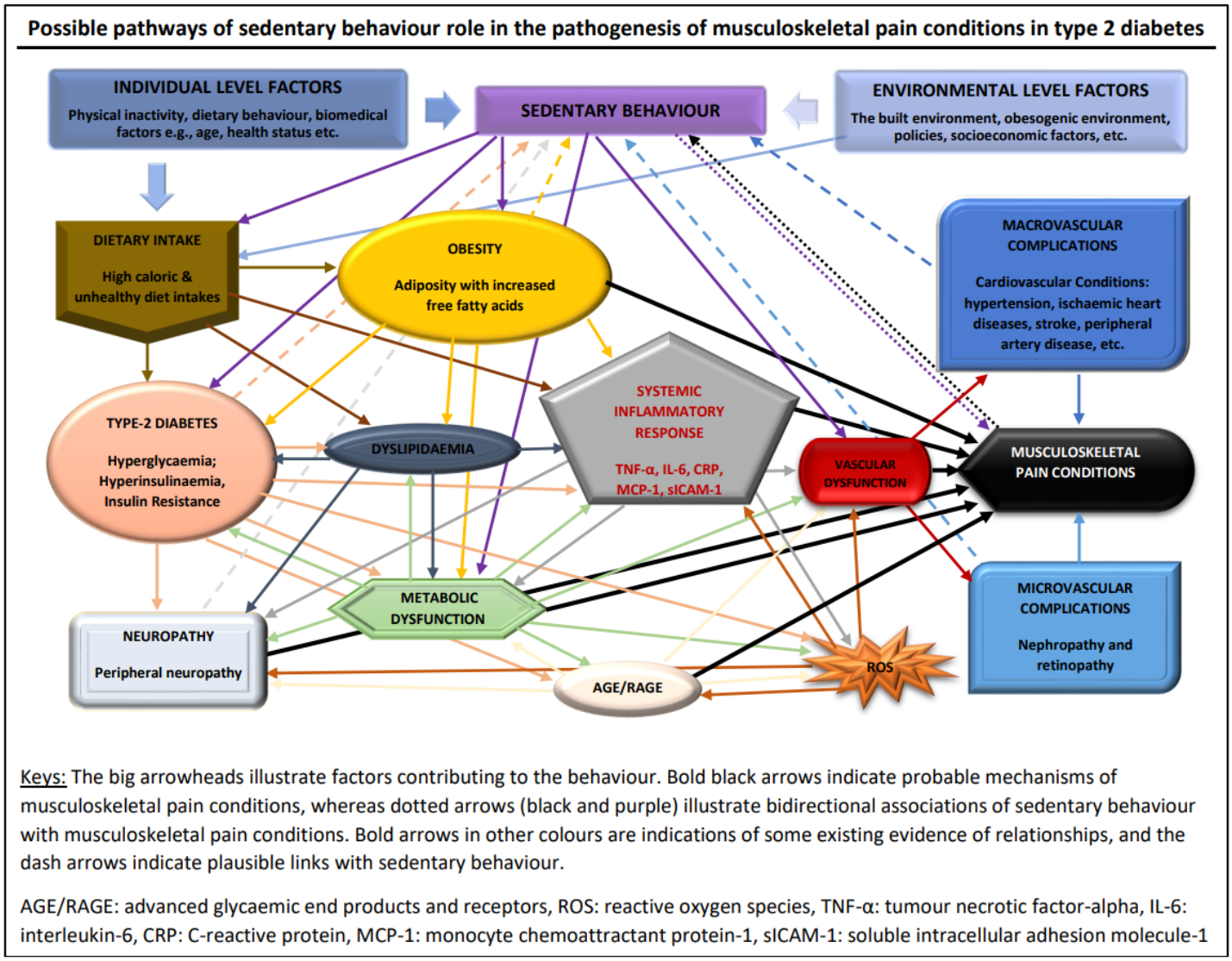

Figure 7.1: Possible pathways of musculoskeletal pain conditions in type 2 diabetes.
This is an illustration of the hypothesised pathways that may explain the plausible biological mechanisms of the associations observed between sedentary behaviour and musculoskeletal pain conditions in type 2 diabetes.

In this context, however, it is important to note that Study 2 and Study 3 undertaken in this thesis accounted for the potential confounding bias of adiposity (BMI in Study 2 and waist circumference in Study 3) and MVPA. Evidence of associations of sedentary behaviour with MSP-

related outcomes (knee pain in Study 2 and bodily pain in Study 3) was observed in these studies, associations which were potentially moderated by T2D. Also, in my systematic review (Study 1), some of the studies reviewed suggest that relationships between sedentary behaviour and MSP conditions may be modulated by adiposity. Taken together, these observations provide some informative evidence on the potential role of behavioural factors such as sedentary behaviour contributing to or augmenting some of the potential pathophysiological pathways of MSP conditions. Sedentary behaviour may potentially act through some of the known relationships with adverse cardiometabolic outcomes, as well as the associations with systemic inflammation and vascular endothelial dysfunction, particularly in those with T2D [40, 203, 221, 306, 332]. Also, there might plausibly be some unknown pathways related to the potential negative pain perception effect of sedentary behaviour [322].

7.3.4 Changing sedentary behaviour and MSP outcomes

In Study 1, evidence synthesised from reviewed intervention and experimental studies indicates changing desk-based (office) workers sitting time can have favourable associations with MSP outcomes. It was found that reducing workplace sitting time was associated with reduced MSP or discomfort at the lower back and neck/shoulder, as well as reduced general MSP. Some previous studies have documented evidence of associations of reduced sedentary behaviour among desk-based workers with reduced MSP-related pain intensity and disability [46-48], which corroborates the findings reported in Study 1 of this thesis. There was no evidence in Study 1, whatsoever, to suggest that workplace sitting reduction correlates with reduced extremities pain.

Study 4 showed that the relative changes in desk-based workers sitting, standing, stepping, and the bout patterns of these behaviours could be important determinants of MSP outcomes. In other words, the balance of changing sitting, standing, and stepping can differentially impact MSP outcomes. The findings indicate that increased standing volume relative to changes in the volume of stepping and sitting in the short term may lead to some increases in multisite MSP outcomes. In contrast, increasing the volume of stepping relative to changes in sitting and standing in the short term could ameliorate MSP symptoms or favourably reduce multisite MSP. In the longer term, increasing standing while reducing sitting and stepping time did not adversely impact multisite MSP outcomes. Furthermore, no significant changes in MSP outcomes were observed for changing short and long bouts of a given behaviour while time spent in the other behaviours remains unchanged. The implications are that changing the volumes of time spent sitting, standing, and stepping may be more important than changing the bout durations of these behaviours for impactful changes in MSP outcomes. However, it is important to note that these observations in Study 4 are dependent on the

bout cut-off thresholds used in the analysis. Previous studies suggest that excessively prolonged static standing bouts of 30 minutes or more could adversely impact MSP outcomes [62, 298].

Therefore, for favourable MSP outcomes, increasing standing as a result of reducing sitting time in the short term should be balanced with concurrent increases in time spent stepping. In the longer term, however, increasing standing alone while reducing sitting time may unlikely worsen MSP outcomes even if stepping remains unchanged or reduced. Observations from hypothetical reallocation of time from sitting to standing or stepping indicate that there are potential benefits of displacing portions of sitting time to standing or stepping while maintaining the usual volume of time spent in the other behaviour. The beneficial impact could be more evident in the longer term. Similarly, a favourable reallocation of time between short and long bouts of activity behaviour (e.g., sitting) with time spent in the volumes of other behaviours held constant could have some beneficial impacts on MSP outcomes.

7.4 Thesis strengths and limitations

This section describes the key strengths and limitations of the thesis that need to be considered while interpreting or making inferences from the findings.

7.4.1 Strengths of the Thesis

The strengths of this thesis have been organised into (1) study designs, (2) datasets and methodology of empirical studies, and (3) statistical analytic approach of empirical studies.

7.4.1.1 Study designs

The four studies conducted in this thesis used different study designs – a systematic review with meta-analysis, a cross-sectional study design, and a prospective study design. Study 1 which is a review study was based on a higher-level study design, a systematic review with evidence synthesised by using both narrative review and meta-analysis. This review study distinctively reviewed cross-sectional and prospective studies, as well as experimental and intervention studies. The evidence synthesis was organised into occupational and non-occupational sedentary behaviour domains with a wide range of outcomes related to MSP conditions examined. Also, evidence was not synthesised from studies conducted exclusively in clinical groups with existing MSP conditions and those of autoimmune-disease-related MSP conditions to provide a better insight into the risk

associations of sedentary behaviour with MSP conditions. Data extracted from homogenous studies were synthesised by using a rigorous meta-analysis, otherwise, evidence was synthesised using a narrative review.

Study 2 utilised a cross-sectional design which is a low-level evidence study design (limiting the drawing of causal conclusions) to examine the associations of sedentary behaviour (daily sitting time) with MSP outcomes in a large population of community-dwelling middle-aged and older adults living with and without T2D. Study 3 and Study 4 were based on a high-level prospective study design, which makes it possible to infer some causal relationships. Study 3 analysed longitudinal data over a 12-year period (the AusDiab Study) to examine the prospective relationships of concurrent changes in sedentary behaviour (TV time) with bodily pain. Whereas, Study 4 utilised data from a prospective cohort of Stand-Up Victoria cluster-randomised controlled trial to examine the relationships with changes in MSP outcomes of changes in the composition of sitting, standing, and stepping, as well as the short and long bouts of these behaviours.

7.4.1.2 Datasets and methodology of empirical studies

Study 2 utilised a cross-sectional dataset of baseline participants of a large sample of middle-aged and older community-dwelling adults from the Maastricht Study. There are several strengths in the Maastricht Study dataset, including the large population-based epidemiological data with the optimisation of the sampling method to oversample people living with T2D. Therefore, it provides a data source with a good representation of people living with T2D, which enhances the generalisability of the findings in this population. The WHO recommended standard clinical assessment and classification methods for T2D were used to ascertain the T2D status of study participants. Furthermore, the sedentary behaviour in this dataset was based on activPAL-derived activity behaviours data. The activPAL is the gold standard instrument with high accuracy for capturing activity behaviours including sitting, standing, and stepping (movement) data to estimate sedentary behaviour and physical activity of different intensities. The Maastricht Study dataset also provides a wide range of measured potential confounding variables which were adjusted for in the analyses.

Study 3 used a three-time point longitudinal dataset over 12 years from the AusDiab Study. The key strength of this dataset is the large nationwide sample of adults sampled from each of the states and territories of Australia, providing some opportunity to generalise the findings in the large population of adults. Also, the AusDiab Study dataset had a sizable number of people with T2D which was assessed according to the WHO recommended standard methods. The main exposure (TV

time) and outcome (bodily pain), as well as the moderator (T2D status), were assessed at each of the data time points. Additionally, this dataset provides a wide range of relevant time-variant and time-invariant covariates which were accounted for in the analytic modelling.

Study 4 utilised a dataset from the Stand-Up Victoria cluster-randomised control trial, which provides prospective data over a 12-month period. The activity behaviours were based on activPAL-derived sitting, standing, and stepping time assessed at the three different time points – baseline, end of the intervention at three-month, and at 12 months after a nine-month maintenance period. In addition, the Stand-Up Victoria Study dataset provides insight into the probable wide variability in changes in activity behaviours to expect in a typical real-world workplace environment when pooling the data by treating the intervention-arm and control-arm participants together as a cohort.

7.4.1.3 Statistical analytic approach of empirical studies

Each of the empirical studies employed a different statistical analytic approach. Whilst Study 2 utilised a simple logistic regression analytical approach, it also examined the non-linear relationships using restricted cubic splines (RCS) with three knots. The RCS analytical method is a rigorous non-linear analytic approach, which helped to compare the linear relationship assumption used in the logistic regressions. The non-linear analysis showed that the relationships observed between daily sitting time (sedentary behaviour) and some of the MSP outcomes, specifically, the neck, shoulder, and low back pain examined in Study 2 may not be linear but curvilinear.

The statistical analytic approach used in Study 3 was based on multilevel growth curve modelling. This analytical approach is the most robust method recommended for the analysis of longitudinally structured data [259, 260]. Also, it is widely considered to be an appropriate approach to handle the multi-level structure in the AusDiab Study which used a stratified cluster sampling method in the recruitment of participants. Furthermore, the multilevel growth curve approach is the most rigorous analytic method to handle missing data in longitudinal studies, by treating them as MAR.

Study 4 used the contemporary compositional data analysis (CoDA) framework. The CoDA method is the most rigorous analytical approach in the behavioural research field for analyses of time-use composite data. The key strength of the CoDA approach in Study 4 is the ability to account for the interdependency of activity behaviours in the composition [261-263]. An additional strength of CoDA is the ability to use the compositional isotemporal substitution method to reallocate time from one behaviour or bouts of a given behaviour at baseline to another behaviour, or a different

bout of that behaviour at follow-up, for an easy and direct interpretation of the effect of compositional changes on the predicted changes in the MSP outcomes.

7.4.2 Limitations of the Thesis

Despite the aforementioned strengths, there are some limitations which need to be considered. The findings in the thesis should, therefore, be interpreted in the context of the limitations described below. The limitations have been organised into (1) casualty inference from low-level evidence-based studies, (2) self-reported data, (3) generalisability of findings, and (4) posthoc analysis of secondary datasets.

7.4.2.1 Casualty inference from low-level evidence-based studies

The empirical studies were based on a wide range of datasets including epidemiological cross-sectional and longitudinal datasets, as well as a prospective dataset from an intervention trial. In addition, Study 1 reviewed cross-sectional and prospective observational studies, as well as experimental/intervention studies. However, some of the thesis' key findings were synthesised from studies that utilised observational cross-sectional data. Specifically, evidence synthesised from the review study (Study 1) was mostly based on findings from cross-sectional studies, as was the evidence from Study 2. Cross-sectional study designs are widely acknowledged to have a high likelihood of reverse causality bias; hence causal conclusions cannot be made from those cross-sectional findings.

In the context of the associations between sedentary behaviour and MSP conditions, reverse causation is a potential bias in cross-sectional findings. MSP and pain-related conditions in most adults, particularly in those living with other co-morbidities such as T2D could adversely impact their physical functioning and mobility, limiting physical activity behaviours and increasing leisure-time sedentary behaviours [126, 333]. Changes in behavioural activities over time may be related to the time course and progression of MSP conditions. Given that there is a probable bidirectional association between MSP conditions and sedentary behaviour [311], further research exploring more large and diverse prospective data to examine relationships between behavioural (activities) changes and MSP conditions may be needed to draw some causal conclusions.

7.4.2.2 Self-reported data

The empirical studies, as well as studies reviewed in the systematic review, used data that were assessed using self-reported subjective instruments which may be liable to estimation bias. In Study 1, most of the observed findings were based on self-reported sedentary behaviour, one of the key limitations identified in the review study. In Study 3, TV time (a common leisure-time sedentary behaviour) was assessed as participants' self-reported time spent watching television on weekdays and weekend days for the past seven days, and there could be a high likelihood of recall bias.

Furthermore, there is no universally acceptable instrument for assessing MSP conditions. Epidemiological studies of MSP or pain-related outcomes often use subjective instruments [162]. Some of these instruments have been shown to have acceptable psychometric properties to accurately assess MSP conditions and related outcomes [162]. The MSP conditions and related outcomes reported in this thesis were mostly based on self-reported data which may be prone to a potential self-reported bias of under- or overestimation which might have influenced the findings of the studies documented in this thesis. Clinical assessments of MSP conditions by medical professionals are more objective with a lower risk of bias [138]; future studies might consider using objective methods of MSP conditions or related outcomes to minimise potential assessment bias.

7.4.2.3 Generalisability of findings

Although empirical Study 2 and Study 3 utilised relatively large sample sizes, these may not qualify as a nationally representative sample to generalise the finding among the middle-aged and older adult population of Australia or the Netherlands. Also, participants recruited into the various empirical studies were mostly white Caucasians, therefore, the findings reflect what might pertain only to this population but not other global population groups. Furthermore, the systematic review (Study 1) did not review sedentary behaviour in all occupational groups, therefore, there should be caution in generalising the findings on the relationships between occupational sedentary and MSP conditions. Likewise, Study 4 consisted of desk-based workers of only one organisation with specific kinds of work groups, hence it may be problematic when the findings are generalised to other organisations with different workgroup populations and environmental structures.

7.4.2.4 Posthoc analysis of secondary datasets

It should be acknowledged that the empirical studies presented in this thesis utilised existing epidemiological observational and intervention-based datasets from three different studies. These studies were designed to answer their specific research questions. While secondary analyses of

these datasets might present some limitations to addressing this thesis' aim, the key exposure variable (sedentary behaviour) and the outcome variable (MSP conditions) of interest in this thesis were measured in each of the datasets used. The empirical studies based on the Maastricht Study (Study 2) and the Stand-Up Victoria Study (Study 4) datasets examined sedentary behaviour which was assessed using activPAL-assessed activity behaviours data, whereas the sedentary behaviour examined in the empirical study based on the AusDiab Study dataset (Study 3) was assessed utilising the study participants' self-reported time spent watching television.

The MSP outcomes examined in the first empirical study (Study 2) were based on acute MSP assessed in the Maastricht Study using a self-reported questionnaire adapted from the United States population-based validated Health Assessment Questionnaire used in the National Health and Nutrition Survey (NHANES) [244]. Study 3 investigated bodily pain which was measured in the Ausdiab Study using the SF36 bodily pain domain questionnaire [162]. The Stand-Up Victoria Study dataset (used for Study 4) used the NMQ instrument to assess acute and chronic MSP outcomes. Furthermore, two of these datasets, the Maastricht Study (used for Study 2) and the AusDiab Study (used for Study 3) also provided comprehensive data on T2D which were clinically (objectively) assessed and classified based on recommended WHO standard guidelines.

7.5 Implications for practice

The thesis findings have some relevant implications for clinical, public health, and occupational health practice in light of the risk associations of sedentary behaviour with MSP conditions and T2D [334]. The clinical burdens of MSP conditions are challenging with regard to their pharmacological management and the adverse impacts they may have on an individual's physical health and functioning, as well as the health care cost and lost productivity [335, 336]. The most concerning is the high prevalence of MSP conditions in people with multi-morbidities [13, 14]. MSP conditions have emerged as one of the common co-morbidities of T2D, and this could pose a challenge for the management of both conditions [21, 23, 79, 80, 119]. For instance, inappropriate pharmacologic management of pain associated with MSP conditions such as the use of some NSAIDs and steroid-based medications can adversely affect glycaemic control in those with coexisting T2D [21]. Also, some MSP conditions can be debilitating, especially multisite MSP and could render many people becoming physically inactive and consequently engaged in excessive sedentary (sitting) behaviours [11, 12, 116, 117, 279, 337]. This could be problematic in those with coexisting T2D since physical activity is widely accepted as being a cornerstone of effective glycaemic control in T2D [20], whereas

sedentary behaviour has been shown to have detrimental impacts on glycaemic control [10, 197-199]. Currently, there is a lack of explicit mechanisms that explain the coexistence of MSP conditions and T2D to inform better management guidelines.

In the context of the thesis findings, the evidence of potential associations of high volumes of sedentary behaviour with adverse outcomes related to MSP conditions and the potential moderation of relationships by T2D could be a stepping stone towards gaining a better understanding of some of the potential biological mechanisms. There is sufficient evidence to suggest that an adequate level of physical activity coupled with reduced sedentary behaviour can be of benefit to reducing MSP outcomes [48, 270, 321-323]. Also, meeting recommended physical activity guidelines is a cornerstone for adequate management of most chronic conditions including T2D and MSP conditions [338]. Although there are no clinical guidelines that specifically outline the reduction of sedentary behaviour for MSP conditions or related outcomes, the importance of physical therapy (which can include exercise prescriptions) has been widely acknowledged [339].

7.5.1 Clinical and public health implications

There is emerging evidence suggesting that reducing the volume of time spent in sedentary behaviour correlates with a reduction in MSP conditions and related outcomes, such as pain intensity and disability [48, 64]. Furthermore, the WHO physical activity and sedentary behaviour guidelines recommend the reduction of volumes of daily sedentary behaviour and breaking up prolonged sitting in addition to adequate levels of physical activity for beneficial health outcomes [272]. Therefore, encouraging people to adhere to the WHO public health guidelines can be a good clinical and public health practice to assist with managing or minimising the risk of MSP conditions. Many vulnerable populations such as older adults with MSP conditions together with other morbidities, especially those with coexisting T2D can find it challenging to engage in adequate levels of MVPA. Public health strategies with realistic goals that encourage and support these vulnerable adults to move more and break up prolonged sedentary behaviours with LIPA such as standing or light walking could lead to important health benefits [340, 341].

Furthermore, public health awareness campaigns directed at highlighting the risk of excessive sedentary behaviour to MSP conditions and related outcomes, and providing practical measures to reduce sedentary behaviour, could help improve the health of many. This could be achieved through increased media messaging to disseminate information on new research findings in this context. For example, a media release on the findings of empirical Study 3 of this thesis attracted both national (Australian) and global media attention [342]; potentially raising public

awareness of the potential risks of MSP conditions, especially in those with cardiometabolic disorders such as T2D of excessive volumes of uninterrupted sedentary time (behaviour).

7.5.2 Occupational health implications

Adults of working age accumulate most of their daily sedentary behaviour in workplace settings [44, 49], most especially in desk-based workers through sitting which can be associated with adverse health outcomes including risk markers of cardiovascular conditions and T2D, as well as MSP conditions and related outcomes [44, 270, 276, 277]. MSP conditions are among the leading cause of ill health and absenteeism among workers [65-68]. There is informative evidence that reducing desk-based workers sitting time can be associated with reduced MSP or discomfort [46, 48, 64, 270], evidence supported by the findings of the thesis. Workplace-based interventions have been demonstrated to be effective in reducing desk-based workers sitting time through increases in standing time and modest changes in stepping [69]. Favourable changes in sitting, standing, and stepping have been shown to have moderate beneficial changes in cardiometabolic risk markers which are more pronounced in the long term [59, 290].

Regarding changes in MSP outcomes of changing these behaviours among desk-based workers, the findings of this thesis suggest there can be some potential beneficial impacts. In the short term, initial MSP or discomforts arising from increasing standing as a result of reduced sitting can be ameliorated when increased standing is concurrently balanced with increased stepping. In the longer term, increasing standing alone as a result of reducing sitting may not worsen MSP symptoms probably due to long-term musculoskeletal systems adaptions and strengthening. Therefore, occupational health advice and strategies that support desk-based workers to reduce time spent sitting through increases in physically active behaviours including standing and stepping, especially during leisure times may not only benefit their cardiometabolic risk markers but also have some favourable impacts on their musculoskeletal health, particularly so in the longer term.

7.6 Implications for future research

The thesis findings also provide some relevant epidemiological insights into developing a better understanding of the role that sedentary behaviour might have in the potential biological mechanisms of MSP conditions in adults with and without T2D. A holistic understanding of the pathophysiological pathways of MSP conditions in adults, including the role of non-modifiable risk

factors (e.g., older age) and modifiable risk factors (e.g., behavioural factors such as sedentary behaviour), would be an important step in developing effective management guidelines. Therefore, further studies in this context may provide additional insights and an in-depth understanding of the associations of sedentary behaviour with MSP conditions and related outcomes. Such future studies could utilise robust study designs, for example, large population-based prospective studies and randomised control trials in diverse populations using reliable assessment instruments, as well as mechanistic studies focusing on potential biological mechanisms that may help to explain the role of sedentary behaviour in MSP conditions in those with and without coexisting T2D. Additionally, future research could also investigate the bidirectional relationships between sedentary behaviour, MSP conditions, and T2D with the exploration of mechanistic roles of attributes of body weight and adiposity in such relationships. Taken together, findings from these future studies could build on and strengthen the evidence from this current thesis' findings.

Currently, there are some ongoing intervention trials, for example, the OPTIMISE your health trial to examine the effects of reducing sedentary behaviour in desk-based workers with T2D on outcomes related to glycaemic management, as well as general health outcomes [343], which has a higher capacity to provide informative evidence in the context of the focus of this thesis. Also, studies utilising large population-based data could explore further the relationships with MSP conditions or related outcomes of temporal patterns of sedentary behaviour accumulation, the interdependency of activity behaviours, and the effects of reallocation of time between activity behaviours. Evidence from such studies would add to the existing body of evidence and insights relevant to identify potential targets for initiatives to reduce sedentary behaviour in those at risk of MSP conditions or related outcomes. Furthermore, in addition to providing evidence for public health initiatives to address excessive sedentary behaviour in the physically inactive, the findings of these future studies could support clinical evidence to inform potential guidelines for non-pharmacologic interventions and adjuvant therapies in vulnerable populations with MSP conditions.

7.6.1 Potential future studies from the OPTIMISE Study

The OPTIMISE Study is an ongoing multicomponent intervention trial at the Physical Activity Laboratory of the Baker Heart and Diabetes Institute to understand the cardiometabolic impacts of reducing middle-aged and older adults desk-based workers with T2D sitting time and increasing their physically active time (standing and stepping) [343]. Several other secondary outcomes are being assessed, including among others musculoskeletal health outcomes using the NMQ assessment tool to capture attributes of MSP conditions. Physical activity behaviours are being assessed by both activPAL and ActiGraph devices as well as Fitbit for tracking activities. Also, self-reported data on

sedentary behaviour and physical activity are being collected [343]. There are six data assessment time points over 18 months period [343]. The OPTIMISE Study dataset would have a high potential and could provide several strengths (objective data) and the capacity to understand the relationships of sedentary behaviour with MSP outcomes exclusively in those living with T2D.

It is important to note here that I have been extensively involved in the OPTIMISE Study throughout my candidature. Specifically, I have been responsible for coordinating the participants' recruitment and management of activity behaviours data. My initial plan was to use the baseline data for a study in this thesis, however, the impacts of the COVID-19 pandemic lockdowns in metropolitan Melbourne significantly affected recruitment. The study was therefore not feasible within the thesis timeline. Future studies exploring the OPTIMISE Study dataset could replicate some of the studies undertaken in this thesis. For instance, empirical Study 4 can be replicated by examining the prospective relationships of changing desk-based workers' sitting, standing, and stepping time composition, as well as changes in the bout patterns of these behaviours with changes in outcomes related to MSP over 18 months. Also, studies can explore the potential moderators and mediators of such relationships.

7.6.2 Other future research prospects

Some previous studies have provided informative evidence of associations between sedentary behaviour and systemic inflammatory biomarkers including TNF-α, leptin, adiponectin, and IL-6 [218-220]. Systemic inflammatory processes associated with systemic response to adiposity have been implicated in the pathophysiology of MSP conditions [329]. Furthermore, the development and the progression of T2D are understood to involve systemic inflammatory processes mediated through adipose tissue-derived cytokines (adipokines), including interleukin (IL)-6 and tumour necrosis factor (TNF-α) which regulates glucose metabolism and insulin resistivity [210-212]. An increased level of IL-6 is known to stimulate hepatic secretion of C-reactive protein (CRP), a systemic biomarker for an inflammatory response which can be clinically assessed [213-215]. This evidence could be explored further in mechanistic studies to specifically examine the biological mechanism of the role of sedentary behaviour in the associations of MSP conditions in those living with T2D.

The OPTIMISE Study dataset, for instance, has included the measurement of some of these systemic inflammatory biomarkers, e.g., CRP, IL-6, and TNF-α which can be objectively (clinically) assessed in addition to cardiometabolic risk markers and biomarkers related to vascular endothelial dysfunction. Such studies could also explore the moderation effects of the presence of MSP on the relationships between sedentary behaviour and systemic inflammatory biomarkers (e.g., CRP, IL-6,

and TNF-α) or biomarkers of vascular endothelial dysfunction in those with T2D. Alternatively, the moderation or mediation by sedentary behaviour of the relationship between systemic inflammatory biomarkers (e.g., CRP, IL-6, and TNF-α) or vascular endothelial dysfunction biomarkers and MSP outcomes in those living with T2D can be investigated.

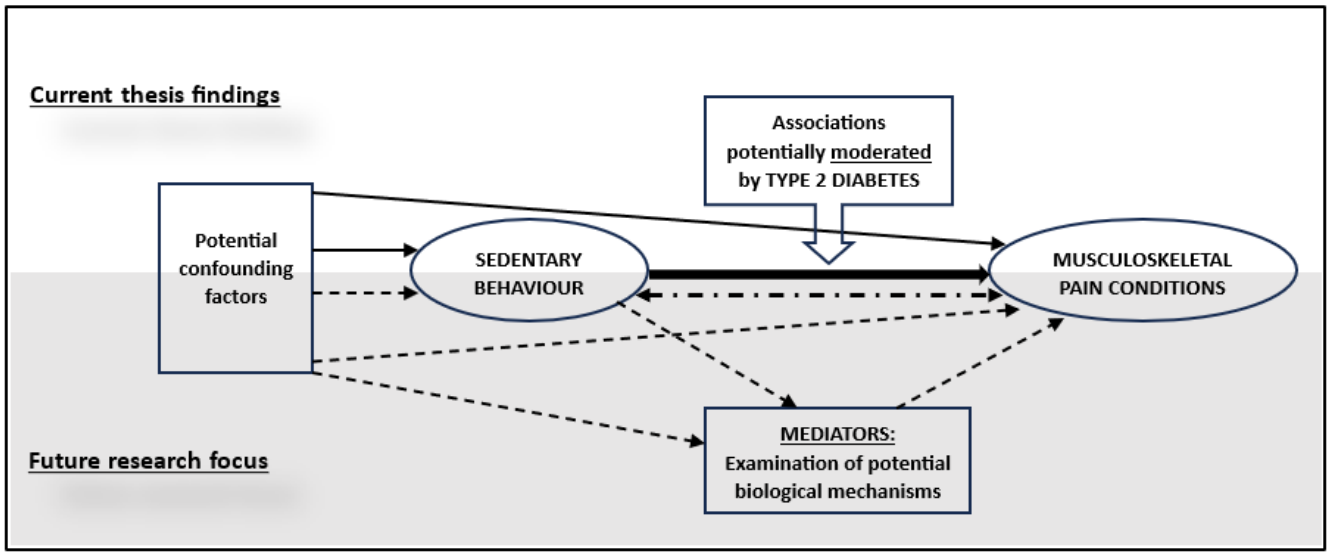

Figure 7.2: Summary of thesis findings and future research focus.
Future research could focus on exploring the potential biological mechanisms that underpin the associations of sedentary behaviour with MSP conditions, especially in those living with T2D. Also, investigate the bidirectional relationships of sedentary behaviour, MSP conditions, and T2D, as well as explore the potential mechanistic role of body weight.

7.7 Conclusions

This thesis found evidence of cross-sectional associations of sedentary behaviour with MSP conditions, though there are some inconsistencies regarding the measure of the sedentary behaviour (self-reported or device measured) and the type of MSP condition. The cross-sectional evidence appears stronger for knee pain, with evidence observed for both self-reported and device-measured sedentary behaviour. The novel contribution of my cross-sectional findings to the existing literature is that the association of sedentary behaviour with knee pain may be driven by T2D. Furthermore, the findings demonstrated the evidence of a prospective association of increased sedentary behaviour (measured as time spent watching television) at any given time of bodily pain trajectory with increased pain severity. This thesis is unique to report that the relationship of increments in TV time at any time point with bodily pain severity is more pronounced in those with

T2D, who are also more likely to accumulate more volumes of sedentary behaviour and experience more severe pain.

In addition, desk-based (office) workers' sedentary behaviour reduction through reducing workplace sitting time was found to correlate with reduced MSP or discomfort. Among desk-based workers, who are more likely to accumulate high volumes of sitting time, displacing portions of time spent sitting by concurrently balancing increments in standing and stepping could ameliorate potential MSP outcomes or discomforts due to increasing standing in the short term. In the longer term, maintenance of the increments in standing as a result of reducing sitting time may be unlikely to adversely impact MSP outcomes, even if stepping reduces. Taking everything into account, reducing sedentary behaviour has the potential to beneficially reduce MSP conditions, however, the intensity of the physically active behaviour that displaces the time spent in sedentary behaviour may be a potential determinant of this outcome. Favourable MSP-related outcomes appear to be more likely to occur when MVPA such as stepping (walking) is increased in addition to LIPA such as standing in the short term. However, the beneficial impacts of isolated increases in LIPA may be more apparent in the longer term. Therefore, advice that encourages vulnerable adults, including desk-based workers to minimise sitting time and break up prolonged sitting by increasing physically active behaviours such as standing and stepping would unlikely adversely impact MSP conditions, especially in the medium- and longer-term but could be of potential benefit to MSP conditions (or musculoskeletal health) in addition to favourable cardiometabolic impacts.

The findings of this thesis provide some relevant implications for clinical, as well as occupational and public health practices, to inform recommendations and management guidelines of MSP conditions in adults, especially in those who may have coexisting T2D. The findings also provide informative epidemiological insights into potential future research for an in-depth understanding of the relationships between sedentary behaviour and MSP conditions. Furthermore, as summarised in Figure 7.2 above, there are some preliminary insights from the thesis' findings that could assist in helping future studies to explore the potential mediation roles of cardiometabolic biomarkers including adiposity or higher body weight, as well as markers of systemic inflammation to better understand the potential biological mechanisms that may explain the sedentary behaviour's roles in the pathogenesis of MSP conditions in adults living with and without T2D. Also, the investigation of bidirectional relationships between sedentary behaviour, MSP conditions, and T2D with the exploration of the potential mechanistic pathways of body weight attributes in such relationships could build on and strengthen the findings of this PhD thesis.

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Appendices

Appendix A: Research portfolios

A1: Manuscripts and publication status

Study One: Published

Dzakpasu FQS, Carver A, Brakenridge CJ, Cicuttini F, Urquhart DM, Owen N, Dunstan DW. **Musculoskeletal pain and sedentary behaviour in occupational and non-occupational settings: a systematic review with meta-analysis.** Int J Behav Nutr Phys Act. 2021 Dec 13;18(1):159. DOI: 10.1186/s12966-021-01191-y.

Study Two: Published

Dzakpasu FQS, Koster A, Owen N, de Galan BE, Carver A, Brakenridge CJ, Boonen A, Bosma H, Dagnelie PC, Eussen SJPM, Sethi P, Stehouwer CDA, Schaper NC, Dunstan DW. **Device-measured sitting time and musculoskeletal pain in adults with normal glucose metabolism, prediabetes and type 2 diabetes – The Maastricht Study**. PLoS One. 18(5): e0285276. DOI: 10.1371/journal.pone.0285276

Study Three: Published

Dzakpasu FQS, Owen N, Carver A, Sethi P, Brakenridge CJ, Salim A, Urquhart DM, Cicuttini F, Dunstan DW. **Television-viewing time and bodily pain in Australian adults with and without type 2 diabetes: 12-year prospective relationships.** BMC Public Health. 2022 Nov 29;22(1):2218. DOI: 10.1186/s12889-022-14566-y.

Study Four: Accepted for publication

Dzakpasu FQS, Owen N, Carver A, Brakenridge CJ, Eakin EG, Healy GN, LaMontagne AD, Moodie M, Straker L, Dunstan DW. **Changes in desk-based workers' sitting, standing and stepping time: short- and longer-term impacts on musculoskeletal pain.** Med Sci Sports Exerc. (Accepted on 22 June 2023)

A2: Conference attended and presentations

Conference presentations

1. The 8th International Society for Physical Activity and Health (ISPAH) Conference, Vancouver, Canada 12th – 14th October 2021) – Virtual oral presentation

   Dzakpasu FQS, Carver A, Brakenridge CJ, Cicuttini F, Urquhart DM, Owen N, Dunstan DW. Musculoskeletal pain and sedentary behaviour in occupational and non-occupational settings: a systematic review with meta-analysis. **ISPAH Conference**, October 2021, Vancouver, Canada.

2. International Society of Behavioral Nutrition and Physical Activity (ISBNPA) Annual Meeting, Phoenix, Arizona, USA (18th – 21st May 2022) – Virtual oral presentation

   Dzakpasu FQS, Owen N, Carver A, Sethi P, Brakenridge CJ, Salim A, Urquhart DM, Cicuttini F, Dunstan DW. *Television-viewing time and prospective changes in bodily pain in middle-aged and older Australian adults with and without type 2 diabetes***. ISBNPA annual meeting**, May 2022, Phoenix, Arizona, USA.

3. The 2nd Asia-Pacific Society for Physical Activity (ASPA) Conference, Melbourne, Australia (28th-29th November 2022) – In-person oral presentation

   Dzakpasu FQS, Owen N, Carver A, Brakenridge CJ, Coenen P, Eakin EG, Healy GN, LaMontagne AD, Moodie M, Sethi P, Straker L, Dunstan DW. *Impacts of changing desk-based workers' sitting, standing and stepping time on musculoskeletal pain.* **ASPA Conference**, November 2022, Melbourne, Australia.

Other presentation

1. San Diego Sedentary Behaviour and Physical Activity Research Collaboration Group for physical activity and sedentary behaviour researchers (3rd March 2021) – Virtual oral presentation

   Title of the presentation: Sedentary behaviour and musculoskeletal pain disorders in occupational and non-occupational settings: a Systematic review with meta-analysis

2. Baker Institute Students' Talk (6th June 2023) – face-to-face oral presentation

   Title of the presentation: Changes in desk-based workers' sitting, standing and stepping time: short- and longer-term impacts on musculoskeletal pain

Appendix B: Declaration of authorship and authors' contributions to the manuscript

B1: Published manuscript

***B1**.1: Study 1*

Dzakpasu FQS, Carver A, Brakenridge CJ, Cicuttini F, Urquhart DM, Owen N, Dunstan DW.

Musculoskeletal pain and sedentary behaviour in occupational and non-occupational settings: a systematic review with meta-analysis. Int J Behav Nutr Phys Act. 2021 Dec 13;18(1):159.

https://doi.org/10.1186/s12966-021-01191-y

Statement of Contributions

FD, AC, NO, and DD contributed substantially to the conceptualisation and development of the scope of the study. FD and CB performed the studies search, screening, and data extraction. FD, AC, NO, and DD synthesized the data and prepared the manuscript. CB, FC, and DU contributed to the revision and realisation of the final draft manuscript. The final manuscript was read and approved by the authors.

Percentage contributions by the authors:

Dzakpasu FQS 65%, Carver A 9%; Brakenridge CJ 3%; Cicuttini F 2.5%; Urquhart DM 2.5%; Owen N 9%; Dunstan DW 9%

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B1.2: Study 2

Dzakpasu FQS, Koster A, Owen N, de Galan BE, Carver A, Brakenridge CJ, Boonen A, Bosma H, Dagnelie PC, Eussen SJPM, Sethi P, Stehouwer CDA, Schaper NC, Dunstan DW. **Device-measured sitting time and musculoskeletal pain in adults with normal glucose metabolism, prediabetes and type 2 diabetes – The Maastricht Study**. PLoS One. 18(5): e0285276. https://doi.org/10.1371/journal.pone.0285276

Statement of Contributions

FD, AK, NO, BG, CB, NS, and DD contributed to the conceptualisation and design of the study. AC contributed to the study design. FD contributed to the statistical analytic design and performed the data analysis and interpreted the results. CB and PS advised on the statistical analysis and results interpretation. FD, AK, NO, BG, AC, NS, and DD prepared the manuscript. AB, HB, PD, SE, and CS contributed to the revision and realisation of the final draft manuscript. The final manuscript has been read and approved by all the authors.

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B1.3: Study 3

Dzakpasu FQS, Owen N, Carver A, Sethi P, Brakenridge CJ, Salim A, Urquhart DM, Cicuttini F, Dunstan DW. **Television-viewing time and bodily pain in Australian adults with and without type 2 diabetes: 12-year prospective relationships.** BMC Public Health. 2022 Nov 29;22(1):2218. https://doi.org/10.1186/s12889-022-14566-y

Statement of Contributions

FD, CB, AC, NO, and DD contributed to the conceptualisation and design of the study. FD and PS contributed to the statistical analytic design. FD performed the data analysis and interpreted the results. PS, CB, and AS advised on the statistical analysis and interpretation of the results. FD, AC, NO, and DD prepared the manuscript. FC and DU contributed to the revision and realisation of the final draft manuscript. The final manuscript has been read and approved by all the authors.

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B1.3.2: Ethics

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This is to certify that amendments to

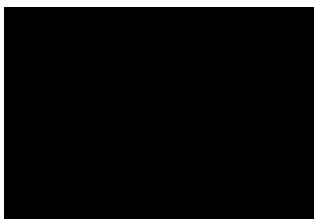
Project: **39/11 AusDiab 3: emerging risk factors for and long-term incidence of cardio-metabolic diseases**

Principal Researcher:
Professor Jonathan Shaw

Amendment:
Change to research personnel – Appointment of Francis Dzakpasu

have been approved in accordance with your amendment application dated **23-Oct-2019** on the understanding that you observe the National Statement on Ethical Conduct in Human Research.

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
Chair, Ethics Committee

Date: **23-Oct-2019**

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).

B2: Submitted manuscripts yet to be published

B2.1: Study 4 – accepted for publication

Dzakpasu FQS, Owen N, Carver A, Brakenridge CJ, Eakin EG, Healy GN, LaMontagne AD, Moodie M, Coenen P, Straker L, Dunstan DW. **Changes in desk-based Workers' sitting, standing and stepping time: short- and longer-term impacts on musculoskeletal pain.** Med Sci Sports Exerc. (Accepted on 22 June 2023 – scheduled to be published in print in December 2023)

Statement of Contributions

FD, NO, AC, CB, and DD contributed to the conceptualisation and design of the study. FD contributed to the statistical analytic design and performed the data analysis and interpreted the results. CB advised on the statistical analysis and results interpretation. FD, NO, AC, and DD prepared the manuscript. CB, EE, GH, AL, MM, CP, and LS contributed to the revision and realisation of the final draft manuscript. The final manuscript has been read and approved by all the authors.

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Note: Evidence of manuscript acceptance and in-press – Study 4

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Action	Manuscript Number	Title	Initial Date Submitted	Status Date	Current Status
Action Links	MSSE-D-23-00142	Changes in Desk-Based Workers' Sitting, Standing and Stepping Time: Short- and Longer-Term Impacts on Musculoskeletal Pain	01 Mar 2023	22 Jun 2023	Accept

Page: 1 of 1 (1 total completed submissions)

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Action	Manuscript Number	Article Title	Initial Date Submitted	Final Decision Date
Fees and Payments Send E-mail	MSSE-D-23-00142R2	Changes in Desk-Based Workers' Sitting, Standing and Stepping Time: Short- and Longer-Term Impacts on Musculoskeletal Pain	01 Mar 2023	22 Jun 2023

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Appendix C: Supplementary materials of the studies

C1: Study 1 supplementary

Supplementary materials for Study 1 have been published online by the International Journal of Behavioral Nutrition and Physical Activity together with the manuscript and are accessible at

DOI: https://doi.org/10.1186/s12966-021-01191-y

Additional file 1: Supplementary Table 1.

C2: Study 2 supplementary

Supplementary material for Study 2 is accessible online together with the published manuscript at PLOS ONE.

DOI: https://doi.org/10.1371/journal.pone.0285276

S1 File.

https://doi.org/10.1371/journal.pone.0285276.s001
(PDF)

C3: Study 3 supplementary

Supplementary material for Study 3 is accessible online together with the published manuscript at BMC Public Health

DOI: https://doi.org/10.1186/s12889-022-14566-y

Additional file 1: 12889_2022_14566_MOESM1_ESM.docx

C4: Study 4 supplementary

<u>Supplementary File:</u> Changes in Desk-Based Workers' Sitting, Standing and Stepping Time: Short- and Longer-Term Impacts on Musculoskeletal Pain

Compositional change estimation

The three- and 12-month compositional changes (e.g., ΔSitting, ΔStanding, ΔShort-stepping bout and ΔLong-stepping bout) were estimated using Aitchison's perturbation principle analogous to arithmetic addition or subtraction. First, each of the compositions at three- and 12-month were expressed as a ratio of the baseline composition, for example, $Sitting_{3M}/Sitting_{0M}$, $Standing_{3M}/Standing_{0M}$, $Short\text{-}bout\ stepping_{3M}/Short\text{-}bout\ stepping_{0M}$ and $Long\text{-}bout\ stepping_{3M}/Long\text{-}bout\ stepping_{0M}$ for three-month and $Sitting_{12M}/Sitting_{0M}$, $Standing_{12M}/Standing_{0M}$, $Short\text{-}bout\ stepping_{12M}/Short\text{-}bout\ stepping_{0M}$ and $Long\text{-}bout\ stepping_{12M}/Long\text{-}bout\ stepping_{0M}$ for 12-month. Secondly, each of the compositions' ratios at three-month was divided by the sum of the three-month compositional ratios for the three-month compositional changes. Similarly, the 12-month compositions' ratios were divided by the sum of the compositional ratios at 12-month for the 12-month compositional changes. Therefore, equal compositions of Sitting, Standing, Short-bout stepping, and Long-bout stepping at baseline and three-month or 12-month would mean equal compositional changes, thus:

$$\Delta Sitting = \frac{1}{4};\ \Delta Standing = \frac{1}{4};\ \Delta Short - stepping\ bout = \frac{1}{4};\ \Delta Long - stepping\ bout\ = \frac{1}{4}$$

Baseline characteristics and activity compositions of the completers and the dropouts.

Table S1a: Baseline characteristics of three-month completer and dropout participants

Variables	Completers (n = 194)	Dropouts (n = 30)	p-value
	Mean (SD) or *%*	Mean (SD) or *%*	
Age	45.2 (9.4)	46.9 (9.5)	0.362
Gender			0.525
Women	67.5*%*	73.3%	
Men	32.5*%*	26.7%	
BMI, kgm^{-2}	28.2 (6.2)	27.0 (5.5)	0.276
Groups			0.940
Intervention	59.3%	60.0%	
Control	40.7%	40.0%	
Education level			0.345
University graduate	37.6%	46.7%	
Non-university graduate	62.4%	53.3%	
Smoking status			0.444
Yes	17.5%	23.3%	
No	82.5%	76.7%	
Activity behaviour (Overall waking hours)			
Sitting, hrs/16 waking hrs	622.0 (79.7)	608.1 (89.7)	0.424
Short-sitting (<20min)	213.6 (61.4)	208.8 (53.2)	0.653
Long-sitting (≥20min)	408.4 (110.0)	399.3 (109.0)	0.671
Standing, hrs/16 waking hrs	234.9 (65.6)	244.1 (67.9)	0.489
Short-standing (<10min)	218.2 (57.1)	228.5 (61.2)	0.388
Long-standing (≥10min)	16.7 (19.7)	15.6 (10.9)	0.653
Stepping, hrs/16 waking hrs	103.1 (28.9)	107.8 (32.0)	0.449
Short-stepping (<1min)	67.0 (20.7)	69.9 (20.0)	0.463
Long-stepping (≥1min)	36.1 (19.3)	37.9 (23.2)	0.687
Multisite Musculoskeletal pain (Average MSP score)			
Acute (i.e., past seven-days)	3.4 (2.6)	3.6 (2.3)	0.664
Chronic (i.e., past three-months)	4.7 (2.8)	4.6 (2.4)	0.836

Note: Only completers were considered in the main analysis. The dropouts include those who dropped out of the study, as well as those with missing activity behaviour (exposure) data and musculoskeletal pain (outcome) data.

Table S1b: Baseline characteristics of 12-month completer and dropout participants

Variables	Completers (n = 151)	Dropouts (n = 73)	p-value
	Mean (SD) or *%*	Mean (SD) or *%*	
Age	45.2 (9.1)	45.9 (10.0)	0.614
Gender			0.727
Women	67.6*%*	69.9%	
Men	32.4*%*	30.1%	
BMI, kgm^{-2}	27.6 (5.3)	29.0 (7.5)	0.154
Groups			0.697
Intervention	60.3%	57.5%	
Control	39.7%	42.5%	
Education level			0.327
University graduate	41.1%	34.3%	
Non-university graduate	58.9%	65.7%	
Smoking status			**0.005**
Yes	13.3%	28.8%	
No	86.7%	71.2%	
Activity behaviour (Overall waking hours)			
Sitting, hrs/16 waking hrs	619.2 (81.2)	622.0 (81.1)	0.809
Short-sitting (<20min)	208.5 (58.1)	222.2 (63.9)	0.123
Long-sitting (≥20min)	410.7 (105.6)	399.8 (118.1)	0.504
Standing, hrs/16 waking hrs	236.5 (67.4)	235.5 (63.0)	0.913
Short-standing (<10min)	219.8 (58.8)	219.2 (55.5)	0.941
Long-standing (≥10min)	16.7 (18.9)	16.3 (18.7)	0.881
Stepping, hrs/16 waking hrs	104.3 (28.6)	102.4 (31.0)	0.660
Short-stepping (<1min)	66.9 (20.8)	68.4 (20.2)	0.607
Long-stepping (≥1min)	37.4 (19.4)	34.0 (20.6)	0.239
Multisite Musculoskeletal pain (Average MSP score)			
Acute (i.e., past seven-days)	3.6 (2.6)	3.3 (2.5)	0.407
Chronic (i.e., past three-months)	4.8 (2.8)	4.4 (2.8)	0.317

Note: Only completers were considered in the main analysis. The dropouts include those who dropped out of the study, as well as those with missing activity behaviour (exposure) data and musculoskeletal pain (outcome) data.

Sensitivity analyses

1. **A 16-hour waking hours three-part composition – Changes in sitting, standing, and stepping**

Time spent in these compositions was standardised to 16-hour waking hours [59]. Participants spent time in each of these compositions at baseline, three-month, and 12-month, hence no issue of zero-time use. Using Aitchison's perturbation principle (a compositional operation which is analogous to arithmetic addition or subtraction [287, 288]), three- and 12-month compositional changes (ΔSitting, ΔStanding, and ΔStepping) were estimated. First, each of the compositions at three- and 12-month were expressed as a ratio of the baseline composition, thus $Sitting_{3M}/Sitting_{0M}$, $Standing_{3M}/Standing_{0M}$, and $Stepping_{3M}/Stepping_{0M}$ for three-month and $Sitting_{12M}/Sitting_{0M}$, $Standing_{12M}/Standing_{0M}$, and $Stepping_{12M}/Stepping_{0M}$ for 12-month. Secondly, each of the compositions' ratios at three-month was divided by the sum of the three-month compositional ratios for the three-month compositional changes. Similarly, the 12-month compositions' ratios were divided by the sum of the compositional ratios at 12-month for the 12-month compositional changes. Therefore, equal compositions of Sitting, Standing, and Stepping at baseline and three-month or 12-month would mean equal compositional changes [59], thus:

$$\Delta Sitting = \frac{1}{3}, \quad \Delta Standing = \frac{1}{3}, \quad and \quad \Delta Stepping = \frac{1}{3}$$

The 3-part compositional change was transformed into two isometric log-ratio (ilr) coordinates = (ilr_1, ilr_2). A sequential binary partition based on a permutation principle [297] was applied and the vector of ilr-coordinates representing $sitting_{\Delta}$ relative to $standing_{\Delta}$ and $stepping_{\Delta}$ were constructed as follows:

1. Model 1 ilr-coordinates – Sitting change relative to non-sitting (others – standing and stepping) changes

$$\text{ilr} = \left(\text{ilr}_1 = \sqrt{\frac{2}{3}} ln \frac{\Delta Sitting}{\sqrt{\Delta Standing \,.\, \Delta Stepping}}, \quad \text{ilr}_2 = \sqrt{\frac{1}{2}} ln \frac{\Delta Standing}{\Delta Stepping} \right)$$

Where, ilr_1 coordinate expresses the relative importance of one behaviour composition (e.g., in the above equation, ΔSitting) to the geometric average of the other behaviour compositions (thus, ΔStanding and ΔStepping), and ilr_2 accounts for the balance of ΔStepping and ΔStanding. The principle used allows different permutations of the activity behaviours for each to in turn be the first part of the composition to be transformed into ilr_1 [261, 297]. Thus, for

2. Model 2 ilr-coordinates – Standing change relative to non-standing (others – stepping and sitting) changes:

$$\text{ilr} = \left(\text{ilr}_1 = \sqrt{\frac{2}{3}} ln \frac{\Delta Standing}{\sqrt{\Delta Stepping \,.\, \Delta Sitting}}, \;\; \text{ilr}_2 = \sqrt{\frac{1}{2}} ln \frac{\Delta Stepping}{\Delta Sitting} \right),$$

and for

3. Model 3 ilr-coordinates – Stepping change relative to non-stepping (others – sitting and standing) changes:

$$\text{ilr} = \left(\text{ilr}_1 = \sqrt{\frac{2}{3}} ln \frac{\Delta Stepping}{\sqrt{\Delta \text{Sitting} \,.\, \Delta \text{Standing}}}, \;\; \text{ilr}_2 = \sqrt{\frac{1}{2}} ln \frac{\Delta \text{Sitting}}{\Delta \text{Standing}} \right)$$

Table S2: Sensitivity analysis: The relative relationships of changes in sitting, standing, and stepping (three-part composition) with multisite musculoskeletal pain

MSP score	Short-term (three-month) changes (n = 194)		Long-term (12-month) changes (n = 151)	
	ilr1	ilr2	ilr1	ilr2
	β **(95% CI)**	***β*** **(95% CI)**	***β*** **(95% CI)**	***β*** **(95% CI)**
Model 1	*Sitting vs. Others*	*Standing vs. Stepping*	*Sitting/ vs. Others*	*Standing vs. Stepping*
Acute	0.85 (- 0.59 to 2.29)	**2.47 (0.63 to 4.32)**	0.69 (- 0.91 to 2.30)	0.43 (- 1.86 to 2.72)
Chronic	0.77 (- 0.56 to 2.16)	**2.07 (0.33 to 3.80)**	0.06 (- 1.51 to 1.63)	- 0.44 (- 2.68 to 1.80)
Model 2	*Standing vs. Others*	*Stepping vs. Sitting*	*Standing /vs. Others*	*Stepping vs. Sitting*
Acute	**1.72 (0.22 to 3.21)**	**- 1.98 (- 3.78 to -0.17)**	- 0.03 (- 1.71 to 1.77)	- 0.82 (- 3.01 to 1.37)
Chronic	1.41 (- 0.01 to 2.79)	**- 1.70 (- 3.42 to -0.03**)	- 0.41 (- 2.11 to 1.29)	0.17 (- 1.97 to 2.31)
Model 3	*Stepping vs. Others*	*Sitting vs. Standing*	Stepping vs. Others	Sitting vs. Standing
Acute	**- 2.57 (- 4.55 to -0.59)**	- 0.50 (- 1.75 to 0.75)	- 0.72 (- 3.20 to 1.76)	0.39 (- 0.92 to 1.69)
Chronic	**- 2.18 (- 4.05 to - 0.33)**	- 0.37 (- 1.51 to 0.84)	0.35 (- 2.06 to 2.77)	0.27 (- 1.00 to 1.54)

- *β* – coefficient, n – sample size, ilr – isometric log-ratio
- For 3-part compositions, ilr1 represents the change in one composition (the first composition in the order) relative to the other two compositions; ilr2 represents the change in the second composition in the order relative to the third composition while holding the first composition constant.
- Models were adjusted for the groups (intervention and control), age, gender, baseline BMI, education level, and smoking status.
- Statistically significant ($p < 0.05$) associations are in boldface.
- Acute – 7-days prevalence of pain; Chronic – 3-month prevalence of pain

2. A 24-hour four-part composition – Changes in sitting, standing, stepping, and 'other-time' (sleep, time in bed, and non-wear time)

This analysis was performed to check whether the decision to exclude 'other-time' in the 16-hour waking hours composition is reasonable.

Model 1: sitting, standing, stepping, and 'other-time'

The ilr coordinates:

$$\text{ilr} = \begin{pmatrix} ilr_1 = \sqrt{\frac{3}{4}} ln \frac{\Delta Sitting}{\sqrt[3]{\Delta Standing \cdot \Delta Stepping \cdot \Delta' Other - time'}}, \\ ilr_2 = \sqrt{\frac{2}{3}} ln \frac{\Delta Standing}{\sqrt{\Delta Stepping \cdot \Delta' Other - time'}}, \\ ilr_3 = \sqrt{\frac{1}{2}} ln \frac{\Delta Stepping}{\Delta' Other - time'} \end{pmatrix}$$

Model 2: standing, stepping, 'other-time', and sitting

The ilr coordinates:

$$\text{ilr} = \begin{pmatrix} ilr_1 = \sqrt{\frac{3}{4}} ln \frac{\Delta Standing}{\sqrt[3]{\Delta Stepping \cdot \Delta' Other - time' \cdot \Delta Sitting}}, \\ ilr_2 = \sqrt{\frac{2}{3}} ln \frac{\Delta Stepping}{\sqrt{\Delta' Other - time' \cdot \Delta Sitting}}, \\ ilr_3 = \sqrt{\frac{1}{2}} ln \frac{\Delta' Other - time'}{\Delta Sitting} \end{pmatrix}$$

Model 3: stepping, 'other-time', sitting, and standing

The ilr coordinates:

$$\text{ilr} = \begin{pmatrix} ilr_1 = \sqrt{\frac{3}{4}} ln \frac{\Delta Stepping}{\sqrt[3]{\Delta' Other - time' \cdot \Delta Sitting \cdot \Delta Standing}}, \\ ilr_2 = \sqrt{\frac{2}{3}} ln \frac{\Delta' Other - time'}{\sqrt{\Delta Sitting \cdot \Delta Standing}}, \\ ilr_3 = \sqrt{\frac{1}{2}} ln \frac{\Delta Sitting}{\Delta Standing} \end{pmatrix}$$

Model 4: 'other-time', sitting, standing, and stepping

The ilr coordinates:

$$\text{ilr} = \begin{pmatrix} ilr_1 = \sqrt{\frac{3}{4}} ln \frac{\Delta' Other - time'}{\sqrt[3]{\Delta Sitting \cdot \Delta Standing \cdot \Delta Stepping}}, \\ ilr_2 = \sqrt{\frac{2}{3}} ln \frac{\Delta Sitting}{\sqrt{\Delta Standing \cdot \Delta Stepping}}, \\ ilr_3 = \sqrt{\frac{1}{2}} ln \frac{\Delta Standing}{\Delta Stepping} \end{pmatrix}$$

Table S3: Sensitivity analysis: The relative relationships of changes in sitting, standing, stepping, and 'other-time' (four-part composition) with multisite musculoskeletal pain

	Short-term (three-month) changes (n = 194)			Long-term (12-month) changes (n = 151)		
	Ilr1	**Ilr2**	**Ilr3**	**Ilr1**	**Ilr2**	**Ilr3**
	***β* (95% CI)**	***β* (95% CI)**	***β* (95% CI)**	***β* (95% CI)**	***β* (95% CI)**	***β* (95% CI)**
Model 1	*Sitting vs All others*	*Standing vs. Stepping & 'Other-time'*	*Stepping vs. 'Other-time'*	*Sitting vs All others*	*Standing vs. Stepping & 'Other-time'*	*Stepping vs. 'Other-time'*
Acute	0.65 (- 1.33 to 2.63)	1.86 (- 0.14 to 3.86)	-1.66 (- 3.67 to 0.35)	**2.20 (0.07 to 4.33)**	1.63 (- 0.65 to 3.91)	1.43 (- 0.86 to 3.72)
Chronic	0.12 (- 1.70 to 2.03)	1.14 (- 0.73 to 3.00)	**-1.96 (- 3.84 to - 0.06)**	1.40 (- 0.69 to 3.48)	0.79 (- 1.44 to 3.03)	1.80 (- 0.45 to 4.05)
Model 2	*Standing vs All others*	*Stepping vs 'Other-time' & sitting*	*'Other-time' vs Sitting*	*Standing vs All others*	*Stepping vs 'Other-time' & sitting*	*'Other-time' vs Sitting*
Acute	1.54 (- 0.05 to 3.12)	**- 2.06 (- 3.82 to - 0.29)**	- 0.23 (- 2.75 to 2.28)	0.80 (- 0.99 to 2.59)	- 0.07 (- 2.21 to 2.06)	**- 2.98 (- 5.68 to - 0.29)**
Chronic	1.03 (- 0.47 to 2.50)	**- 1.94 (- 3.60 to - 0.29)**	0.56 (- 1.85 to 2.88)	0.28 (- 1.47 to 2.03)	0.77 (-1.32 to 2.86)	- 2.27 (- 4.91 to 0.37)
Model 3	*Stepping vs All others*	*'Other-time' vs Sitting & standing*	*Sitting vs Standing*	*Stepping vs All others*	*'Other-time' vs Sitting & standing*	*Sitting vs Standing*
Acute	**- 2.45 (- 4.34 to - 0.56)**	- 0.58 (- 3.16 to 1.99)	- 0.54 (- 1.87 to 0.78)	- 0.34 (- 2.66 to 1.99)	**- 2.95 (- 5.73 to - 0.17)**	0.86 (- 0.51 to 2.22)
Chronic	**- 2.18 (- 3.95 to - 0.40)**	0.31 (- 2.12 to 2.70)	- 0.56 (- 1.77 to 0.73)	0. 63 (- 1.65 to 2.91)	- 2.23 (- 4.95 to 0.50)	0.68 (- 0.65 to 2.02)
Model 4	*'Other-time' vs All others*	*Sitting vs standing & stepping*	*Standing vs Stepping*	*'Other-time' vs All others*	*Sitting vs standing & stepping*	*Standing vs Stepping*
Acute	0.27 (- 2.17 to 2.70)	0.78 (- 0.81 to 2.37)	**2.44 (0.57 to 4.31)**	**- 2.67 (- 5.29 to - 0.05)**	1.39 (- 0.33 to 3.12)	0.70 (- 1.58 to 2.97)
Chronic	1.03 (- 1.29 to 3.29)	0.49 (- 0.97 to 2.02)	**1.97 (0.20 to 3.71)**	- 2.31 (- 4.87 to 0.25)	0.66 (- 1.03 to 2.36)	- 0.21 (- 2.44 to 2.02)

- *β* – coefficient, n – sample size, ilr – isometric log-ratio **Note:** *'Other-time'* include time in bed, sleep time, and non-wear time

- The ilr1 represents change in the volume of one activity composition (the first activity composition in the order) relative to changes in volumes of all the other compositions; ilr2 represents change in the volume of the second activity composition in the order relative to change in volume of the third and fourth activity compositions in the order while holding the first composition constant; ilr3 represents the ratio of the third composition with the fourth composition in the order with the first and second activity compositions held constant.
- Models adjusted for the groups (intervention and control), age, gender, baseline BMI, education level, and smoking status.
- Statistically significant ($p < 0.05$) associations are in boldface.
- Acute – 7-days prevalence of pain; Chronic – 3-month prevalence of pain

3. Imputation sensitivity analysis

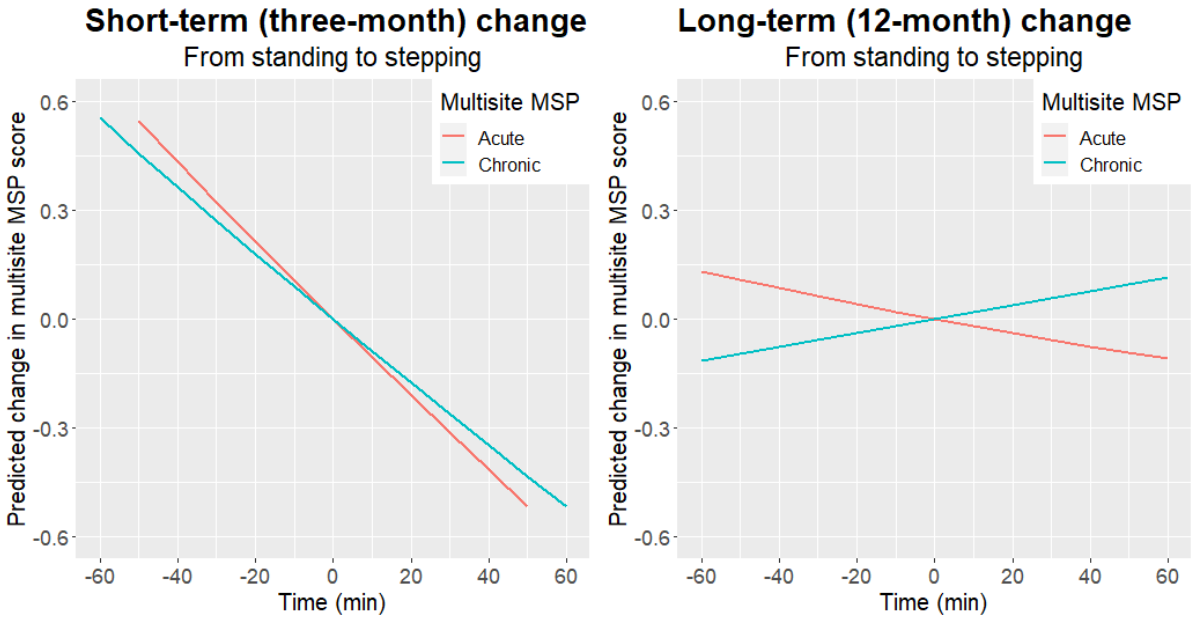
A sensitivity analysis to check whether attrition had any impact on the findings using an imputation method. The drop outs, especially in the intervention group were mainly due to adverse events with some being musculoskeletal pain related [69]. Last-observation-carried-forward (LOCF)' imputation was used with baseline data imputed for missing data at three-month follow-up, and three-month data was imputed for missing data at the 12-month follow-up.

Table S4: Imputation sensitivity analysis: The relative relationships of changes in sitting, standing, and stepping (three-part composition) with multisite musculoskeletal pain (n = 224)

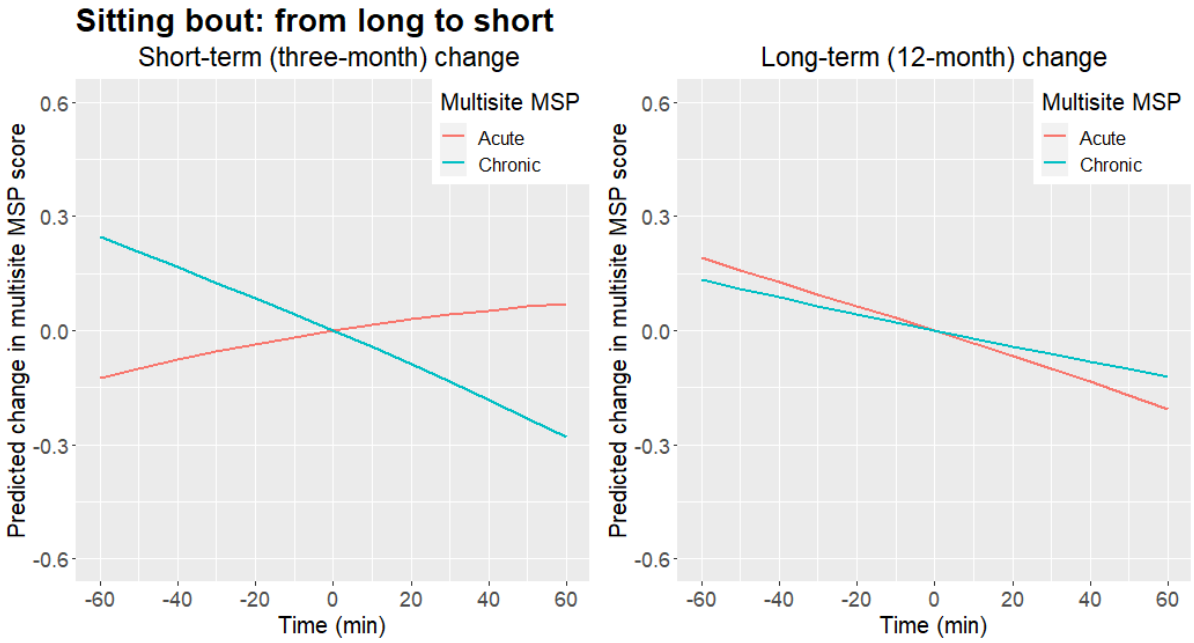
MSP score	Short-term (three-month) changes		Long-term (12-month) changes	
	ilr1	ilr2	ilr1	ilr2
	β (95% CI)	*β* (95% CI)	*β* (95% CI)	*β* (95% CI)
Model 1	*Sitting vs. Others*	*Standing vs. Stepping*	*Sitting/ vs. Others*	*Standing vs. Stepping*
Acute	0.80 (- 0.46 to 2.05)	**2.06 (0.42 to 3.70)**	0.54 (- 0.71 to 1.80)	0.76 (- 0.88 to 2.41)
Chronic	0.72 (- 0.44 to 1.94)	**1.60 (0.05 to 3.15)**	0.01 (- 1.30 to 1.32)	- 0.14 (- 1.86 to 1.59)
Model 2	*Standing vs. Others*	*Stepping vs. Sitting*	*Standing /vs. Others*	*Stepping vs. Sitting*
Acute	**1.39 (0.06 to 2.72)**	**- 1.72 (- 3.30 to -0.14)**	0.39 (- 0.90 to 1.68)	- 0.85 (- 2.47 to 0.76)
Chronic	1.02 (- 0.25 to 2.27)	- 1.43 (- 2.95 to 0.05)	- 0.12 (- 1.48 to 1.23)	0.06 (- 1.64 to 1.75)
Model 3	*Stepping vs. Others*	*Sitting vs. Standing*	Stepping vs. Others	Sitting vs. Standing
Acute	**- 2.19 (- 3.93 to -0.44)**	- 0.34 (- 1.45 to 0.76)	- 0.93 (- 2.72 to 0.85)	0.09 (- 0.96 to 1.14)
Chronic	**- 1.75 (- 3.41 to - 0.11)**	- 0.17 (- 1.19 to 0.90)	0.11 (- 1.76 to 1.98)	0.08 (- 1.02 to 1.18)

- *β* – coefficient, n – sample size, ilr – isometric log-ratio
- The imputation used last-observation-carried-forward (single imputation) – baseline data imputed for missing data at three-month and three-month data for missingness at 12-month.
- For 3-part compositions, ilr1 represents the change in one composition (the first composition in the order) relative to the other two compositions; ilr2 represents the change in the second composition in the order relative to the third composition while holding the first composition constant.
- Models were adjusted for the groups (intervention and control), age, gender, baseline BMI, education level, and smoking status.
- Statistically significant ($p < 0.05$) associations are in boldface.
- Acute – 7-days prevalence of pain; Chronic – 3-month prevalence of pain

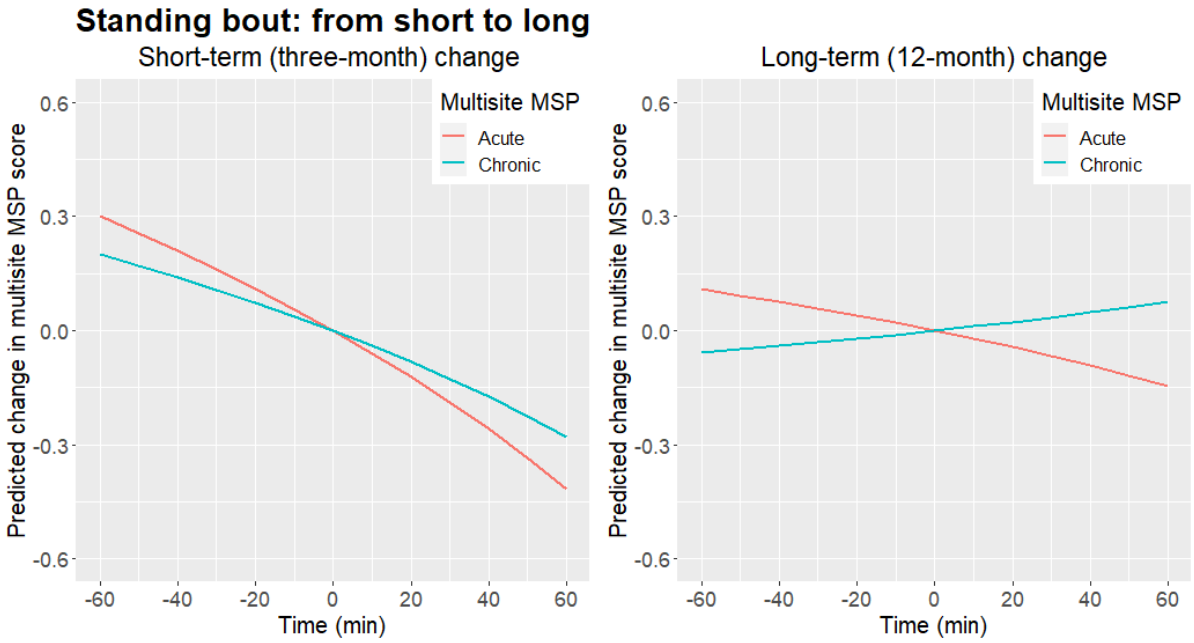
Compositional isotemporal reallocation



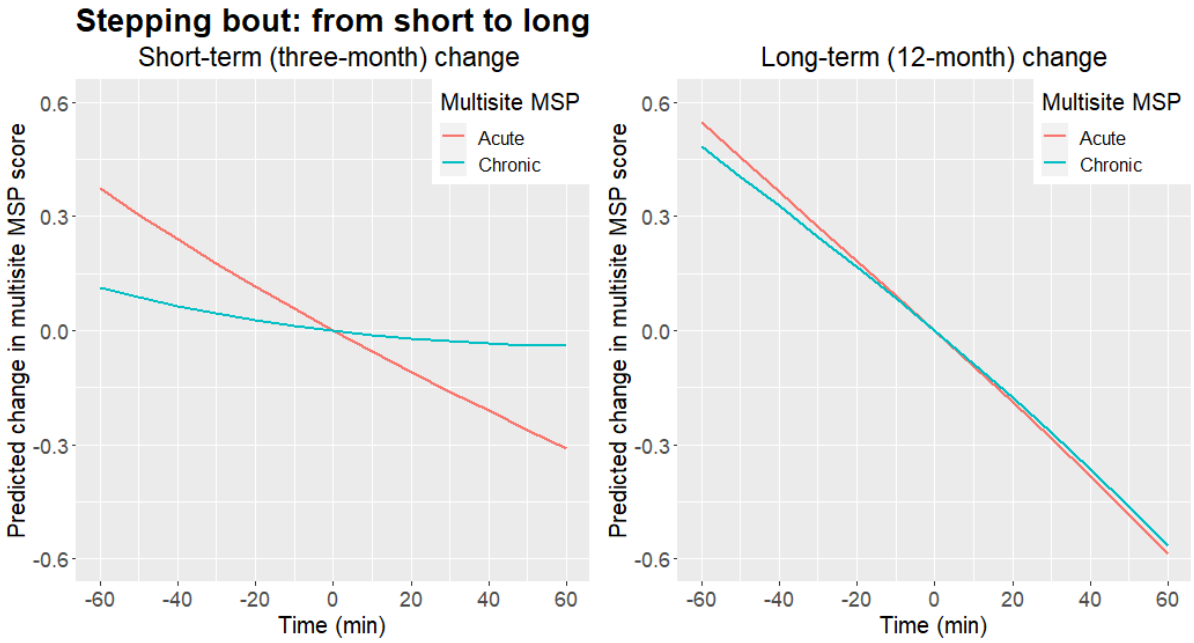
Supplementary Digital Content 2: Isotemporal reallocation of time from standing at baseline to stepping at three- and 12-month follow-ups with the predicted changes in multisite MSP scores.



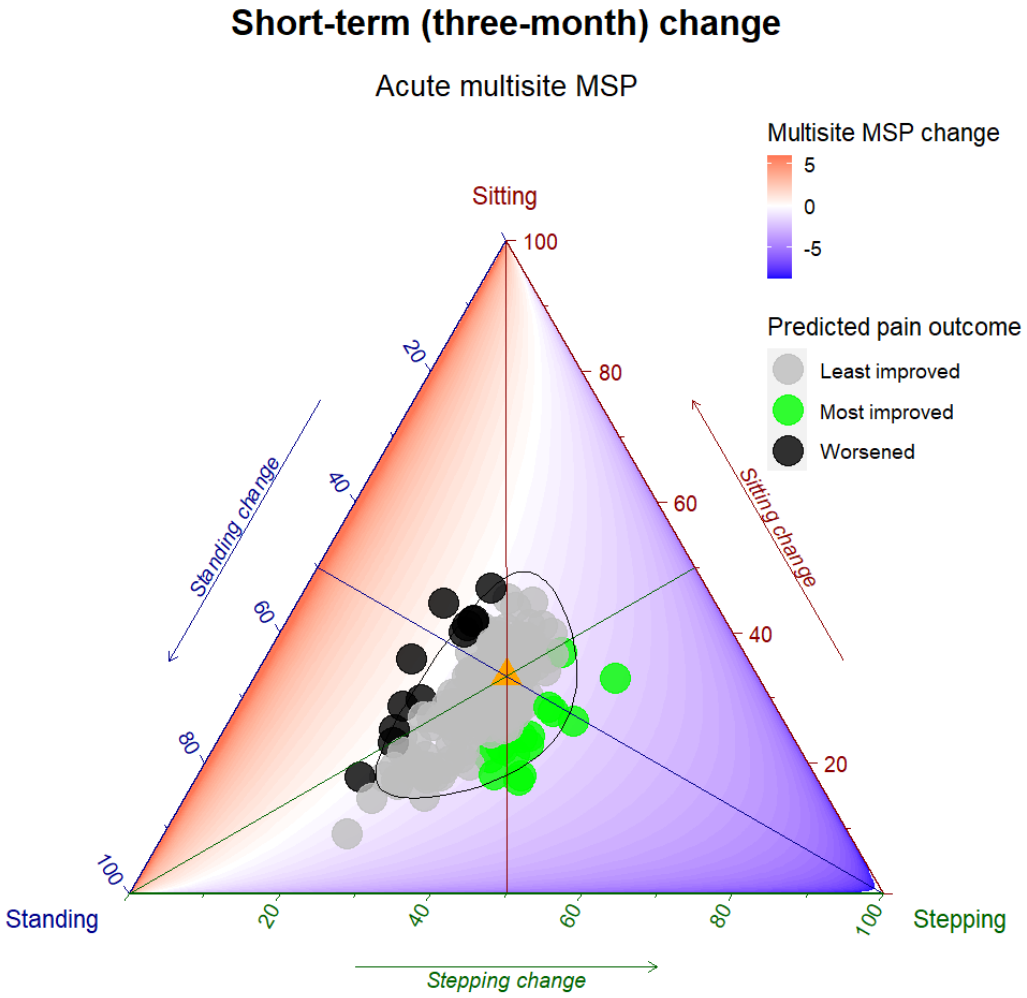
Supplementary Digital Content 3: The predicted changes in multisite MSP score when reallocating time from long-sitting bouts at baseline to short-sitting bouts at follow-ups with the total time spent in standing and stepping, as well as covariates adjusted for in the models, held constant at their mean.



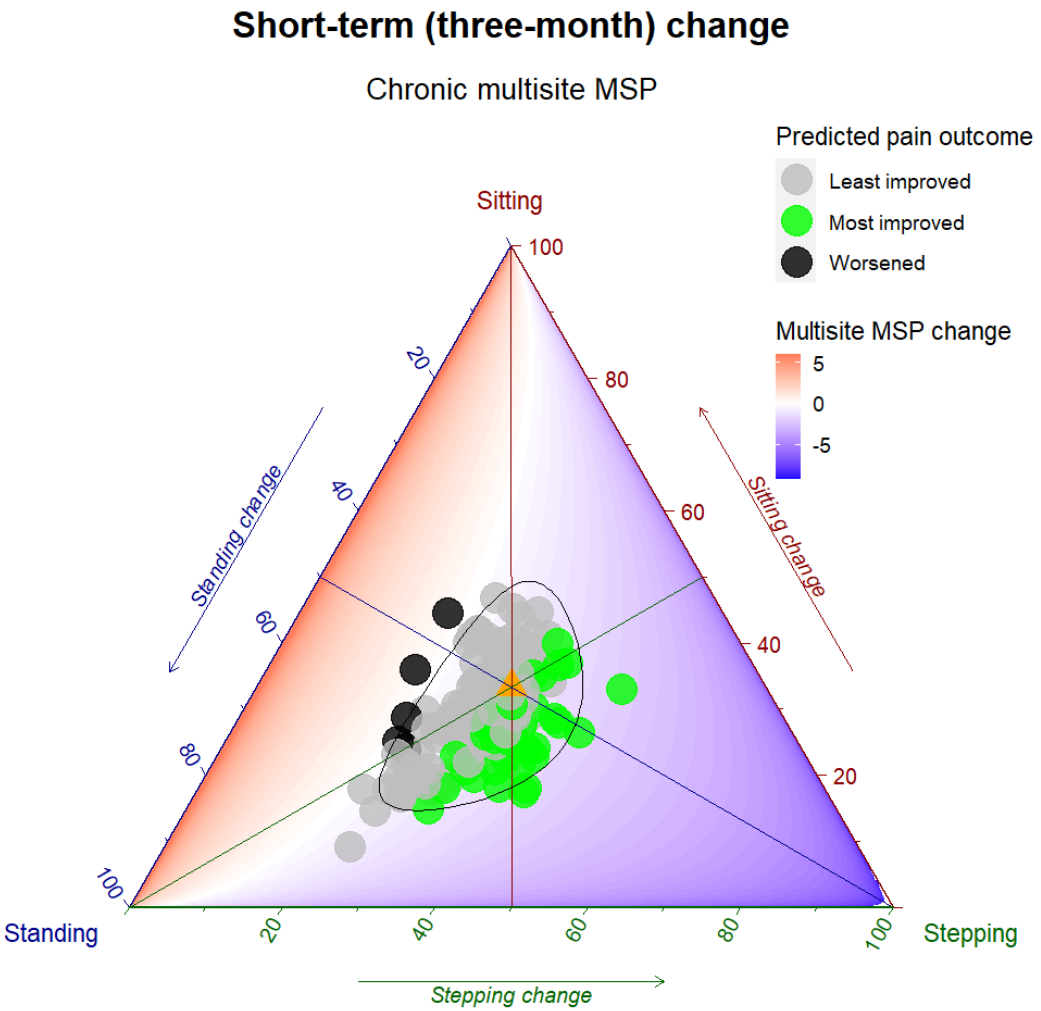
Supplementary Digital Content 4: The predicted changes in multisite MSP outcomes when reallocating time from short-standing bouts at baseline to long-standing bouts at follow-ups with stepping and sitting volumes, as well as models' adjusted covariates held constant at their mean.



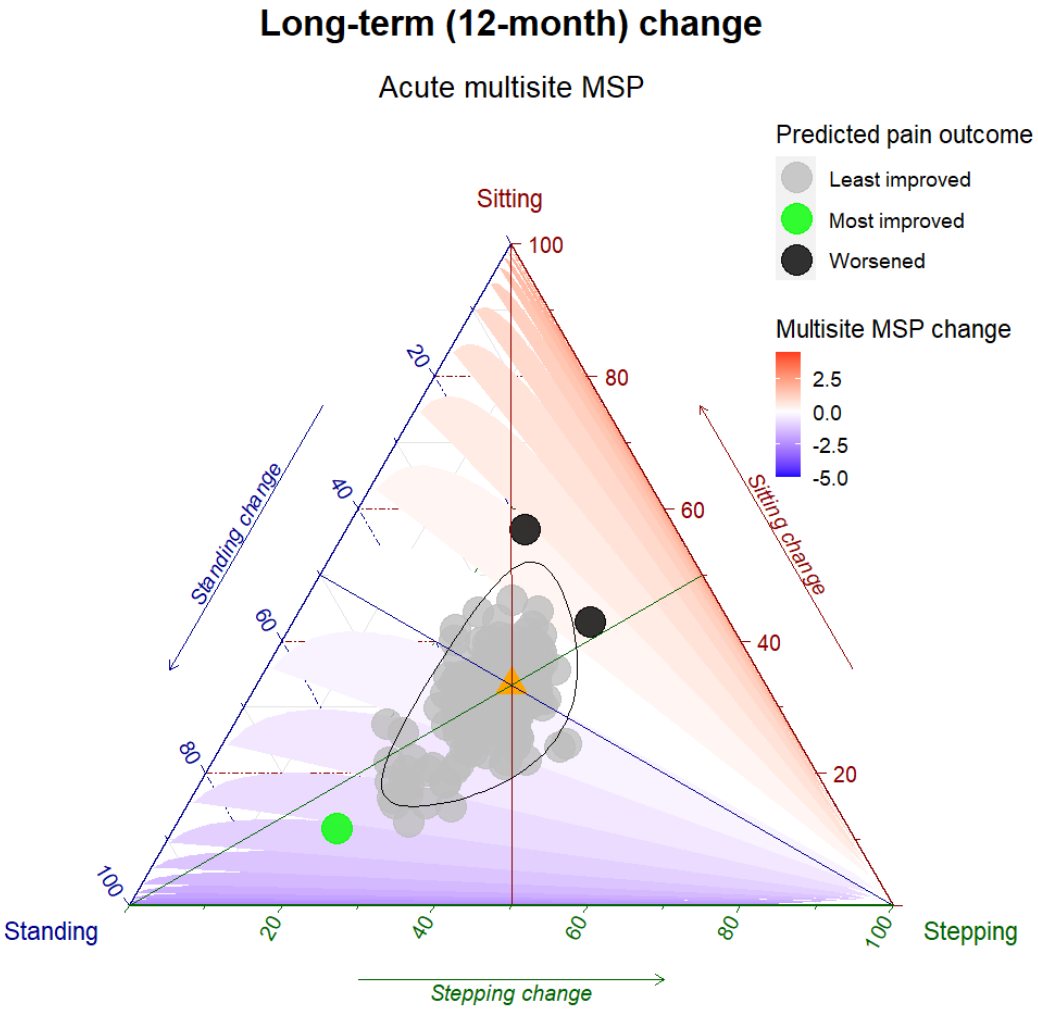
Supplementary Digital Content 5: The predicted changes in multisite MSP outcomes when reallocating time from short-stepping bouts at baseline to long-stepping bouts at follow-ups while sitting and standing volumes, as well as models' adjusted covariates held constant at their mean.



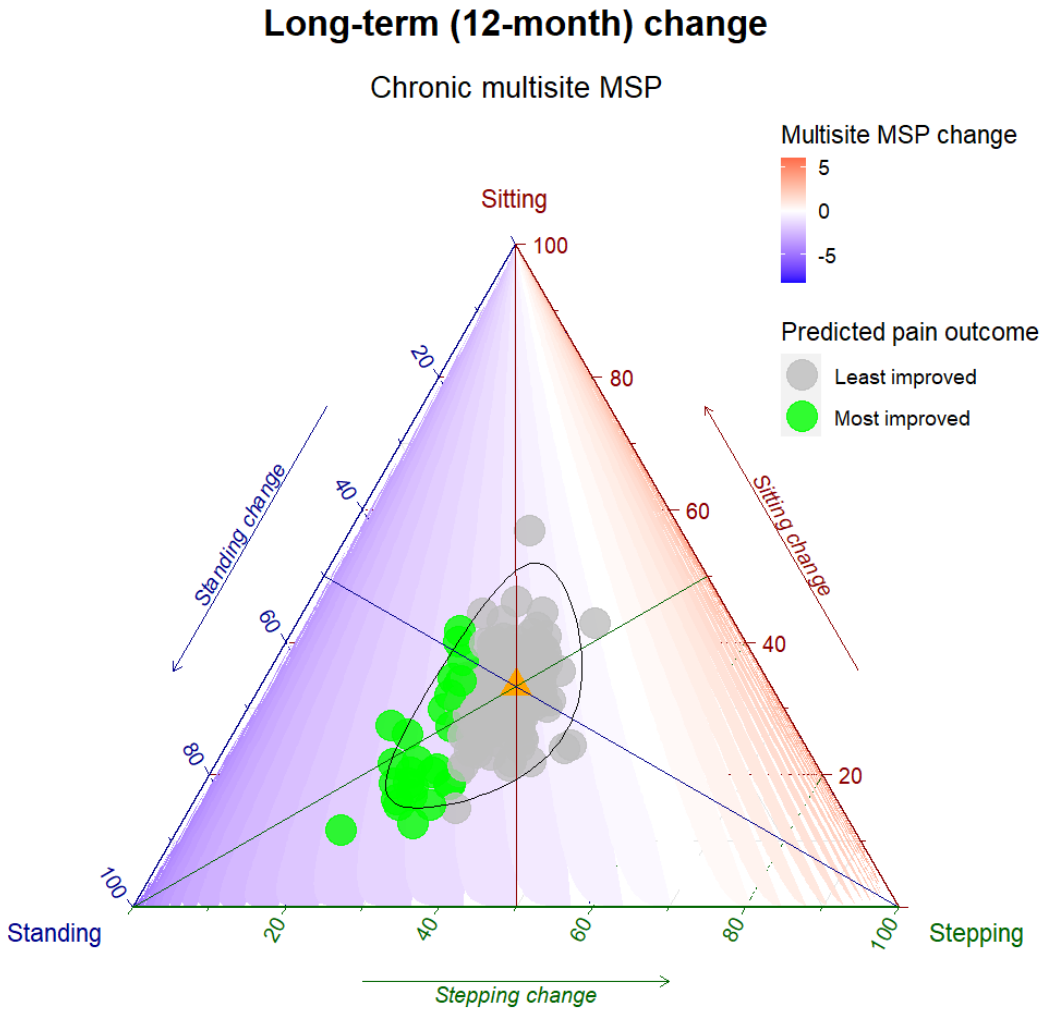
Supplementary Digital Content 6: The relationships of the activity compositional changes at three months with the predicted change in acute multisite MSP.



Supplementary Digital Content 7: The relationships of the activity compositional changes at three months with the predicted change in chronic multisite MSP.



Supplementary Digital Content 8: The relationships of the activity compositional changes at 12 months with the predicted change in acute multisite MSP.



Supplementary Digital Content 9: The relationships of the activity compositional changes at 12 months with the predicted change in chronic multisite MSP.

References

Bibliography list is part of the main thesis references list.

Appendix D: Other research activities

D1: Activities related to the OPTIMISE Study

Throughout my candidature, I have been actively involved in the Optimise Your Health Study (OPTIMISE). I have been contributing to the recruitment of participants and have had the responsibility of coordinating the physical activity monitoring devices for activities behaviours and survey data collection. The Covid-19 pandemic and related lockdown restrictions have impacted the project and delayed the recruitment process. Unfortunately, however, the target population of adult desk-based office workers with T2D have increased risk and are more vulnerable to the complications of Covid-19 infection. This could be a challenge in getting people to willingly come forward to participate in the study.

Initially, I planned to use the baseline dataset for a study in this thesis. The proposed study was intended to explore the relationships of sedentary behaviour and its related attributes such as bout patterns and frequencies with MSP outcomes exclusively in adults with T2D, as well as some outcomes related to vascular endothelial function and systemic inflammation. However, the uncertainties with the COVID-19 pandemic and the delay in participants recruited made the study unfeasible within my PhD timeline. Therefore, an alternative arrangement was made to acquire external data from the Maastricht Study which was used for the thesis' Study 2.

D2: Conference attendance certificates

CERTIFICATE FOR PRESENTERS

This certifies that

Francis Quarshie Senanu Dzakpasu

presented at the 8th International Society for Physical Activity and Health Congress, held virtually from Vancouver, Canada from October 12-14, 2021.

[redacted]

DR. DARREN WARBURTON
Conference Co-Chair

DR. SHANNON BREDIN
Conference Co-Chair

ISBNPA

Advancing Behavior Change Science

PHOENIX, ARIZONA, USA

MAY 18–21, 2022

Certificate of Attendance

This is to certify that

Dr Francis Dzakpasu

has attended virtually the

ISBNPA 2022 ANNUAL MEETING

held from

May 18, 2022

to

May 21, 2022

[redacted]

Meg Bruening
Organizing Committee Co-Chair

[redacted]

Marc Adams
Organizing Committee Co-Chair

aspa
Asia-Pacific
Society for
Physical Activity

Certificate of Presentation

This is to certify that:

Francis Dzakpasu

attended and presented at the

ASPA 2022 CONFERENCE

Nov 28 - 29, 2022

Organising Committee Chair

D3: Media

Media release by the Baker Heart and Diabetes Institute about the findings of the published study 3

Watching TV is such a pain

https://baker.edu.au › news › media-releases › tv-watchi...

10 Dec 2022 — The ***more TV you watch, the more bodily pain you have over time***, a new study out of the Baker Heart and Diabetes Institute has found.

Local and international media links:

https://transition.meltwater.com/paywall/redirect/MoxzxMVSPLSV9MrfQf6F6A2Xzno?keywords=Baker%20Institute&cid=5ed22fda-262e-4c20-9d56-839860eba972&productType=content-stream

https://transition.meltwater.com/paywall/redirect/p2XMd4uPlDGm3nt83rua_4tlu8I?keywords=Baker%20Institute&cid=ffb63923-de3c-4ecf-8127-c49fb3e2c073&productType=content-stream

https://transition.meltwater.com/paywall/redirect/3H9LW2NGcoGlulS2aeuRcX4MkxU?keywords=Baker%20Heart%20and%20Diabetes%20Institute&cid=b3be0d41-488c-4422-8dce-7d3ef8eba58d&productType=content-stream

Watching More TV Could Also Mean More Bodily Pain In The Long Run

International Business Times

Diabète de type 2 : cette activité quotidienne peut amplifier vos douleurs

Pourquoi Docteur

The More TV You Watch, the More Bodily Pain You Have Over Time - journalbreak

journalbreak.Com

Fernsehen ist so ein Schmerz ~ Nach Welt

Nachrichten Welt

News story from Mundodeportivo on Friday 06 January 2023

Mundodeportivo

10 Dec 2022
Author: Sarah Booth
Article type: Publication
Page: 3
Herald Sun, The
Readership: 623000
AVE: $4795.31

Couch addicts binge on pain

Sedentary life warning

EXCLUSIVE
SARAH BOOTH

WATCHING TV for just one hour a day has been linked to an increase in body pain equal to two years of ageing.

A surprising new Melbourne study has also found those pain levels could be even worse for people who binge watch multiple hours of their favourite shows.

Researchers had already linked sedentary behaviour to metabolic health, increasing the risk of cardiovascular disease and some cancers.

But the Baker Heart and Diabetes Institute study, published in BMC Public Health, has revealed even more consequences.

"It's a call to action that we need to take stock about how much time we're spending sedentary," the institute's lifestyle and diabetes department head David Dunstan said.

"Long periods of time without moving, that's not great for our body system and our musculoskeletal system."

The study analysed data from more than 4000 Australian adults and measured pain on a scale from zero to 100, with the latter indicating "severe bodily pain".

The pain levels of participants aged 50 years old at the start of the study increased by an average of 0.3 every year they aged.

In comparison, watching an extra hour of television was linked to an increase of more than double, with pain levels rising by 0.69 units.

Professor Dunstan said he feared the problem was even worse now, because the study was based on data collected prior to the popularity of streaming services.

"We at least know that during television, we do get breaks from our show by the end of the show, and also the commercial breaks, which can serve as a useful prompt to distract yourself by getting up and moving," he said.

"When we're watching streaming services, the next show can just roll on to the next."

Professor Dunstan said physical inactivity led to "substantial costs to the health system".

"Doing something as simple as reducing daily TV-watching time can have a profound effect on bodily pain trajectories that occur with ageing, and also potentially be a non-pharmacological intervention or work hand-in-hand with other therapies for chronic pain management."

The study found people with type 2 diabetes also reported higher levels of bodily pain, and were more likely to watch more television.

But Professor Dunstan said for some people time spent on the couch could become a vicious cycle.

"You've got pain, don't want to move, so you sit and watch more television, so it leads to greater pain," he said.

"So we really need to cut into that vicious cycle, because we know that moving more can help mitigate some of that musculoskeletal pain."

sarah.booth@news.com.au

D4: The Maastricht Study dataset request application

I successfully wrote an application to acquire an external dataset from the Maastricht Study in 2020. The Maastricht dataset was used for the thesis' first empirical (Study 2). A copy of the completed application form is here provided.

Appendix B

Analysis Plan/Application data/materials

Analysis plan #: Date received: Date approval:

To be filled in by The Maastricht Study.

1. **Title**

Associations of Sitting Time with Musculoskeletal Pain Disorders in Adults with and without Type 2 Diabetes

2. **First author**

Name: Francis Quarshie Senanu Dzakpasu

Position: PhD Candidate

Institute: Baker Heart and Diabetes Institute; Australian Catholic University

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Provide list of co-owner(s) who agreed to be co-author:

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Prof. Nicolaas C. Schaper,
Prof. Hans Bosma,

Prof. Hans Savelberg,
A/Prof. Simone Eussen,
Prof. Pieter Dagnelie

Are you a student and will this work be part of your bachelor/master thesis? ☒Yes* ☐No
If yes, please provide details about your program:

I am a PhD research student (by publication) at Australian Catholic University, but I am currently based at Baker Heart and Diabetes Institute for my research work. I have just entered the second year of my candidature. My research focuses on sedentary behaviour and musculoskeletal pain disorders in type 2 diabetes. The research approach is using statistical modelling to understand the associations of sedentary behaviour with musculoskeletal pain disorders in people living with type 2 diabetes using an existing epidemiological data (Australian Diabetes and Lifestyle study - AusDiab) and datasets from an ongoing Randomised Controlled Trial, the Optimise Your Health study.

* Please send your final thesis to the MT of the Maastricht Study via research.dms@mumc.nl

4. Research questions and hypotheses

This cross-sectional study aims to examine whether the associations between total daily volumes of sitting and musculoskeletal pain disorders differ in adults with or without type 2 diabetes. It will examine also whether the direct association of total sitting time with musculoskeletal pain disorders will be modified by moderate-to-vigorous physical activity (MVPA) after accounting for all relevant covariates, including socio-demographic and health-related confounding variables and sleep time. Further, the interaction effect of type 2 diabetes and non-diabetes status on the relationship between sitting time and musculoskeletal pain disorders will be tested. Specifically, the study will focus on the following research questions:

a. What are the associations of overall sitting time with musculoskeletal pain disorders in a population of adults with and without type 2 diabetes?

b. Are the associations with sitting modified by (MVPA) after accounting for all relevant covariates including sleep time?

c. Will the interaction of type 2 diabetes/non-diabetes status have a significant effect on the association of sitting time with musculoskeletal pain disorders?

Hypotheses:

a. Total sitting time will be positively associated with musculoskeletal pain disorders in a population of adults with and without type 2 diabetes.

b. The association of sitting time with musculoskeletal pain disorders will remain after adjusting for MVPA.

c. There will be a significant interaction effect of type 2 diabetes/non-diabetes status on the association of sitting time with musculoskeletal pain disorders.

5. Background

Background and rationale for addressing the research questions and hypotheses.

Introduction:

Musculoskeletal pain disorders (MSPDs), conditions that affect musculoskeletal structures (bones, cartilages, muscles, tendons, ligaments, nerves) and surrounding tissues[1], are a common comorbidity in adults with type 2 diabetes (T2D). Some MSPDs such as Dupuytren's disease, tenosynovitis, and stiff hand syndrome are exclusively prevalent in T2D[2]. Nevertheless, other MSPDs have emerged and frequently reported in people with T2D, including osteoarthritis, back pain neck-shoulder pain, and lower/upper extremities pain [3,4]. Several factors may contribute to the increasing prevalence, however, high volumes of sitting could plausibly be an important contributing factor[5,6].

Clinically, MSPDs are mostly characterised by chronic and persistent pain, as well as functional disabilities which adversely impact effective glycaemic management in T2D[2]. For instance, MSPDs are a barrier for many patients to regularly engage in an adequate level of physical activity, a cornerstone for T2D management[7]. That said, there is consistent evidence that supports the benefit of moderate-to-vigorous physical activity (MVPA) in MSPD-related pain management[8]. However, it may be difficult for most adults with coexisting T2D and MSPD to meet the minimum recommended level of MVPA for health benefits. Many will engage in prolonged sitting, due at least in part to functional impairment and pain. Doing so may adversely impact both T2D and MSPD. Despite the evidence of detrimental associations of T2D with MSPDs, there is no explicit mechanism that explains these associations[4,9].

High volumes of daily accumulated sitting are linked with increased risk of chronic conditions and unfavourable health outcomes, including T2D which are most pronounced in those who are also physically inactive[10-12]. From a general population perspective, there is equivocal evidence of association of sitting time with MSPDs[6,13,14]. Total sitting time, for instance, has been

associated with the risk of some MSPDs such as low back pain in some population cohorts[6]. However, other studies in different population cohorts have observed inconsistent associations, with some documenting no association between sitting and some MSPDs[13,14]. Thus, there could be inherent characteristics of a study population that explain the ambivalent associations of sitting time with MSPDs. Also, the moderation effect of MVPA on the association of sitting time with MSPDs is not clear. Currently, no population-based study has examined and compared the association of daily sitting time with MSPDs in populations of adults living with and without T2D. Specifically, evidence-based studies on the association of daily sitting time with MSPDs in T2D is lacking. A population-based epidemiological study, therefore, is needed to fill some of these significant knowledge gaps.

The proposed study, therefore, will examine the associations of activPAL derived sitting time with MSPDs in a large population of adults with and without T2D. Further, it will examine the potential effect modification by physical activity (measured as activPAL derived MVPA) on the associations after adjusting for other relevant covariates. Additionally, the study will examine the potential interaction for type 2 diabetes and non-diabetes status in the association of sitting time with MSPDs.

References:

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13. Chen SM, Liu MF, Cook J, Bass S, Lo SK. Sedentary lifestyle as a risk factor for low back pain: a systematic review. *Int Arch Occup Environ Health.* 2009;82(7):797-806.

14. Korshøj M, Jørgensen MB, Hallman DM, Lagersted-Olsen J, Holtermann A, Gupta N. Prolonged sitting at work is associated with a favorable time course of low-back pain among blue-collar workers: a prospective study in the DPhacto cohort. *Scandinavian Journal Of Work, Environment & Health.* 2018;44(5):530-538.

6. Design and sample

Study design and main in- and exclusion criteria of the study sample, e.g. cross-sectional study in participants with type 2 diabetes.

Study design: Cross-sectional; to examine the associations of activPAL derived total sitting time with musculoskeletal pain disorders in participants with and without type 2 diabetes. Also, to examine the effect modification by physical activity (activPAL derived MVPA) on the associations after accounting for potential covariates.

Inclusion criteria: The study will consider the inclusion of all adult participants. However, to minimise the potential likelihood of reverse causality bias due to medical conditions, including fracture, cardiovascular diseases, kidney diseases and cancers, as well as physical function, the analysis will control for these confounders. Further, participants with at least 1 day of activPAL data will be selected.

7. Variables

All requested variables should be identified. Please list the variable names from the code books of The Maastricht Study.

Variable Name	General Description	"Co-owner(s)"

Main independent variable(s)		
activPAL measured physical activity parameters *(sedentary, LiPA, MVPA, sleeping)*		
VALID_DAYS_T	Total number of valid calendar days	N. Schaper, H. Savelberg, A Koster
N_ActivPal_reason	Reason missing data	
MEAN_ STEP_MIN_WAKE_T	Mean number of stepping minutes per day	
PROP_STEP_MIN_WAKE_T	Mean percentage stepping minutes per day	
MEAN_MVPA_MIN_WAKE_T	Mean number of minutes per day spent in MVPA	
PROP_MVPA_MIN_WAKE_T	Measure for the mean percentage minutes per day spent in MVPA	
MEAN_VPA_MIN_WAKE_T	Mean number of minutes per day spent in VPA	
PROP_VPA_MIN_WAKE_T	Measure for the mean percentage minutes per day spent in VPA	
MEAN_SED_MIN_WAKE_T	Mean percentage sedentary minutes during waking time on valid waking days	
PROP_SED_MIN_WAKE_T	Mean sedentary minutes during waking time on valid waking days	
MEAN_VALID_MIN_WAKE_T	mean valid wake minutes per day total	
MEAN_VALID_MIN_SLEEP_T	mean valid sleep minutes per day	
MEAN_LiPA_MIN_WAKE_T	Mean proportion of LiPA wake minutes per day total	
PROP_LiPA_MIN_WAKE_T	percentage LPA wake minutes of waking time total	
MEAN_Li_step_MIN_WAKE_T	Mean proportion of light stepping minutes per day total	
PROP_Li_step_MIN_WAKE_T	percentage light stepping minutes of waking time total	
Outcome variable(s)		
Musculoskeletal health/disorders *(knee pain, osteoarthritis, chronic back pain, neck/shoulder pain, extremities pain, gout, rheumatoid arthritis)*		
REpainK	Knee pain	A Boonen, P Emans
Blok05 (B5_MS22.1.a1.10)	Knee pain	
REpainH	Hip pain	
Blok05 (B5_MS22.1.a1.9)	Hip pain	

Blok05 (B5_MS22.1.a1.8)	Pelvic pain	
Blok05 (B5_MS22.1.a1.11)	Ankle pain	
Blok05 (B5_MS22.1.a1.12)	Foot pain	
Blok05 (B5_MS22.1.a1.2)	Neck pain	
REpainShoulder	Shoulder pain	
Blok05 (B5_MS22.1.a1.4)	Shoulder pain	
Blok05 (B5_MS22.1.a1.5)	Elbow	
Blok05 (B5_MS22.1.a1.6)	Wrist	
Blok05 (B5_MS22.1.a1.7)	Hand	
Blok05 (B5_MS22.1.a1.3)	Low back	
Blok05 (B5_MS22.3b.3)	Chronic back pain	
Blok05 (B5_MS22.3b.2)	Osteoarthritis	
Blok05 (B5_MS22.3b.4)	Rheumatoid arthritis	
Blok05 (B5_MS22.3b.9)	Gout	
Confounders		
Demographic and Anthropometric parameters *(gender, age, BMI, and waist circumference)*		
Sex	Sex	
N_age	Age	
BMI, BMI_CAT	Body mass index	
Waist	Waist circumference (cm)	
Socioeconomic status *(education, income, and employment)*		
N_Education_3cat	Education level	
Employment_status	Employment status	
Income_equivalent	Income	H. Bosma
Lifestyle *(energy intake, alcohol intake, smoking status)*		
Smokingcat3	Smoking	
N_alcohol_cat	Alcohol consumption	
DHD	Dutch healthy diet index	Martien van Dongen, Pieter Dagnelie, Simone Eussen
Kcal	Energy intake	Martien van Dongen, Pieter Dagnelie, Simone Eussen
Glucose Metabolism Status *(normal glucose metabolism, prediabetes, type-2 diabetes)*		

N_GTS_WHO N_T2DM_new_diagn GTS_WHO2_2	Normal glucose metabolism, Impaired Fasting Glucose/ Impaired Glucose Tolerance, Type 2 diabetes	
Musculoskeletal-related health *(fracture; physical function and disability)*		
Mobility_lim	Mobility limitation	
Fracture_ever	Self- reported fracture history	GJ Dinant; J vd Bergh; P Geusens
SF36_PF	SF-36 physical function score	H Bosma
ActivitiesRestriction_GARS4_pack	Groningen Activities Restriction Scale (GARS) for disability	
WT_Distance; WT_speed	Performance-based physical function - 6-minute walk test	H Savelberg; A Koster; N Schaper; GJ Dinant
TCSTtime	Performance-based physical function - timed chair stand test	H Savelberg; A Koster; N Schaper; GJ Dinant
Health/medical history *(hypertension, kidney disease, cardiovascular disease, psychological diseases, and cancers)*		
N_CVD	History of cardiovascular disease	
N_HT; OSBP; ODBP	Hypertension status	
MINIcurrdepr	Depression based on the MINI	M Schram, S Koehler
Medication history *(medication in use, e.g., analgesics, diabetes medication, lipid-lowering drugs, and anti-hypertensives)*		
LP_med	Lipid-lowering Medication	
HT_med	Blood pressure medication	
DM_med	Diabetes medication	

8. Statistical analyses

Briefly describe the statistical analyses.

The characteristics of the study parameters as well as glucose metabolism status (normal glucose metabolism, impaired glucose metabolism – prediabetes and type 2 diabetes) will be described across the total population. Continuous variables will be calculated and summarised as means and standard deviations and categorical variables as proportions (percentages).

First, to examine the association of the volume of sitting time with musculoskeletal pain disorders (osteoarthritis, chronic back pain, knee pain, rheumatoid arthritis, gout, extremities pain and neck/shoulder pain), progressively adjusted multiple logistic regression will be modelled,

regressing each of the musculoskeletal pain disorders (present-Yes/absent-No) as the dependent variable and total sitting time organised into quantile (from low to high) as the primary independent variable. There are suggestions that the relationship between sedentary time and some health outcomes may be non-linear. Therefore, modelling sitting time as a continuous variable may bias the estimation of the association being examined. Total sitting time quantile will be modelled, rather than the continuous linear variable, to better understand the true nature of the relationship and to avoid the linear relationship assumption (Unkart et al., 2020). The model will be adjusted systematically for demographic and anthropometric parameters; some socioeconomic (education) and lifestyle (smoking and energy intake) parameters; and sleep time.

Second, the model will be further adjusted by including physical activity (MVPA) into the model to examine whether the direct association of the sitting time with musculoskeletal pain disorders will be attenuated. Additionally, effect modification will be examined by modelling the interaction of sitting time with physical activity (MVPA) in the adjusted model.

Third, to test the interaction of type 2 diabetes/non-diabetes status on the association, glucose metabolism status (as three categorical variable - normal glucose metabolism, impaired glucose metabolism – prediabetes, and type 2 diabetes) and the interaction of sitting time with glucose metabolism status will be added to the model as explanatory variables. Furthermore, potential confounders and reverse causality bias will be accounted for by adding to the adjusted model the following as covariates: medical conditions (hypertension, kidney disease, cardiovascular disease, psychological diseases, etc.); medication use (analgesics, diabetes medication, lipid-lowering drugs, anti-hypertensives, etc.); fracture; impaired physical function and disability.

Fourth, the linear trend across the sitting time quantile will be examined by fitting other models using sitting time as a continuous variable. Categorising the sitting time into quantiles may risk missing some important relationships. Therefore, the nonlinear association of the sitting time with musculoskeletal pain disorders will be examined by restricted cubic splines (RCS). The RCS will be modelled with a 3 – 5 knots (depending on the sample size) placed at locations based on the quantile of the continuous sitting time.

Finally, the robustness of the analysis will be tested by sensitivity analysis, by excluding all individuals with a reported history of fracture, chronic medical conditions such as cardiovascular diseases, cancers as well as impaired physical function and disability. Also, the sensitivity analysis model will be further adjusted for other socioeconomic and lifestyle parameters, including income status and alcohol intake. All statistical analysis will be performed with STATA version 16 statistical software, and the significance of associations considered at a p-value less than 0.05.

Reference:

Unkart, J. T., Allison, M. A., Parada, H., Criqui, M. H., Qi, Q., Diaz, K. M., . . . Bellettiere, J. (2020). Sedentary time and peripheral artery disease: The Hispanic Community Health Study/Study of Latinos. *American heart journal, 222*, 208-219. doi:https://doi.org/10.1016/j.ahj.2020.02.005

9. Mock Tables

Include mock-up of key tables.

Characteristics of The Study Population

Variables	Overall (N=)	NGM (N=)	IGM (N=)	T2D (N=)	p-value
Age, mean(SD)					
Gender, % Male					
BMI, Kg/m2					
Biomarkers					
Fasting glucose, mean (SD)					
HbA1c, %					
Insulin, mean (SD)					
Total Cholesterol, mean (SD)					
C-reactive protein, mean (SD)					
Lean mass, mean (SD)					
FMD, mean (SD)					
Socioeconomic **status**					
Education level					
Above college degree, %					
Below college degree,%					
Income					
High,%					
Low,%					
Not provided,%					
Employment					
Yes, %					
No, %					
Lifestyle					
smoking status					
Current, %					
Ex-smoker, %					
Non-smoker, %					
Energy intake, mean (SD)					
Alcohol intake, mean (SD)					
Medical history					
Hypertension status					

No %	
Yes no therapy, %	
Yes on therapy,%	
Medication use	
Analgesics	
Yes, %	
No, %	
Cholesterol-lowering drugs	
Yes,%	
No%	
Diabetese Therapy	
Insulin, %	
Non-insulin, %	
No-therapy, %	

BMI=Body Mas Index; NGM=Normal Glucose Metabolism; IGM=Impaired Glucose Metabolism(Prediabetes); T2D=Type 2 Diabetes

Table 2: Sitting, Physical Activity, and Sleep Times According to Glucose Metabolism Status

Variables	Overall	NGM	IGM	T2D	p-value
Sitting time, min/day					
Sitting time Quantile					
1					
2					
3					
4					
Physical activity (MVPA time), min/day					
Sleep time, min/day					

NGM = Normal Glucose Metabolism; IGM = Impaired Glucose Metabolism (Prediabetes); T2D = Type 2 Diabetes; MVPA = Moderate-to-vigorous physical activity

Table 3: Percentage Prevalence of Musculoskeletal Pain Disorders According to Glucose Metabolism Status

	Overall		NGM		IGM		T2D	
Variables	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Osteoarthritis								
Total Sitting time								
Sitting time Quantile								
1								
2								
3								

4

Chronic back pain

Total Sitting time

Sitting time Quantile

1

2

3

4

Knee pain

Total Sitting time

Sitting time Quantile

1

2

3

4

Neck/shoulder pain

Total Sitting time

Sitting time Quantile

1

2

3

4

Extremities pain

Total Sitting time

Sitting time Quantile

1

2

3

4

Rheumatoid arthritis

Total Sitting time

Sitting time Quantile

1

2

3

4

Gout

Total Sitting time

Sitting time Quantile

1

2

3

4

NGM = Normal Glucose Metabolism; IGM = Impaired Glucose Metabolism (Prediabetes); T2D = Type 2 Diabetes

Table 4: Association of Sitting Time with Musculoskeletal Pain Disorders

Variables	Model A OR (95%CI)	Model B OR (95%CI)	Model C OR (95%CI)	Model D OR (95%CI)
Osteoarthritis				
Total Sitting time				
Sitting time Quantile				
1				
2				
3				
4				
Glucose Metabolism Status				
NGM				
IGM				
T2D				
Back pain				
Total Sitting time				
Sitting time Quantile				
1				
2				
3				
4				
Glucose Metabolism Status				
NGM				
IGM				
T2D				
Neck-Shoulder pain				
Total Sitting time				
Sitting time Quantile				
1				
2				
3				
4				
Glucose Metabolism Status				
NGM				
IGM				
T2D				
Extremities pain				
Total Sitting time				
Sitting time Quantile				
1				
2				
3				
4				
Glucose Metabolism Status				
NGM				

IGM				
T2D				
Gouty arthritis				
Total Sitting time				
Sitting time Quantile				
1				
2				
3				
4				
Glucose Metabolism Status				
NGM				
IGM				
T2D				

NGM = Normal Glucose Metabolism; IGM = Impaired Glucose Metabolism (Prediabetes); T2D = Type 2 Diabetes; OR = Odds ratio; CI = Confidence Interval

Model A: Adjusting for demographic and anthropometric parameters; socioeconomic and lifestyle status; and sleep time

Model B: Adjusting for Model A + physical activity (stepping time) and the interaction of sitting times with physical activity (stepping time)

Model C: Adjusting for Model B + Glucose metabolism status

Model D: Adjusting for Model C + medical and potential reverse causality confounders

Table 5: Restricted cubic splines (RCS) Nonlinear Association of Sitting Time with Musculoskeletal Pain Disorders

	Model A	Model B	Model C	Model D
Variables	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**	**OR (95%CI)**
Osteoarthritis				
Total Sitting time				
5.2				
6.5				
7.2				
8.5 (Median)	Reference	Reference	Reference	Reference
9.2				
10.5				
11.2				
Glucose Metabolism Status				
NGM				
IGM				
T2D				
Back pain				
Total Sitting time				
5.2				
6.5				
7.2				
8.5 (Median)	Reference	Reference	Reference	Reference
9.2				

10.5				
11.2				
Glucose Metabolism Status				
NGM				
IGM				
T2D				
Neck-Shoulder pain				
Total Sitting time				
5.2				
6.5				
7.2				
8.5 (Median)	Reference	Reference	Reference	Reference
9.2				
10.5				
11.2				
Glucose Metabolism Status				
NGM				
IGM				
T2D				
Extremities pain				
Total Sitting time				
5.2				
6.5				
7.2				
8.5 (Median)	Reference	Reference	Reference	Reference
9.2				
10.5				
11.2				
Glucose Metabolism Status				
NGM				
IGM				
T2D				
Gouty arthritis				
Total Sitting time				
5.2				
6.5				
7.2				
8.5 (Median)	Reference	Reference	Reference	Reference
9.2				
10.5				
11.2				
Glucose Metabolism Status				
NGM				
IGM				
T2D				

NGM = Normal Glucose Metabolism; IGM = Impaired Glucose Metabolism (Prediabetes); T2D = Type 2 Diabetes; OR = Odds ratio; CI = Confidence Interval

Model A: Adjusting for demographic and anthropometric parameters; socioeconomic and lifestyle status; and sleep time
Model B: Adjusting for Model A + physical activity (stepping time) and the interaction of sitting times with physical activity (stepping time)
Model C: Adjusting for Model B + Glucose metabolism status
Model D: Adjusting for Model C + medical and potential reverse causality confounders

NB: Tables for sensitivity analysis will be added

10. Timeline

A timeline for completion and submission of the paper.

October 2021

11. Agreement for the of data and/or materials of the Maastricht Study

This agreement is for the analysis plan entitled:

Associations of Sitting Time with Musculoskeletal Pain Disorders in Adults with and without Type 2 Diabetes

The participating researchers are:
A/Prof. Annemarie Koster,

Prof. Nicolaas Schaper,

Prof. Bastiaan de Galan

Prof. David Dunstan

Prof. Neville Owen

Dr. Alison Carver

Mr Christian Brakenridge

Mr. Francis Dzakpasu

I certify that I am aware of the rules described in 'Procedure Data/Materials - The Maastricht Study' which include:

- The data/materials should be treated confidentially
- The data/materials may not be shared with others who are not included in this project
- I agree with the "Maastricht Study Data License Agreement" as stated in Appendix D (see below)
- The approval is valid for 1 year: After a year a written progress report should be submitted.
- For publications the rules as described in the 'Procedure Publicatie' are applicable.

Date
20 July 2020

Name first author
Francis Quarshie Senanu Dzakpasu

Signature 

Appendix D

Maastricht Study Data License Agreement

This end-user License Agreement is a legal agreement between (fill in institution name and address) .
Baker Heart and Diabetes Institute, Level 4, 99 Commercial Road, Melbourne, VIC 3004, Australia legally represented by Francis Quarshie Senanu Dzakpasu (fill in name).

The "Licensee"

and

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D5: Systematic review protocol

The systematic review conducted as Study 1 followed a PROSPERO registered protocol. The link to the protocol is provided below:

https://www.crd.york.ac.uk/PROSPEROFILES/166412_PROTOCOL_20210805.pdf

D6: Some skills and experience acquired during my candidature

I acquired a lot of skills and also achieved some level of competence through learning and workshops during my candidature which may be noteworthy, including:

- Systematic review and meta-analysis – I acquired skills on how to use some systematic review tools, and through Study 1 I gained a comprehensive understanding of the processes of performing a systematic review and meta-analysis.
- Research tools and scientific writing – I steadily improved my scientific writing skills and have been able to write full manuscripts that have been accepted and published in a high-impact journal. This process included responding to reviewers' comments in a timely manner. I had training on scientific data measurements (collection) and management using the REDCap software.
- Application proposal for sourcing external datasets – I had experience and successfully wrote an application research proposal to the Maastricht Study administrators in the Netherlands to access their dataset.
- Programming, downloading, and processing of physical activity monitoring devices – I have enhanced my skills in managing both the activPAL and actiGraph devices' data.
- STATA statistical software – my competence in the use of STATA software for data analysis has improved significantly. Likewise, my understanding of some statistical concepts underpins the statistical analyses.
- Mixed-effects random modelling (growth curve modelling) – I developed a competent understanding of the multilevel modelling approach for analysing longitudinal and nested data through the conduct of Study 3.
- I gained a competent understanding of R statistical analytical techniques and compositional data analysis framework through workshops and the application in Study 4.