Step cadence and sedentary behaviour – developing the links to physical function and glucose control

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Thesis Abstract

Background

Adults with type 2 diabetes, and those at high risk of developing it (prediabetes) typically have poorer cardiometabolic health profiles and are at higher risk of impaired physical function, placing them at greater risk of developing co-morbidities, increased hospital use, multiple medication use, and premature death than their counterparts without diabetes. Furthermore, evidence suggests that aside from the increased risk of cumulating poor cardiometabolic health markers, impaired physical function increases risk of mortality in people with type 2 diabetes. Fostering adaptations to physical activity and sedentary behaviour may elicit a plethora of benefits on physical function and cardiometabolic health in people with type 2 diabetes or prediabetes including reduced cardiovascular disease risk, better mobility and walking speed, heightened musculoskeletal function, and improved overall functional capacity. However, research investigating the benefits of adapting physical activity and sedentary behaviour habits to improve physical function has typically been limited to older adults.

Aims

1: To investigate the association between activPAL-measured step cadence and physical function in older adults.

2: To explore associations between change in step cadence and change in markers of cardiometabolic health in people with prediabetes.

3: To assess a personalised home-based intervention to encourage adults with type 2 diabetes or prediabetes to reduce sitting time with the aim of improving cardiometabolic health and physical function.

Methods

1: Post-hoc analysis was conducted in a cohort of 104 healthy older adults (age = 72 ± 5; 46% female). Generalised Linear Models were used to assess the associations between step cadence variables and performance in the sit-to-stand-60 test, stratified by ethnicity.

2: Post-hoc analysis was conducted in a cohort of 794 adults with a history of prediabetes (age = 60 ± 9 years, 49% female). Generalised Estimating Equations were used to assess the associations between change in step cadence variables and change in cardiometabolic health outcomes over four years, additionally stratified by ethnicity.

3: Nineteen adults with type 2 diabetes (age = 61 ± 7, 47% female) completed a personalised intervention designed to use targeted physical activity and breaks in sedentary behaviour to improve glucose control and physical function. Healthy volunteers (age = 52 ± 9, 64% female), free from type 2 diabetes were recruited for baseline case-control comparison.

Key findings

1: Higher step cadence is associated with greater physical function in healthy older adults, with greater associations seen in White Europeans compared to South Asians.

2: Increase in step cadence over four years is associated with modest improvement in several markers of cardiometabolic health in people with prediabetes, with associations differing across White European and South Asian ethnicities.

3: A personalised intervention may reduce sitting time and improve physical function in people with type 2 diabetes over the short term. However, the intervention was not successful in improving glucose profiles.

Conclusions

The overall findings of this research help to bridge the gap in knowledge around the relationships between step cadence, sedentary behaviour, physical function, and cardiometabolic health in those with and without impaired glucose regulation. The research also offers some insight into potential ethnic differences in these relationships. Future large-scale randomised controlled trials are needed to establish the effectiveness and economic viability of a programme to increase step cadence and reduce sedentary behaviour in people with, and at high risk of developing, type 2 diabetes.

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Abbreviations

T2D – Type 2 Diabetes

IR – Insulin Resistance

HbA1c – Glycated Haemoglobin A1c

IGT – Impaired Glucose Tolerance

IFG – Impaired Fasting Glucose

COVID-19 – SARS-CoV-2 Virus

CVD – Cardiovascular Disease

CHD – Coronary Heart Disease

SA – South Asian

WE – White European

BMI – Body Mass Index

GDM – Gestational Diabetes Mellitus

PA – Physical Activity

SB – Sedentary Behaviour

PF – Physical Function

mPPT – modified Physical Performance Test

CI – Confidence Interval

SPPB – Short Physical Performance Battery

6-MWT – 6-minute Walk Test

ISWT – Incremental Shuttle Walk Test

SCPT – Stair Climb Power Test

STS-30 – Sit-to-Stand-30

STS-60 – Sit-to-Stand-60

STS-5 – Sit-to-Stand-5

TUG – Time to Up-and-Go

ICC – Interclass Correlation Coefficient

Katz ADL – Katz Activities of Daily Living

OARS-IADL – Older Americans Resources and Services Instrumental Activities of Daily Living

SF-36 – 36-item Short Form Survey

FRAIL Scale – Fatigue, Resistance, Ambulation, Illness, and Loss of weight Scale

LPA – Light-intensity Physical Activity

MET – Metabolic Equivalent of Task

MPA – Moderate-intensity Physical Activity

VPA – Vigorous-intensity Physical Activity

MVPA – Moderate-to-Vigorous-intensity Physical Activity

RCT – Randomised Controlled Trial

CGM – Continuous Glucose Monitor

SD – Standard Deviation

NHANES – National Health and Nutrition Examination Survey

HOMA-IR – Homeostatic Model Assessment for Insulin resistance

iAUC – incremental Area Under the Curve

WC – Waist Circumference

LDL-C – Low-Density Lipoprotein Cholesterol

HDL-C – High-Density Lipoprotein Cholesterol

MCID – Minimum Clinically Important Difference

GLM – Generalised Linear Model

EMM – Estimated Marginal Mean

IMD – Index of Multiple Deprivation

GEE – Generalised Estimating Equation

FCS – Fully Conditional Specification

PAD – Peripheral Arterial Disease

REC – Research Ethics Committee

NIHR – National institute for Health and Care Research

CRN – Clinical Research Network

PIC – Participant Identification Centre

UoL – University of Leicester

UHL – University Hospitals of Leicester Trust

SOPs – Standard Operating Procedures

LDC – Leicester Diabetes Centre

HRA – Health Research Authority

PIS – Participant Information Sheet

TIR – Time in Range

TAR – Time Above Range

TBR – Time Below Range

HBGI – High Blood Glucose Index

LBGI – Low Blood Glucose Index

MAT-sf – Mobility Assessment Tool-short form

MEQ – Morningness-Eveningness Questionnaire

WHO-DAS – World Health Organisation – Disability Assessment Schedule

SARC-F – Strength, Assistance with walking, Rising from a chair, Climbing stairs, and Falls

HADS – Hospital Anxiety and Depression Scale

mMRC – Modified Medical Research Council

UKDDQ – UK Diet and Diabetes Questionnaire

CFQ-11 – Chalder Fatigue Questionnaire

NMQ – Nordic Musculoskeletal Questionnaire

AE – Adverse Event

SAE – Severe Adverse Event

IQR – Interquartile Range

Chapter 1: Background

1.1 Type 2 Diabetes and Prediabetes

1.1.1 Definitions

Type 2 Diabetes (T2D) is a condition characterised by persistent hyperglycaemia, resulting from defects in hepatic and peripheral glucose uptake, insulin secretion, β-cell dysfunction, or a combination of these (1). When the body develops insulin resistance (IR), insulin is no longer able to effectively take up glucose into muscle cells (2). When IR is identified during the early stages, it is often categorised as prediabetes – a state of intermediate, non-diabetic hyperglycaemia (3). There are other definitions of this phenomena, such as impaired glucose regulation and non-diabetic hyperglycaemia; but for the purposes of this thesis, the term "prediabetes" will be used throughout. During the early stages in the development of IR, the body combats the lack of response to insulin by signalling pancreatic beta cells to produce more insulin – resulting in hyperinsulinemia (4). However, this can only be maintained for a limited time and unless changes are made to lifestyle it is likely to progress into T2D. Incidence of T2D development in the five years following prediabetes diagnosis is estimated to be between 26% and 50% (5). Identifying people with prediabetes is an important stage in the prevention of T2D which offers a potential window of opportunity to detect elevated blood glucose levels early without the added complications of exposure to further hyperglycaemia and the presence of fewer co-abnormalities. This importance is highlighted by diabetes prevention programmes, such as that run through the UK National Health Service (6).

1.1.2 Diagnosing T2D and Prediabetes

There are a number of techniques for diagnosing T2D and prediabetes (7). Details of the most common diagnostic criteria are detailed in Table 1. An initial diagnosis of prediabetes is likely; typically via glycated haemoglobin A1c (HbA1c) levels, impaired glucose tolerance (IGT), or impaired fasting glucose (IFG), which will be given based on a fasting plasma glucose test and/or a two-hour plasma glucose test – test choice is dependant on guidelines within individual countries. T2D would then be diagnosed if the patient received a positive result for any one or more of the HbA1c, fasting plasma glucose, two-hour plasma glucose, or random plasma glucose.

Table 1 Diagnostic criteria for type 2 diabetes and prediabetes

	Diabetes (if one or more criteria are met)	***Impaired Glucose Tolerance (if both criteria are met)***	***Impaired Fasting Glucose (if the first or both criteria are met)***
Test			
Fasting Plasma Glucose	≥7.0 mmol/L	<7.0 mmol/L	6.1 – 6.9 mmol/L
Two-hour Plasma Glucose	≥11.1 mmol/L	≥7.8 and <11.1 mmol/L	<7.8 mmol/L
HbA1c	≥48 mmol/mol (6.5%)	*HbA1c can be used independently to diagnosed prediabetes (6.0-6.4% according to National Institute for Health and Care Excellence (8) or 5.7-6.4% according to American Diabetes Association (9))	
Random Plasma Glucose	≥11.1 mmol/L		

Fasting Plasma Glucose: determined by taking a blood sample from a participant/patient who has fasted for at least 8 hours; Two-hour Plasma Glucose: determined by taking a blood sample from a participant/patient before and two hours after consumption of a specific glucose drink; HbA1c (glycated haemoglobin A1c): determined by taking a blood sample from a participant/patient; Random Plasma Glucose: determined by taking a blood sample from a participant/patient at any time

1.1.3 Prevalence and Burden of T2D and Prediabetes

From 1980 to 2004 the global prevalence of T2D quadrupled (10). The current estimates from the International Diabetes Federation suggest there to be around 536.6 million adults living with some form of diabetes throughout the world, with the most common form – over 90% of cases – being T2D (5). Current predictions suggest that, unless changes are made, by 2045 the number of cases will increase to around 783.2 million (5). T2D also presents a substantial burden to national and global healthcare costs. It was recently estimated that the global economic burden of T2D is in excess of 825 billion USD (11). Further to this, in the UK alone, a study on relative cost of diabetes treatment reported a 11.7 billion GBP yearly spend on T2D (12). In addition to the financial burden, T2D is a major cause of worldwide mortality. In 2021, 6.7 million adults aged 20-79 are estimated to have died because of diabetes and its associated complications – excluding mortality risks associated with the SARS-CoV-2 Virus (COVID-19) (5). This makes T2D one of the top 10 leading causes of death worldwide (13). Together with cardiovascular disease (CVD), cancer, and respiratory disease, these conditions account for over 80% of all worldwide premature non-communicable disease deaths (14, 15).

In addition to the growing burden of T2D, as of 2021, there are an estimated 541 million adults thought to have IGT and a further 319 million who have IFG – indicating prediabetes in approximately 16.8% of the worlds adult population (5). By 2045, these figures are projected to rise to 730 million and 441 million for IGT and IFG, respectively (5). Prediabetes is not only

a risk factor for development of T2D; meta-analysis of over 10 million participants from 129 studies found 7.36% greater risk for all-cause mortality, 8.75% greater risk for CVD, 6.59% greater risk for coronary heart disease (CHD), and 3.68% greater risk for stroke in people with prediabetes compared to people with normoglycaemia, per 10,000 person years (16). Prediabetes can be identified initially through computer-based risk-assessment tools such as the Cambridge Diabetes Risk Score (17) or the Leicester Practice Risk Score (18). People with high risk scores are then offered venous blood tests to assess their HbA1c and/or fasting plasma glucose (19) and potentially referred to a diabetes prevention programme such as the NHS Diabetes Prevention Programme (6).

1.1.4 T2D Risk Factors

Although the precise causes of the metabolic defects associated with T2D are largely unknown (20); there are several factors which can contribute to IR and subsequent onset of T2D, including genetics (21), obesity (22), physical activity and inactivity (23), age (24), and sedentary behaviour (25).

Unmodifiable Risk Factors

There is a wide body of evidence suggesting that there are unmodifiable aspects to the onset of T2D. Identification of unmodifiable risk factors is vital in monitoring and limiting the number of risk factors a person has (2).

Family History

Parental transmission has long been understood to play a key role in an individual's risk for developing T2D. In the Framingham Offspring Study (26), the risk for people with one parent with T2D was 3.5 times greater than those without. For people with two parents with T2D, the risk was 6 times greater. Further to this, there are reports that having siblings with T2D increased an individual's risk by two to three times (27).

Genetics

There is also evidence of genetic predisposition of T2D. As early as 1998, Hani, et al. had identified genetic variants that were associated with T2D (28). More recently, researchers have identified over 300 novel loci that are associated with T2D – including 4 that were found solely in people of Black African ancestry (29). Combined, these account for around 20% of T2D heritability (29). Further to this, a number of genome-wide association studies (30, 31)

and meta-analyses (32) have reported on the associations between various gene variants with HbA1c, glucose, and insulin.

Ethnicity

Research has found that specific minority groups such as South Asian (SA), Black African, and Black Caribbean are more predisposed to developing IR and T2D (33). Specifically in the UK, prevalence of T2D was considerably lower in people from White European (WE) (~5.0%) backgrounds compared to Asian (~7.7%) and Black (~ 5.6%) ethnicities (34). Compared to WEs in the study, likelihood of developing T2D was around double for Asian people, around 65% greater for Black people, and around 17% greater for people from Mixed/Other ethnicities. In addition to higher prevalence, it has been reported that onset of T2D may occur as much as 12 years earlier in SA and Black populations, compared to WE populations (35). Dysglycaemia also appears to present at a lower body mass index (BMI) in SAs compared to WEs, with equivalent prevalence being seen at 22.6 kg/m^2 in SAs compared to 30 kg/m^2 in WEs (36). However, despite SAs exhibiting greater metabolic dysfunction that WEs, people within this population are likely to see greater benefit with the introduction of light-intensity physical activity (37-39). Finally, there appears to be differences in responses of different ethnic groups in relation to the complications associated with diabetes, such as diabetic retinopathy (40) and diabetic foot ulceration (41). The 2012 study found that in people with T2D, there was greater risk to SAs and African/Afro-Caribbean people compared to WEs, showing prevalence of diabetic retinopathy was 38.0% in WEs, 42.3% in SAs, and 52.4% in African/Afro-Caribbeans (40). Whereas for diabetic foot ulcers, WEs appear to be at greater risk with 5.5% prevalence compared to 2.7% in African Caribbeans and 1.8% in SAs (41).

Gestational Diabetes Mellitus

Children of women with a history of Gestational Diabetes Mellitus (GDM) are also at greater risk of developing diabetes, as are the women themselves. GDM is glucose intolerance that occurs and/or is diagnosed during pregnancy (42). The prevalence of GDM varies depending on a number of factors. For example, in the UK and Republic of Ireland, rates of GDM have been found to be as low as 0.4% in WE and as high as 5.8 in Asians (43).

Age

Historically, T2D was thought of as a condition that typically only impacted middle-aged and elderly individuals. This pattern still exists, with rates of T2D consistently increasing across age groups – prevalence in 75-79 year olds is estimated to be around 24% (5). However, more recently there has been growing concern over the accumulating evidence demonstrating increasing rates of T2D in people under 30 years, including in children – throughout different ethnic groups and countries of differing economic statuses (44-46). Compounding this concern is evidence that age at diagnosis is associated with elevated risk for undesirable CVD outcomes (47).

Modifiable Risk Factors

Diet and Nutrition

There are numerous dietary factors that have been suggested to lead to increased risk of overweight, obesity, and T2D. These include, but are not limited to increased intake of red and/or processed meat, refined grains, high-fat dairy, eggs, fried products, and sugar-sweetened soft drinks (48). It is also likely that a range of dietary interventions may be effective in the prevention and management of T2D (49).

Smoking

Cigarette smoking has previously been identified as a modifiable risk factor for T2D, largely due to the effects on body weight and composition, peripheral insulin sensitivity, and pancreatic β-cell function (50). Smoking in people with T2D has also been linked to the premature development of associated macrovascular and microvascular complications (51). However, it is important to monitor body weight and promote weight control during times of smoking cessation, as these periods have been associated with weight gain and greater risk of insulin resistance and T2D (52, 53).

Alcohol Intake

High levels of alcohol intake likely share an association with increased risk for T2D (54). Some previous research has reported a U shaped relationship between alcohol consumption and T2D, with moderate consumption being associated with decreased risk for T2D (55). However, more recent meta-analysis has suggested that reductions in risk at moderate levels of alcohol consumption may be confined to females (56). Further to this,

alcohol consumption has previously been reported as a marker for poor adherence to self-care behaviours in people with T2D (57).

Overweight and Obesity

In England alone, 68% of men and 60% of women (aged 16 and above) were classified as overweight or obese in 2019 (58). Compounding this are the increasing global rates of childhood obesity, with prevalence increasing from 0.7% and 0.9% in 1975 for girls and boys, respectively, to 5.6% and 7.8% in 2016 (59). It has long been established that obesity is a major risk factor for the development of T2D. Excess levels of adipose tissue in overweight and obese individuals are thought to lead to increased secretion of hormones, glycerol, and other compounds including leptin, cytokines, adiponectin, and inflammatory substances (60). Further to this, obesity, in particular abdominal obesity, has been reported to increase risk of T2D and cause the condition to develop at an earlier age (61). Conversely, every kilogram of weight lost is associated with an additional 16% relative risk reduction in risk of progression to diabetes (62). A 5% reduction in body weight versus baseline is deemed a realistic and meaningful target, which equates to a ~30% improvement in whole body insulin sensitivity (63) and decreases the conversion rate of prediabetes to T2D by 56% (64).

Although there are multiple modifiable and non-modifiable risk factors for IR and T2D – some of which have been discussed briefly here – a discussion of the true impact of these on development, progression, and outcomes associated with T2D is beyond the scope of this thesis. Here the primary focus will be on physical activity (PA), sedentary behaviour (SB), and ethnicity. This thesis will also place an emphasis on one of the key complications associated with T2D – impaired physical function (PF), discussed in the next section.

1.2 Physical Function

The previous section discussed T2D and prediabetes. This section will expand on this by exploring a common impairment experienced by people with T2D – impaired physical function (PF). Compared to people without, those with T2D are at greater risk of developing impairments to PF, and over recent years this has increasingly become a major cause for concern for people living with T2D and associated stakeholders (65).

1.2.1 Definition

PF is the ability of adults to perform basic physical activities of daily living, the impairment of which is typically caused by declines in the structure and function of skeletal muscle (66). Impaired PF is closely related to frailty – a condition characterised by increased vulnerability of a person to various stressors (67). Although frailty and impaired PF are distinct conditions, the two are closely interrelated – with skeletal muscle dysfunction detected in around 2/3 people with frailty (68). Impaired PF and frailty are also closely tied to sarcopenia – an age-related skeletal muscle disorder (69). Sarcopenia has typically been poorly defined; however, the 2018 European Working Group on Sarcopenia in Older People published a revised definition centred around criteria of: low muscle strength, low muscle quantity or quality, and low physical performance (69). Due to the close relationship and overlap between impaired PF, frailty, and sarcopenia, when examining populations with high levels of frailty or sarcopenia, it is likely that impairments to PF will be present.

1.2.2 Prevalence and Pathogenesis

Impaired PF is a growing concern within a range of populations. Evidence suggests that, in England, as many as 35% of the population aged >65 are currently living with some form of impaired PF (70). Age-related declines in PF are substantial – analysis of around 500 men aged 65-90 noted yearly declines of 1.54%, 1.38%, and 1.52% to chair rise capacity, gait speed, and hand grip strength, respectively (71). Interestingly, the study concluded that osteoporosis and sarcopenia were unlikely to be related to these declines in PF. There was also an inverse correlation between BMI and PF; however, it remains unclear whether high BMIs are causing functional decline, or a higher BMI is simply another indication of insufficient levels of PA, leading to a decline in performance.

Impaired Physical Function and Type 2 Diabetes

A recent analysis of UK Biobank participants found that 13% of people with T2D also experienced severe frailty as a comorbidity, and 54.8% were found to have mild frailty, suggesting there may be considerable issues with PF within this population (72). This may be partly due to the impact that T2D has on skeletal muscle (73). As depicted in Figure 1, IR in T2D can lead to mitochondrial dysfunction, autophagy, and muscle protein degradation. These pathways can progress to losses in muscle strength and mass. IR can then be compounded by the progression of mitochondrial dysfunction and the subsequent loss in muscle mass and strength due to decreased area for glucose transport (74-81). Likely because of these pathways, cross-sectional and longitudinal studies have found that loss of muscle mass and strength in people with T2D is accelerated in people with longer duration T2D or higher HbA1c (82, 83). These losses to muscle size and strength may also be exacerbated by age – in people aged 50 and older, longer duration T2D has been associated with lower quadriceps strength (84). However, these mechanisms may not be limited to people with T2D. In people aged 70 and above, without T2D, high fasting and post-challenge glucose and insulin concentrations were independently associated with muscle loss (85). Further to this, in non-diabetic men aged 50 and above, severe hyperglycaemia and IR was associated with walking speed – a key component of PF (86).

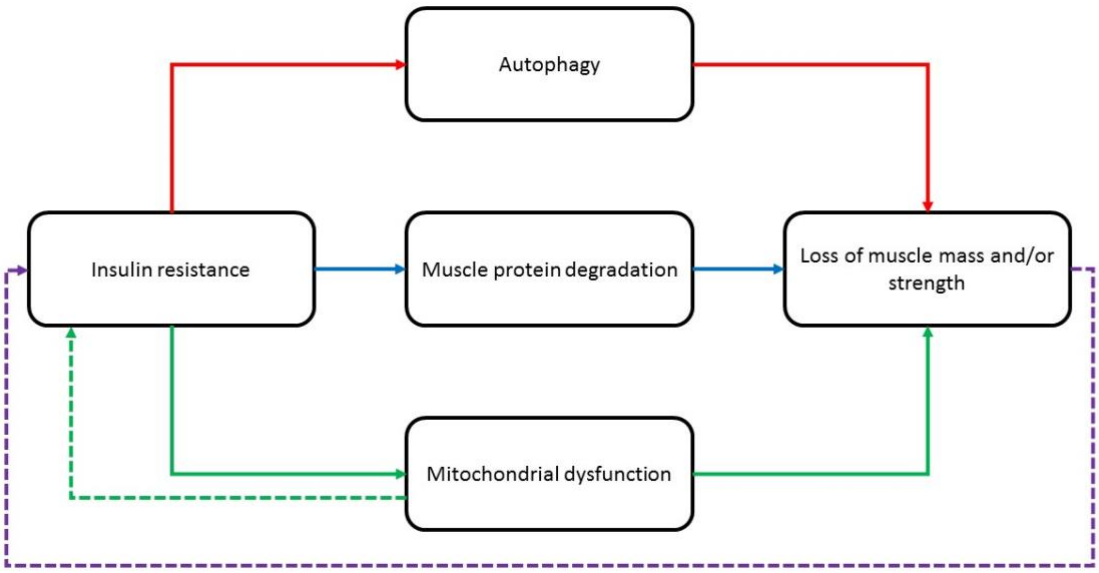


Figure 1 Muscle loss pathways in people with type 2 diabetes
Solid coloured arrows (red, blue, and green) represent pathways through which insulin resistance impacts muscle mass and/or strength. Dashed coloured arrows (purple and green) represent the compounding factors which will further exacerbate insulin resistance.

1.2.3 Epidemiological Evidence

It is evident from previous research that limitations to PF can predict risk of disability, use of health care systems, admission to care homes, and mortality (87-89). Furthermore, it has been estimated that, dependant on the number of factors present, impaired PF can increase healthcare costs by over 100% (90). A recent UK Biobank analysis suggested that varying degrees of frailty were significantly associated with mortality in men and women for all age groups, except for women aged 37-45 (72). However, it has previously been highlighted that people with T2D very often have an accelerated ageing process, meaning that people with T2D may be more susceptible to frailty and its associated impairments at an earlier age (91). T2D is also associated with increased likelihood for the development of depression, cognitive impairment, ulcers, infections, falls, chronic pain, urinary incontinence, and use of multiple medications (92). All of these factors can increase the progression of frailty and impairments to PF.

Tuttle et al. conducted assessments in people with T2D and peripheral neuropathy and found them to be 7.4 times more likely to experience early-onset impairment to PF than their control counterparts (93). Though the only method used for assessing PF was the modified Physical Performance Test (mPPT), so it is possible that the inclusion of other assessment methods may lead to different conclusions. This impairment in PF can have a major impact on the outcomes of people with T2D. Results from several studies have demonstrated that people with T2D who also suffer from some form of frailty are considerably more likely to experience hospitalisation or mortality (94). According to Chao and associates, for each additional criteria from a pre-defined scale to determine frailty that the patient experiences, they will have a 6-7% increased risk of hospital utilisation and premature mortality (92). This appears to be supported by the meta-analysis by Ida et al (94). The analysis of 565,039 patients resulted in a pooled hazard ratio of 1.35 (95% confidence interval (CI) 1.05-1.74; $p = 0.02$) of frailty related to mortality in T2D patients. However, there could be issues in that the studies included in the analysis used different scales for the definition of frailty. Further, the participants were gathered from only 8 studies in total. These issues could potentially have forced some limitations on the analysis. People with T2D appear to be at a greater risk of developing frailty and related impairments to PF at a much earlier age and possibly to a more severe degree than their apparently healthy counterparts.

1.3 Measurement of Physical Function

As the need for understanding the potential risks associated with impaired PF increase, so too does the need to accurately and efficiently measure PF. There are a number of methods that are currently accepted in clinical practice and research. Though there is still debate over which methods provide the most accurate assessment.

1.3.1 Physical Measures of Physical Function

Common physical measures of PF are detailed in Table 2.

Table 2 Physical measures of physical function

Test	***Description***	***Use and Validity***
Short Physical Performance Battery (SPPB)	Consists of a timed 4m walk, a timed chair sit-to-stand test, and three 10-second balance tests (feet side-by-side, feet semi-tandem, and feet full tandem) (95).	Frequently used in community settings, care homes, and hospital settings to provide a measure of PF (87, 96-98). The test is relatively quick and easy to administer, does not require any large amount of training for the tester or the testee, and it requires minimal equipment (99).
Modified Physical Performance Test (mPPT)	The test includes seven standardised tasks: walking 50ft, putting on and removing a coat, picking up a penny, standing up from a chair, lifting a book, climbing one flight of stairs, and safely turning 360°.	Has been strongly correlated with disability and PF (100). Some research has suggested that although more complex than the SPPB, the mPPT may be a more accurate measure of functional decline in some clinical populations (101).
6-Minute Walk Test (6-MWT)	The 6-MWT measures how far a person can walk on a hard, flat surface over 6 minutes (102). The test is usually conducted along a 100m corridor.	The test has been widely validated in a range of populations for its use as a measure of PF and walking capacity (103-105).

Incremental Shuttle Walk Test (ISWT)	The ISWT (106) is similar to the 6-MWT in that it focuses solely on walking capacity. Participants walk 10m shuttles in time with a beep that becomes progressively faster.	The ISWT has advantages over the 6-MWT in that it requires less space to administer, and it has a stronger correlation with peak oxygen uptake (107, 108). However, it has not been validated as much as the 6-MWT and there is potentially greater risk for cardiovascular events during the ISWT (102).
Gait Speed Tests	Gait Speed Tests are usually conducted over 4-6m distances and assess maximum gait speed achieved over this distance (89).	Gait speed assessments are generally accepted as measures for determining extended life, risk of early mortality, stratifying risks from surgery, repeat monitoring of overall health, and for the measurement of the effectiveness of interventions targeted at improving PF (89).
Stair Climb Power Test (SCPT)	Participants ascend a 10-step flight of stairs as quickly as possible, and power is calculated from the velocity (stair-climb time and height of the stairs) and the force (body mass and acceleration due to gravity).	The SCPT is designed to measure impairments to lower limb power in an "activity of daily living" situation (109). The test has been used with varying outcomes in a range of populations (110-112).
Chair Stand Tests	There are various modes of Chair Stand Tests (113). The most frequently used are 30-second (STS-30) and 60-second (STS-60) versions, and 5 timed repetitions (STS-5). In	These tests are widely accepted in the research community and are generally recommended for clinical populations (113, 114). Although various types of these assessments are used, it has been suggested that the STS-60 (ICC

	these tests, participants complete repetitions moving from sitting on a hard chair to standing for the specified time period.	0.927) is a much more reliable measure than the STS-5 (ICC 0.676) (115).
Timed Up-and-Go (TUG)	TUG tests time the participant to stand up from an armchair, walk 3m, turn around, walk back to the armchair, and sit back down (116).	The test was originally scored qualitatively (117) but has since been adapted to be scored based on time to complete the task (118). The tests are reliable measures of PF (118, 119).
6-MWT: 6-minute walk test; ICC: interclass correlation; ISWT: incremental shuttle walk test; mPPT: modified physical performance test; PF: physical function; SCPT: stair climb power test; SPPB: short physical performance battery; STS-5: 5 repetition sit-to-stand test; STS-30: 30-second sit-to-stand test; STS-60: 60-second sit-to-stand test; TUG: timed up-and-go		

1.3.2 Written Measures of Physical Function

In addition to the range of physical measures, there are also a number of written measures that can help to determine PF. Many of the scales and questionnaires used to measure PF also include other elements of clinical frailty. Because PF is only a small part of these assessments, their validity can be brought into question when purely measuring impaired PF. Common written measures of PF are detailed in Table 3.

Table 3 Written measures of physical function

Test	***Description***	***Use and Validity***
Katz Activities of Daily Living (Katz ADL)	The Katz ADL is a 6-point measure that looks at bathing, dressing, toileting, transferring, continence, and feeding.	The test has previously been found to be a good measure of PF in older adults, but care needs to be taken when applying the test to participants of various nationalities, as some deviations have been observed (120).
Older Americans Resource Scale for Instrumental Activities of Daily Living (OARS-IADL)	The OARS-IADL is similar to the Katz ADL but slightly longer and more in-depth. The test assesses various “essential” ADLs	It appears to be a valid and reliable method of assessment (121) that has been utilised in older persons and various clinical populations (122-124).

	(eating, walking, bathing, dressing, grooming, transferring, toileting); and also assesses IADLs necessary for independent living (housework, shopping, travelling, meal preparation, telephone use, medication management, and money handling).	
Medical Outcomes Study Short Form-36 (SF-36)	The SF-36 is a multi-item scale that assesses various aspects under the themes of: limitations to physical activities, limitations to social activities, limitations to usual role activities due to physical health, bodily pain, general mental health, limitations to usual role activities due to mental health, vitality, and general health perceptions (125).	The SF-36 is widely used by researchers in a range of populations (126). Though, it should be noted that, although considered a valid and reliable measure, some researchers have suggested that the SF-36 alone may be an inadequate measure in certain clinical populations – T2D – and that it should only be used in conjunction with an additional measure (127).
Fatigue, Resistance, Ambulation, Illness, and Loss of weight (FRAIL) Scale	This is a 5-item scale that has been developed comparatively recently (128).	It has been validated for use in a number of populations, both community-dwelling and based in a clinical setting (128-131).
Fried Criteria	The Fried criteria are a system of categorising accumulating deficits to identify frailty, and as a by-product – PF (132).	The Fried frailty phenotype criteria have been verified for use with elderly, comorbid, and functionally impaired individuals (133). The system has primarily been adopted for use in community-dwelling populations (134, 135) but it has also been successfully used in

		clinical settings, such as geriatric inpatients (133).

ADL: activities of daily living; FRAIL Scale: fatigue, resistance, ambulation, illness, and loss of weight scale; IADL: instrumental activities of daily living; Katz ADL: Katz activities of daily living; OARS-IADL: older americans resource scale for instrumental activities of daily living; PF: physical function; SF-36: medical outcomes study short form-36

Here, some of the most frequently used methods of measuring PF in research have been discussed. However, most of these tests impose a significant time and complexity burden on researchers and participants and could present as a potential barrier to recruitment (136). It is evident that none of these methods are ideal for collecting data from a large group. Even the simplest of these physical tests will involve a participant attending an assessment centre and a researcher taking them through the test. Further, it is not ideal to only use a single assessment. Most of the aforementioned tests do not incorporate enough dimensions of PF to yield an all-encompassing assessment of functional impairment in a clinical population, and so multiple methods are often used (137, 138). What is of note regarding the content of these tests, is that the majority of them contain some assessment of walking ability. Although the associations between habitual stepping and PF measures are not completely understood, walking ability is included in many activities of daily living, is a key component of PF, and is a preferred mode of PA (139).

1.4 Physical Activity as a Determinant of Cardiometabolic Health and Physical Function

1.4.1 Definition

Physical Activity (PA) is any bodily movement that is generated by the contraction of skeletal muscle that raises energy expenditure above resting metabolic rate (140). PA is often categorised based on Metabolic Equivalent of Task units (METs); one MET being defined as the amount of oxygen consumed while sitting at rest (3.5ml O2 per kg of bodyweight x min) (141). Typical sub-classifications of PA are light intensity (LPA) (1.6 – 2.9 METs), moderate intensity (MPA) (3.0 – 5.9 METs), and vigorous intensity (VPA) (≥6.0 METs) – the latter two often being represented together as moderate-to-vigorous PA (MVPA) (142). Physical inactivity is an insufficient PA level to meet the present PA recommendations (143) – though the content of this thesis will not focus on physical inactivity.

1.4.2 Recommendations

In the United Kingdom, PA guidelines suggest that adults should "do at least 150 minutes of moderate intensity activity a week or 75 minutes of vigorous intensity activity a week" (144). Despite this, estimates suggest that around half of adults do not perform enough PA to meet guidelines of 150 minutes of MVPA per week (145) – rates which seem to have gotten worse since the recent COVID-19 pandemic (146).

1.4.3 Physical Activity and Cardiometabolic Health

A large meta-analysis has provided strong evidence for an inverse association between PA and risk of T2D (147). These associations appear to persist across most levels of PA; however, it also appears to be the case that the greatest reduction in risk is yielded by moving from little/no activity to small amounts of PA (148). However, one systematic review also suggested that, in people with prediabetes, it is difficult to attribute the prevention of T2D to PA independent of dietary or weight loss changes (149). Notwithstanding this, a lack of PA, particularly in symphony with overweight or obesity has been shown to increase risk for T2D (150). The population attributable fraction of T2D associated with insufficient PA is, by some estimates, as high as 40% (151). In people with T2D, meta-analysis of 47 randomised controlled trials (RCT) demonstrated that structured PA consisting of aerobic, resistance, or combined PA was associated with reduction in HbA1c (152). In the analysis, PA durations of at least 150 minutes of PA yielded the greatest reduction in HbA1c (0.89%), and durations under 150 minutes yielded a lesser reduction (0.36%).

Along with being effective overall, there is evidence that suggests the effectiveness of PA's influence on cardiometabolic health may be maximised through timing – with research into this possibility growing over recent years, particularly with respect to timing of structured exercise and postprandial metabolic responses. Borror et al.'s review looked at studies which have investigated various timings, durations, intensities, and modalities of exercise and the effects of glucose control in people with T2D (153). The studies varied in their results, with the most effective outcomes being seen in aerobic type activities and resistance type activities. The consensus from this review appears to suggest that it is important for people with T2D to increase energy expenditure and limit time spent sedentary following the largest meal of the day. Several studies have shown that postprandial exercise is effective at lowering the glycaemic impact of a meal (154-157). Here, continuous glucose monitoring (CGM) can offer a valuable insight into the most beneficial timings of activity breaks – CGM can help to identify the largest postprandial spikes in the day which may help to tailor activity breaks to those periods. In addition to this, there is evidence which has shown that exercise performed before breakfast is effective in increasing fat oxidation over the course of the day and reducing postprandial triglyceride response (158). More recently, a study showed that a 6-week aerobic exercise training programme was more effective in improving appetite control, calorie intake, and weight loss in inactive, overweight women when performed in the morning (159). Applying these principles of timing of activity to programmes designed to increase PA and reduce sedentary time may prove to be more successful than a generic approach.

1.4.4 Physical Activity and Physical Function

Large-scale questionnaire data have reported a significant positive relationship between PA and PF in older adults (160). Studies have also shown that those who were engaged in more MVPA were less likely to experience loss of PF (161). A further meta-analysis investigating the impact of PA on PF in older women suggested that achieving more than 60 minutes of self-reported, structured PA per week yielded more favourable scores in measurements of PF than those who reported less than 60 minutes (162). Similarly, cross-sectional analysis of older adults has revealed a positive association between LPA and MVPA with various assessments of PF, including 10m walk and 6-min walk results (163). Another, larger cross-sectional analysis found significant associations between PA with PF test performance in people with T2D and impaired PF – with each standard deviation (SD) increase in PA volume and intensity being associated with 17% more STS-60 repetitions (164). Further to this, a systematic review

of thirty studies, representing nearly 25,000 older adults found significant associations between higher PA with better PF (165).

There is also strong experimental evidence demonstrating the benefits of PA on improving PF – a systematic review and meta-analysis on the effectiveness of PA interventions for improving PF and slowing the rate of impairment to PF in older adults found that PA interventions are likely beneficial for improving muscle strength, walking speed, mobility, balance, and a range of PF assessments (166). However, due to the lack of homogeneity among the intervention characteristics of each study, it is difficult to determine what modality of PA might yield the most benefit. Regardless of modality, there is evidence demonstrating that aerobic, resistance training, or multi-component PA interventions delivered in the community or at home can elicit beneficial improvements to PF – with as much as a 40% reduced risk of fall-related injuries (167, 168). In an attempt to improve PA uptake and adherence, recent public health campaigns have focused on walking as a preferred choice of PA – in particular brisk walking (169). As walking has been identified as a preferred and popular choice of PA modality, it is of benefit to explore the links between walking behaviours with markers of cardiometabolic health and PF.

1.5 Step Accumulation and Step Cadence as a Measure of Physical Activity

Despite the demonstrated benefits of PA, it appears difficult for people to adhere to a programme of PA long-term (170). Additionally, efficient and accurate measurement of PA is potentially challenging, particularly when examining large populations (171). The number of steps taken in a day is a simple measure of PA (172), and the capacity for the general public to monitor steps is now more feasible than ever before, as fitness trackers and mobile devices have grown in popularity (173). Accumulation of steps is a commonly referenced method of improving health and wellbeing, and a goal of 10,000 steps per day is commonly cited; however, this figure is likely derived from a marketing campaign in the 1960's by the Japanese company – Yamasa as part of their promotion of the Manpo-Kei (roughly translated to "10,000 steps meter"), as opposed to any scientific investigation (174-176). Numerous large cohort studies and meta-analyses have established the association between accumulation of more steps per day and decreased risk of mortality and cardiometabolic risk (for example (147, 172, 177, 178). However, what may also be an important consideration is step cadence, or the speed at which steps are taken (179-182).

1.5.1 Step Cadence

Step cadence has previously been strongly linked to objectively measured walking speed and intensity (183). Additionally, the use of step cadence as a goal to encourage individuals to accumulate time in MVPA has proven to be effective in helping people to reach PA recommendations (184). Patterns of step cadence are often categorised in various ways; frequently, slow (≤79 steps/minute), medium (80-99 steps/minute), brisk (100-119 steps/minute), and fast (≥120 steps/minute) (185). Further to this, it is generally accepted that the majority of physiological benefits will come about when accumulating steps at 100 steps/minute or more (179). In younger adults (21-40 years old), step cadence thresholds of 100 steps/minute and 130 steps/minute have been cited as strong indicators of MPA and VPA, respectively (180). MPA is said to begin at 3 METs (186); and a controlled study of over ground walking suggested that 3 METs would be achieved at speeds of 2.7mph (4.3km/h) (187). Slow to fast walking speeds (2.0–4.0 mph or 3.2–4.6 km/h, respectively) correspond with step cadences of 96–134 steps per minute (183).

1.5.2 Peak Step Cadence

Although total steps at a specific cadence are of value, they can be accumulated through sporadic bursts of stepping. Some research has focussed on time-restricted bouts at specific

cadences. Full 1-minute bouts are more strongly associated with unhindered, purposeful travel, whereas shorter periods of time are more likely to be based around movement in the home or workplace (188). However, strictly reporting on bouts in this fashion could limit the amount and quality of the data available. It has previously been suggested that only 40% of walking bouts last longer than 30 seconds, and that only 1% of walking bouts lasted 2 minutes (189). So instead, peak step cadence values are often used to represent the highest (consecutive or non-consecutive) bout of stepping accumulated in the day. These values, particularly 1-minute and 10-minute step cadences, have previously been negatively associated with age and BMI (179). The use of specific epochs to demonstrate step cadence has been criticised in the past, with researchers suggesting that it is actually demonstrating step accumulation and that true step cadence within those times could be different (188, 190).

1.5.3 Brisk Stepping and Health

The associations between steps above the threshold for brisk stepping (≥100 steps/minute) is an area of growing interest. There are large analyses that have suggested that daily step count is more important that step cadence (172, 174, 177, 178). However, these studies are focused on mortality, in typically healthy populations. Evidence investigating brisk stepping in different populations, with a focus on more specific health outcomes other than mortality is lacking, though initial results appear positive. The accumulation of brisk steps has been previously associated with a number of beneficial health outcomes, including BMI, comorbidity, obesity, PF, and T2D (179, 191-193). For example, 6-year follow-up in a cohort of over 6,500 Hispanic adults concluded that those who accumulated 17 minutes/day of brisk stepping had a 31% lower risk of developing T2D compared with those who accumulated less than 2 minutes/day (194). Further, 6.9-year follow-up in nearly 5,000 older women (78.9 ± 6.7 years) found that although each 2,000 steps/day increment – at any intensity – was associated with a 12% lower hazard rate for T2D, this association was stronger for steps accumulated ≥100 steps/minute than for those <100 steps/minute (195). Analysis of the National Health and Nutrition Examination Survey (NHANES) cohort has also shown that there is a beneficial link between brisk step cadence and cardiometabolic outcomes (196). The study also concluded that time accumulated at ≥120 steps/minute was associated with absence of cardiometabolic risk.

1.6 Linking Sedentary Behaviour to Physical Activity, Cardiometabolic Health, and Physical Function

Taking into consideration the rates of adults who are not performing enough PA to meet guidelines of 150 minutes of MVPA per week (145), it has been argued that it may be beneficial to explore other strategies of increasing PA, perhaps through reduction of sedentary behaviour (SB) (197).

1.6.1 Definitions

There are various conflicting views on the definition of SB. Within this thesis, the term is defined in accordance with the Sedentary Behaviour Research Network (198). SB is defined as "any waking behavior characterized by an energy expenditure ≤1.5 METs, while in a sitting, reclining or lying posture" (199). Frequently, SB shares an unsurprising association with PA, whereby increased SB accompanies decreased PA and vice versa (200). However, it is possible for high levels of SB and high levels of MVPA to coexist (201).

1.6.2 Recommendations

Guidance from around the world, including the UK Chief Medical Officer's recommendations on PA and ageing has highlighted the potential dangers associated with SB as an independent risk factor for health in adults and called for further research which explores the benefits of replacing SB with bouts of PA (144, 202). The UK recommendations also call for people to reduce time spent sitting or lying down and to break up periods of extended sitting with PA (144). The most recent World Health Organisation guidelines for PA have placed particular emphasis on encouraging all people to strive for a combination of an increase in PA and a limitation on SB (203). The American Diabetes Association make specific recommendations to limit time spend engaging in SB and to break up prolonged sitting with LPA every 30 minutes – particularly for people with T2D (204).

1.6.3 Sedentary Behaviour as a Risk Factor

The average adult typically spends between 55 and 75% of their waking day engaging in SB (205). Assuming an 8-hour sleeping pattern, this equates to around 11 hours per day sedentary (206), with people at high risk of chronic disease tending towards the upper end of this range (207). In response to mounting evidence, research output surrounding SB has increased over recent years (208). High levels of SB have been associated with an increased risk of all-cause mortality (209-213). The dose-response relationship between time engaging in SB and mortality has previously been demonstrated to increase gradually from 7.5 to 9 hours

and starts to increase drastically at around 9.5 hours (214). Those people who spend 10 and 12 hours per day sedentary potentially have a 1.48 [95% CI 1.22, 1.79] and 2.92 [2.24, 3.83] greater risk of death, respectively (214).

1.6.4 Sedentary Behaviour and Cardiometabolic Health

High levels of SB are potentially damaging to cardiometabolic health. For example, declining occupational energy expenditure in the United States has previously been mapped against increasing rates of obesity (215). It has similarly been noted that there is a stronger correlation between increased rates of obesity and the sale of energy-saving devices, which facilitate increases in SB, than there is between the obesity rates and increases in energy intake (216). Further to the aforementioned increased risk of mortality, research has also suggested that spending high levels of time in SB can be a key factor in the development of CVD (209-211) and T2D (209, 211). Time spent in SB has also been identified as an independent risk factor for T2D (217), and people with T2D appear to sit on average 26 minutes more per day than people with normal or prediabetes-related impaired glucose control (218). The detriments of extended periods of SB on glucose regulation have been previously established (219-221) and research has endeavoured to investigate this in a variety of ways. Cross-sectional analysis has suggested that a 1-hour increase in time engaging in SB may be associated with increased odds of 22% for T2D (218). In the analysis by Wilmot et al., individuals with the highest time spent engaging in SB had more than twice the risk of developing T2D compared to those with the least amount. Additional measures of SB, such as television viewing time, have also been found to be associated with T2D – each 2-hour difference in television viewing time was associated with a 20% difference in T2D risk (209). A further analysis has estimated that 29% of T2D incidence within the English population is attributable to television viewing time (222). Additionally, in people who have recently been diagnosed with T2D, higher levels of time spent engaging in SB are associated with worse cardiometabolic profiles (223); for example, each additional hour of sedentary time was associated with 1.89cm [95% CI 0.94, 2.83] greater WC and each additional break in sedentary time associated with 0.15cm [0.05, 0.24] lesser WC. Cooper and associates (223) also concluded that each additional hour of sedentary time was associated with greater Homeostatic Model Assessment for Insulin resistance (HOMA-IR) (0.42 [0.14, 0.70]) and greater fasting insulin (8.22 mmol/l [2.80, 13.65]), but that these associations were largely attenuated after additional adjustment for WC. These findings are corroborated by meta-analysis which concluded that each additional hour of sedentary time per day increased risk of T2D by 5% and hypertension by 4%; and each additional hour of

television viewing time per day increased risk of T2D by 8% and hypertension by 6% (224). Further to the threat of SB as a stand-alone risk factor for cardiometabolic conditions, cancer, and mortality; SB in symphony with chronic disease or elevated BMI, further increases risk of all-cause mortality (225).

1.6.5 Sedentary Behaviour and Physical Function

Evidence has suggested that spending high levels of time in SB can also be a key factor in the development of impaired PF (226). Increased time spent engaging in SB has been linked to accelerated decline in skeletal muscle mass and PF, particularly as people age (227, 228). Data from older adults (aged 65-100 years) has demonstrated associations between increased sitting time and greater risk of impaired PF (229). In the study, mean sitting bout duration and time spent in SB were both inversely associated with performance in the SPPB, with associations being strongest in those participants with the lowest levels of MVPA. Cross-sectional analysis of older adults demonstrated that each additional hour of time spent in SB was associated with an additional 21 seconds required to complete a 400m walk and a 0.55 lower score in the SPPB (228). These associations were independent of time spent in MVPA, suggesting that the increased time in SB could be leading to reductions in overall muscle stimulus and subsequent decline of PF. Older adults taking fewer than 7 breaks per hour in time spent in SB have also been suggested to be at 2-5 times greater risk of reporting impairments to PF (230). A study, by Ida et al., also suggests that time spent in SB is a key factor in the impairment of PF in various clinical populations (94). In people with T2D and impaired PF, typically more time in prolonged SB (at least 30-minutes) is observed than in non-diabetic people, and each SD increase in time spent in prolonged SB has been associated with a 15% decrease in PF assessment scores (164). Further to this, the high prevalence of T2D in people who already have impaired PF presents an additional barrier to increasing their levels of PA and reducing time spent engaging in SB (231). Recent research has demonstrated that a higher ratio of LPA to time engaging in SB is significantly associated with higher results from PF assessments. Each one unit increase in the ratio of LPA to time spent sedentary was associated with approximately one additional point in the SPPB (β 95% CI 0.96 [0.09, 1.82]), suggesting that people who engage in more LPA in proportion to time engaging in SB will have less impairment to PF (232). This study also highlights the independent benefits of decreasing time spent sedentary – categorical analysis suggested that people who were physically active with low levels of SB (in the lowest quartile of time spent sedentary) might score .43 more in the SPPB compared to people who are physically active with high levels of SB (in the highest

quartile). This is supported by a recent meta-analysis that has highlighted that the links between SB and PF may be independent of PA levels (222).

The next section will explore how increasing PA through reductions in SB might impact cardiometabolic health and PF.

1.7 Improving Cardiometabolic Health and Physical Function by Promoting Physical Activity through Reductions in Sedentary Behaviour

Although both PA and SB have been highlighted in previous sections as risk factors for various health outcomes, PA has been shown to be a potential method for reducing the all-cause, cardiovascular, and cancer mortality risks associated with increased SB, with higher volumes of MVPA being required to potentially eliminate risk (233, 234). The two meta-analyses by Ekelund and associates concluded; that in order to counteract the detrimental impact on mortality of sitting 8 hours or more per day, people would need to engage in 60-75 minutes of MVPA per day (234), and similarly around 60 minutes of MVPA would be required to reduce risk of CVD or cancer mortality (233). However, intervention approaches that have a singular focus on increasing PA have been criticised for being too restrictive and potentially leading to missed opportunities to encourage populations to reduce time spent in SB, which would be of further benefit (235). Consequently, other prominent investigators have highlighted that for those who are unable and/or unwilling to increase their PA time to the required amount to significantly reduce their risk of disease and mortality, emphasis should be placed on replacing any amount of time spent in SB with any intensity of PA (236).

1.7.1 Cardiometabolic Health and Breaking up Sedentary Behaviour

Any change from sitting or lying postures to LPA or MVPA can elicit an increase in energy expenditure; these increases are potentially seen through simply standing – largely due to increased muscle activation driven by postural muscles (206). There is some debate, however, over the benefits of standing; for example, there are studies that have concluded the difference in energy expenditure between sitting and standing is negligible (237). Conversely, there is evidence from meta-analysis that indicates that standing can have a notable, beneficial impact on energy expenditure (238). In response to the evidence around reducing and breaking up SB, the 2022 Consensus Statement from the American College of Sports Medicine on exercise and PA in people with T2D highlights the importance of using "small doses of physical activity throughout the day to break up sitting" (239). The 2022 American Diabetes Association consensus statement also includes recommendations for people with T2D to break up prolonged sitting (over 30 minutes) with short bouts of walking and/or resistance exercise to improve glucose regulation (240). These reductions and breaks in SB may be particularly important in people with high levels of SB, as purposeful PA will only take up a small proportion of the day, if at all (197). This is supported by research showing that, compared to

people who typically engage in prolonged uninterrupted sitting, those who regularly break up sitting have more desirable cardiometabolic risk profiles (223, 241).

Lab-based Evidence

There are several lab-based studies that have demonstrated the impact that breaking up SB with LPA (242-245), standing (243), and resistance exercise (245, 246) can have on markers of cardiometabolic health. One such study looked into interrupting SB over 5 hours with a 2-minute light or moderate walking break every 20 minutes (247). The results showed that light- and moderate-intensity walking had a similar impact on reducing postprandial glucose and insulin area under the curve (iAUC) by 24% and 23%, respectively. Another study supported these findings, demonstrating that regular breaks in time spent sedentary (1 minute, 40 seconds walking every 30 minutes) were more effective than continuous PA for reducing glucose area under the postprandial curve in healthy, normal weight adults (248). Breaking up sitting with light-intensity aerobic and simple resistance exercises, as supported by a consensus statement by the American Diabetes Association (240), may also have a beneficial effect on the postprandial lipidome (249), 22-hour hyperglycaemia (250), postprandial glucose, insulin C-peptide, and triglyceride responses (251) of people with T2D. Interrupting sitting with standing or light-intensity cycling for 10-30 minutes every hour over 8 hours improved 24-hour glucose control in overweight or obese adults (242). Interrupting a 7.5-hour sitting period with 5 minutes of standing or light-intensity walking led to improvement in postprandial metabolic responses in overweight or obese, dysglycaemic, post-menopausal women (243). In people with T2D, resting blood pressure was improved by interrupting 8 hours of sitting with light-intensity walking or resistance training exercise for 3 minutes every 30 minutes (245). Similarly, in overweight or obese people, breaking up sitting time every 30 minutes over 6 hours with 3 minutes of resistance training exercise led to improvements in postprandial insulin levels (246). Further to this, breaking up sitting time with PA appears to be more beneficial to those with poorer health profiles – in response to 5-minute light-intensity walking breaks every 30 minutes, those with less favourable cardiorespiratory profiles at baseline showed much more positive responses, in relation to glucose regulation than those with less positive profiles (252). There is also evidence that adopting an upright posture may not be necessary to elicit the benefits of breaking up sedentary time – a study investigating the effectiveness of 5-minute bouts of arm-ergometry every 30 minutes saw attenuation of postprandial glycaemia without changing posture from a seated position (253).

Although these experimental studies are promising, there are studies to the contrary, such as that by Freire et al. investigating the effects of breaking up time spent engaging in SB with standing for 10 or 20 minutes in middle-aged and older adults with T2D that have found there to be no significant relationships with postprandial glycaemia (254). This may be explained somewhat by research into the frequency and duration of breaks in SB which concluded that frequent 2-minute moderate-intensity breaks may be more effective in attenuating postprandial insulin concentrations than less frequent 10-minute bouts of equivalent intensity (255). Although not totally equivocal, these lab-based studies yielded valuable data, and have been instrumental in the development of investigations into free-living experiments

Free-living Evidence

Over recent years, studies have also begun to highlight the potential benefits of breaking up SB in free-living environments. What is more, although the primary focus of chronic SB studies thus far has been on the behavioural efficacy of the proposed interventions, some studies have also focused on the impact of reducing sedentary time for health-related outcomes. For example, a recent systematic review and meta-analysis reported that, although interventions (≥7 days) targeting SB yielded significant improvements in markers of cardiometabolic health, the differences were minimal and arguably not clinically meaningful (256). However, a systematic review and meta-analysis including 18 studies, confined to a clinical population (overweight or obesity, T2D, cardiovascular, neurological/cognitive, and musculoskeletal diseases), demonstrated that behavioural lifestyle interventions can reduce SB by ~90 minutes per day and markedly improve markers of cardiometabolic health (HbA1c , percentage body fat, and waist circumference (WC)); though, this could be, at least in part, due to these people having higher absolute baseline values (257). Further, meta-analysis of 42 studies investigating the effects of breaking up prolonged sitting with PA on glucose, insulin, and triacylglycerol measures found that breaking up prolonged sitting moderately attenuated post-prandial glucose, insulin, and triacylglycerol, with stronger relationships observed in those with a higher BMI (258).

Existing behaviour change interventions delivered over the longer term have demonstrated success for changing behaviour, but less so for markers of metabolic health. Such programmes typically use a number of behaviour change techniques aimed at reducing and breaking up SB (259-266). Large-scale interventions like *SMART Work and Life* (267), and its

predecessor – *SMArT Work* (260), were both successful in reducing sitting time. Participants who received the *SMART Work and Life* intervention alone saw a 22.2 [95% CI 5.7, 38.8] minutes/day reduction in sitting time and participants who received the *SMART Work and Life* intervention plus a standing workstation saw a 63.7 [47.4, 80.1] minutes/day reduction. The original *SMArT Work* yielded an 82.4 [50.3, 114.5] minutes/day reduction in sitting time. This was achieved through organisational strategies in the workplace (such as enabling senior leaders to offer more support and training workplace "champions" who would help facilitate the intervention); environmental strategies (such as small-scale restructuring of the office environment, motivational posters, and encouragement to make adjustments to home life); group and individual strategies (including a one-off online education programme and group catch-up sessions); and in the case of the *SMART Work and Life* plus standing workstation group, a standing desk (267). However, despite the success in reducing sitting time, no differences were observed in bodyweight, BMI, WC, percent body fat, blood pressure, fasting glucose, HbA1c, or lipid levels. Though, this could be, in part, due to the recruitment of a healthy sample of office-based workers. A similar large-scale intervention – *Stand and Move at Work* – incorporated organisational changes (managerial support, new worksite policies and practices, and motivational messaging); environmental strategies (sit-stand workstations, motivational signage throughout the workplace, reorganisation of office environment to promote walking); social strategies (contests, events, and role modelling); and individual strategies (education, behavioural cues, goal setting, and relapse prevention) (268). The intervention saw a -59.2 [95% CI -74.6, -43.8] minute per 8-hour work day difference in sitting time after 12 months. In the cohort as a whole, the effect on cardiometabolic health was negligible; however, in those with prediabetes or T2D, there were clinically meaningful differences to blood glucose, triglycerides, blood pressure, HbA1c, low-density lipoprotein cholesterol (LDL-C), bodyweight, and percent body fat. Additionally, pooled effects from meta-analysis of SB interventions in non-clinical populations, lasting between 2 weeks and 6 months, demonstrated statistically significant changes to weight (-0.56kg [95% CI -0.94, -0.17]), WC (-0.72cm [-1.21, -0.22]), body fat percentage (-0.26% [-0.50, -0.02]), systolic blood pressure (-1.05mmHg [-2.08, -0.02]), insulin (-1.42pM [-2.82, -0.02]), and high-density lipoprotein cholesterol (HDL-C) (0.04mM [0.02, 0.07]); though these changes, from a clinical perspective, were minor (256). Notwithstanding these encouraging results, sustained behaviour change is difficult to achieve, and work is needed that explores multiple approaches to changing PA and SB behaviours to elicit change to cardiometabolic health.

1.7.2 Physical Function and Breaking up Sedentary Behaviour

Analysis of older adults has revealed associations between the reallocation of sedentary time with LPA and MVPA and improved performance in assessments of HGS, STS-30, and TUG (269). Further, isotemporal substitution of SB to LPA or MVPA has also shown promising results. Lai and associates concluded that, in older adults, reallocating 60 minutes of SB per day to LPA was associated with improved HGS, TUG test results, and gait speed; and reallocating to MVPA was associated with improvements to gait speed and STS-5 (270). The same analysis showed that reallocating 60 minutes of sedentary time with a combination of 30 minutes LPA and 30 minutes MVPA was also associated with a decrease in STS-5 time. Other studies looking at replacing SB with LPA have also shown some promising results for improving PF (e.g., 400m walk) (271). Taken together, these studies suggest a good case for PF in people with T2D being improved through reductions in SB.

Free-living Evidence

There is RCT evidence highlighting potentially encouraging results regarding reducing and breaking up time engaging in SB to improve PF. In a trial focussed on simply increasing the number of sit-to-stand transitions each day, participants in the intervention group experienced significantly less decline to PF over 6 months than those in the control group (272). However, the aforementioned study was conducted in nursing homes with health care assistants prompting participants to repeat sit-to-stand activities throughout the day; therefore, the applicability to free-living participants is uncertain. A further study, by Barone Gibbs et al., conducted a 12-week trial in older adults which found that participants in the sedentary reduction group (who had a goal of reducing sedentary time by 1 hour per day) saw a statistically significant 0.5 point increase in SPPB score where the PA group (who had a goal of achieving 150 minutes of MVPA per week, in bouts of at least 10 minutes) did not (273). It should be noted that the presence of T2D has previously been recognised as a potential factor that may impact the effectiveness of an intervention targeted at increasing PA time, due to multiple factors such as lack of capacity or motivation (274, 275). Therefore, an initial focus purely on reducing SB time in this population may have a more beneficial impact on health outcomes and eventually aid in transitioning to more intense PA (276). Moreover, older adults who have participated in interventions designed to reduce their sitting have reported greater interest in participating in PA post-intervention (277). Despite this, experimental evidence focussing specifically on the effects of SB and PA changes on PF in people with T2D or prediabetes is sparse.

1.7.3 Factors Influencing Associations

When looking to elicit improvements to cardiometabolic health and PF through breaks in time spent in SB, different break types, durations, modalities, and intensities may be more appropriate for different populations based on their pre-existing conditions, their symptoms, and habitual PA levels (278). Previous meta-analysis investigating the effectiveness of interventions designed to reduce time spent in SB has been promising; though suggests interventions should typically include a component directly focussed on reducing SB as opposed to simply increasing PA in order to produce clinically meaningful reductions in SB (279). It has also been hypothesised that the effectiveness of any given PA bout to stimulate beneficial responses is highly dependent on the levels of nutrients consumed and that CGM data may be an effective tool to aid in the prescription of SB reduction and PA (280). Continuous monitoring of blood glucose could help to inform the frequency of PA bouts to break sedentary time and yield greater improvements in glucose control. Though, some evidence has suggested that there may not be any difference in the benefits of interrupting sedentary time with increased frequency when compared to less frequent interruptions (281). Another study found similar results, with glucose remaining unchanged regardless of differing frequency of breaks; however, postprandial insulin responses were improved with more frequent breaks (255). Although it is unclear whether there are particular modalities of PA that are more beneficial to be used when interrupting SB, meta-analysis has suggested that MPA is the most optimal strategy (282). Therefore, when targeting breaks in SB with MPA, it may be shrewd to consider the modes of activity that are most likely to be adopted by high-risk populations, such as walking (283, 284).

It is also likely that demographic variables will have an impact when looking to influence markers of PF and cardiometabolic health through changes to PA and SB habits, as specific populations – females, SAs, and people with higher BMI ($\geq$27.2 kg/m^2) – have been shown to have greater postprandial glucose and insulin responses to interrupting sitting time and worse responses to prolonged sitting (37). For example, studies have previously reported on differences in PA and SB based on ethnicity – baseline RCT data from nearly 1,000 UK adults recently suggested that although SA people may undertake less PA than WE people (24 minutes versus 33 minutes of MVPA per day in SAs and WEs, respectively), they are also less sedentary than their WE counterparts (516 minutes versus 552 minutes of sedentary time per day in SAs and WEs, respectively) (285). The positive influence of PA on markers for PF has

previously been successfully demonstrated in SA populations by Barrett et al. (286). Particularly for HGS which shared statistically significant associations with all four PA measures used in the study (total daily energy expenditure, PA levels, daily average activity count, and activity energy expenditure). However, it is worth noting that participants in this study fell within a very narrow range with respect to risk of impaired PF and were fairly young (49-50 years) (286). Larger studies in SA people have gone on to support these findings, also highlighting benefits of PA for numerous other aspects of health and wellbeing, including mental health, life satisfaction, and decreased risk for T2D, heart disease, stroke, and several other non-communicable diseases (287). Despite the apparent health benefits for SAs of increasing PA time and reducing SB, a recent analysis of SA adults living in Canada found that participants accumulated mean 673.5 min/day of time engaging in SB and only 2.3 min/day of MVPA (288).

1.8 Measurement of Sedentary Behaviour and Physical Activity

In order to objectively measure PA and SB in free-living conditions, accelerometers are typically used. However, the generation of specific outcomes of interest is dependent on the wear location of the accelerometer and the processing methods. Some studies have also observed disagreement between the various devices depending on the activity, generally as a result of differing wear locations and method of data analysis (289). Previous comparisons between the wrist- and hip-worn ActiGraph and the thigh-worn activPAL have suggested that the reliability of the data gathered from these devices is highly dependent on the activities (290). The study by Steeves et al. suggests that the ActiGraph data were more accurate for reporting upright walking activities, but that the activPAL is better at recognising more specific activities such as walking down or up a set of stairs and running (2.91 m/s). Similarly, Crowley and associates found there to be considerable differences in the classification of physical behaviours from the ActiGraph GT3X+, the Axivity AX3, and the activPAL Micro4 (291). Other studies have noted that wrist- and hip-worn devices such as the ActiGraph are more accurate for measuring steps, but that the thigh-worn activPAL is superior when measuring sitting or standing activities (292). Several other accelerometers and wear locations have been compared against the activPAL for their accuracy in estimating SB. For example, ActiGraph accelerometers worn on the hip, dominant, and non-dominant wrist were found to estimate time spent sedentary with moderate to high accuracy in comparison to the activPAL (289). But importantly, the study also reported that a considerable amount of time where ActiGraph designated sedentary time, activPAL reported standing time. However, three thigh-worn accelerometers (ActiGraph GT3X+, Axivity AX3, and activPAL Micro4 – all processed in the same software using raw acceleration data) were found to have negligible difference between classification of different intensities of PA and SB (291), suggesting that harmonisation across devices may be possible.

When using wrist-worn and waist-worn accelerometers to assess PA, researchers use markers of minimal acceleration/movement to categorise time spent sedentary, which may not give an accurate representation of the postural element of SB (sitting, lying, or reclining) because it would also include standing and very light movement (293). Other studies have also suggested that placement of devices on the waist can result in poor accuracy for detecting sitting (294). In order to address issues with the measurement of posture (i.e., people standing, walking/running, sitting, or reclining), researchers have generally adopted the activPAL thigh-worn accelerometer (295). For the research conducted as part of this thesis, the activPAL

device will be used throughout. In addition to the device's capabilities to determine postural changes and step cadence, this also allows for a greater degree of cross-comparison between conclusions from each chapter.

1.8.1 The activPAL

The activPAL 3 (PAL Technologies, Glasgow, UK) is a triaxial accelerometer which uses static acceleration to assess the orientation of the device (to determine posture) and dynamic acceleration to assess movement (stepping) (296). The device is attached to the front of the thigh. Wear time protocols have varied over time, but recent protocols frequently waterproof the device and use a 24-hours per day wear time protocol (297). The use of the activPAL device to measure various aspects of SB and PA in research has increased dramatically over the last decade (according to the Scopus database, there were 8 papers published that mentioned "activPAL" in 2010; in contrast to 2022 when there were 64 papers published, representing a 700% increase). This is likely to be in large due to its unique qualities. While there are a number of devices available that estimate PA and SB, at present the activPAL is one of the most frequently used for measuring posture, and is considered the gold standard accelerometer for identifying sitting and distinguishing between sitting and standing (297). When measuring sitting/lying time, upright time, and detecting transitions between postures, the activPAL has been shown to have excellent agreement with direct observation (295, 298-300). Further to this, it has proven to be adept in recognising the difference between standing and stepping (295) and highly accurate in determining step cadence at speeds ≥0.5 m/s (296, 301).

1.9 Summary of Research Gap

Habitual walking activity forms the basis of many tasks of daily living and is the preferred form of PA within the population. Stepping cadence is also a central measure of PF. However, the importance of how habitual walking activity is accumulated through different cadence levels and intensities is debated. Research is needed to investigate how step cadence is associated with PF and cardiometabolic health. SB is also associated with cardiometabolic health and PF and offers a novel approach to intervention development with the promotion of short bouts of "breaking" activities, including walking, throughout the day.

1.10 PhD Aims

Based on the existing literature and gaps in the knowledge base, this programme of work identified three primary aims:

1: To interrogate the associations between device-measured step cadence and PF in older adults.

2: To explore associations between change in step cadence and change in markers of cardiometabolic health in people with prediabetes over longer-term periods.

3: To assess outcomes from a personalised intervention to encourage adults with T2D or prediabetes to reduce and break-up sitting time with the aim of improving cardiometabolic health and PF.

Chapter 2: Ethnic differences in the association between step cadence and physical function in older adults

Chapter Overview

This chapter reports on a cross-sectional analysis of data from the *STAND UP* study. Originally it was hoped that this analysis would also include data on peak velocity of transitions during sit-to-stand and stand-to-sit movements, using code developed at University of Salford. However, due to issues with the code, it was not possible to complete this analysis as planned. Therefore, the research was refocused on step cadence and peak step cadence and the associations with PF, as assessed by the STS-60 test. The chapter presents the associations between various step cadence variables and PF, stratified by WE and SA ethnicities. The chapter concludes with a discussion around the potential reasons for ethnic differences in these relationships and explores the degree of change to stepping cadence that would be required to see a clinically significant difference in STS-60 performance.

Key Findings

- SAs take fewer steps per day than WEs (8986 ± 3450 vs 7780 ± 2340 steps/day, p = 0.040 [mean ± SD])
- SAs take fewer brisk steps per day then WEs (5515 ± 2866 vs 3723 ± 2083 steps/day, p = 0.001)
- Minimum clinically important difference (MCID) in STS-60 repetitions could be achieved (in WEs) through:
    - Walking additional 2777 brisk steps/day
    - Increasing peak 1-minute step cadence by 15 steps/minute
    - Increasing peak 30-minute step cadence by 12 steps/minute
    - Increasing peak 60-minute step cadence by 9 steps/minute

Publications and Conference Presentations

The original work relating to this chapter was published in the Journal of Sports Sciences:

McBride, P., Yates, T., Henson, J., Davies, MJ., Gill, J., Celis-Morales, C., Khunti, K., Maylor, B., Rowlands, A., & Edwardson, C. (2022). Ethnic differences in the relationship between step cadence and physical function in older adults. *Journal of Sports Sciences*, 40(10), 1183–1190 (302).

The original work was also presented at:

PHE Public Health Research and Science Conference 2021, May 2021, London, UK.

Author Contribution

This was a secondary data analysis and all the data collection had been completed by researchers at University of Leicester and University of Glasgow prior to the commencement of my PhD project. In order to conduct this analysis, I received training on the cleaning and processing of activPAL data within Processing PAL by one of my supervisors (Dr Charlotte Edwardson). Following this training, I cleaned and processed all of the activPAL files and produced the summary variables used in the analysis. Dr Charlotte Edwardson oversaw the cleaning and organisation of the data to ensure accuracy. Prof. Thomas Yates designed the statistical analysis methods and trained me in their execution and interpretation. I performed the statistical analyses. I wrote the first draft of the manuscript with the assistance of Dr Joseph Henson and addressed reviewer comments prior to publication.

2.1 Introduction

As discussed in the Background to this thesis, in England, an estimated 35% of the population aged >65 are currently living with some form of impaired PF (70). It is clear from previous research that limitations to PF can predict risk of disability, use of health care systems, admission to care homes, and mortality (87, 89).

Certain ethnic minority groups in economically developed Western countries are more likely to exhibit impaired PF than White ethnic groups, and are more likely to start presenting with impairments to PF at a younger age (303). SA people have specifically been reported to have lower levels of cardiovascular fitness, lower HGS, and to score lower in PF or walking assessments, than WE people (304-307). There is evidence highlighting potentially diminished levels of skeletal muscle oxidative capacity in SAs compared to WEs; however, there are also studies suggesting that these differences are minimal and not of note (308-310). These observed differences in markers of fitness and PF are clinically important as cardiorespiratory fitness and walking pace are strong markers of health status and longevity, and as such have been acknowledged as important cardiometabolic risk factors (191, 311-313). The relevance of this is highlighted by evidence that people with poor cardiometabolic health typically experience impairments to PF and decreased capacity to perform ADLs (314); and considerable prevalence of impaired PF has been observed in elderly obese individuals (315). Whilst differences between ethnicities in the performance of laboratory walking and fitness tests have been established, it is unclear how these differences translate into habitual walking behaviours, movement intensity, and the impact of these on PF. Moreover, previous research into step cadence and the associations with health-related outcomes has typically been undertaken in WE populations, with a lack of research investigating whether associations differ across different ethnic groups. Given the accelerated decline in PF observed in SAs (304-307), identifying metrics that represent behavioural patterns of ambulatory activity in free-living contexts, whilst having clinical and practical value is needed to inform future interventions. Therefore, this chapter aimed to quantify the associations between different step cadence metrics and PF in healthy SA and WE older adults.

2.2 Methods

2.2.1 Design and procedure

The analysis included data from the *Sedentary behaviour in older adults: investigating a new therapeutic paradigm (STAND UP)* study which recruited participants aged ≥60 years, free of chronic disease, in Leicester and Glasgow, UK between 2015 and 2017 (38). PF was measured using the STS-60 test. Free-living sitting, standing, and stepping were measured using the activPAL3™ accelerometer for 7 days on the thigh. Demographic information (sex, age, ethnicity, and BMI) was collected via self- and assessor-administered questionnaires.

2.2.2 Participants

STAND UP was a multi-centre study (Leicester and Glasgow, UK) conducted across two work packages. The first (Leicester only) consisted of a cross-sectional study collecting accelerometer data during free-living conditions followed by a lab-based assessment of different physical activities under direct observation, with the aim of developing age-appropriate cut-points for SB and MVPA in older adults within the UK. The second (Leicester and Glasgow) was a randomised crossover acute lab-based design aiming to investigate whether breaking up sitting with regular bouts of standing or light ambulation resulted in reduced area under the insulin curve in adults (38). Recruitment and measurements across both phases and sites were standardised to the same protocol.

Participants were initially screened to confirm that they were ≥60 years of age, were able to walk without assistance from devices or other persons, were able to communicate in verbal and written English, were free from any condition or limitation that would render them unable to participate in the study, and able to give informed consent. Ethics approval was granted by East Midlands – Derby Research Ethics Committee (14/EM/1217). Participants provided written informed consent.

2.2.3 Device-assessed physical activity and sedentary behaviour

In this study, participants were asked to wear the activPAL3™ device (PAL Technologies, Ltd., Glasgow, UK) 24 h/day for 7 days on the midline anterior aspect of the right thigh. The activPAL device has already been discussed in the ‘Background’ chapter of this thesis (section *1.8.1 The activPAL*). For the processing of data in this thesis, the Processing PAL software was chosen due to its validated algorithm, ability to create user-defined

variables, and the allowance of corrections to the data where the algorithm has misclassified data.

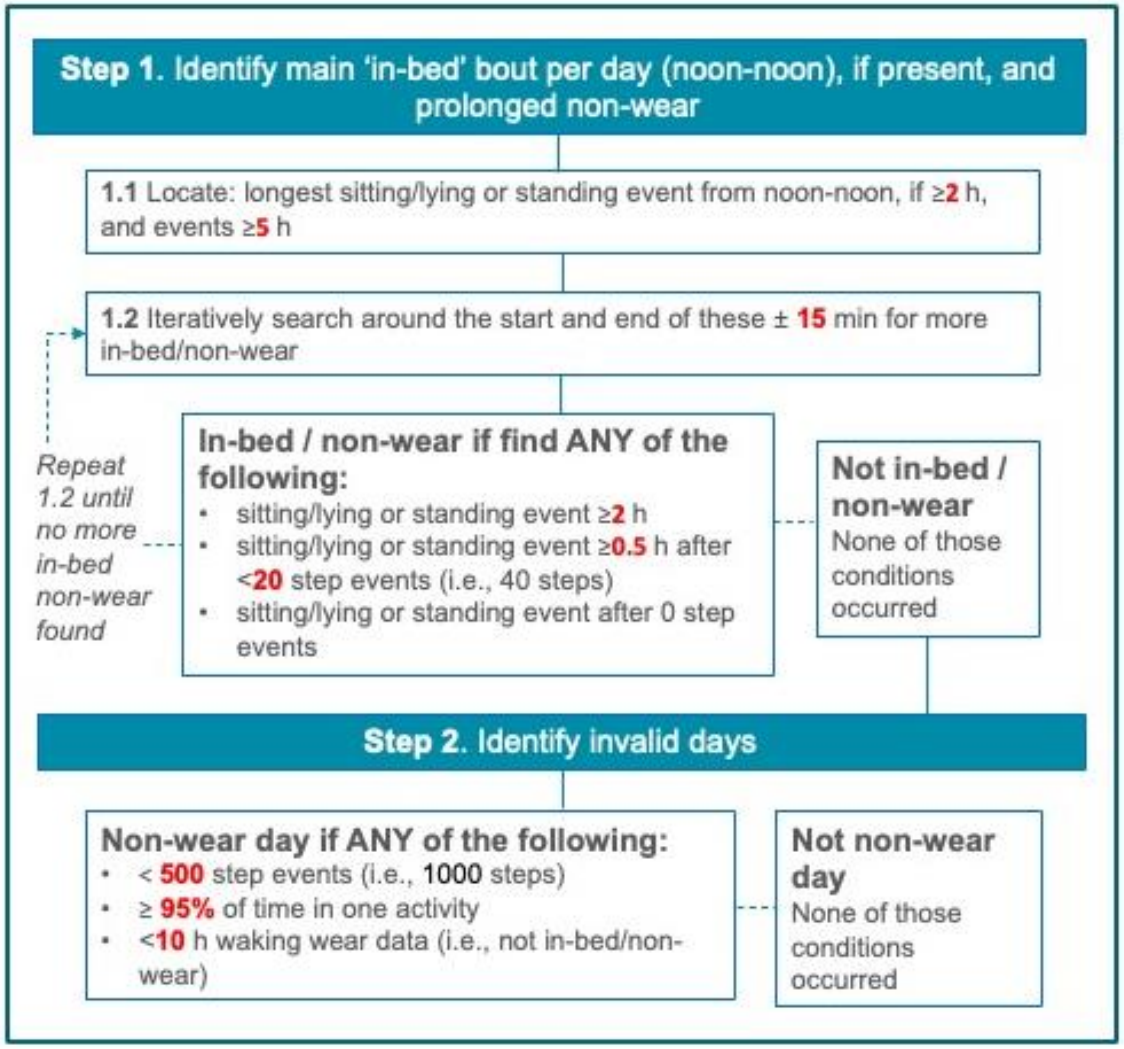
2.2.3.1 Processing PAL

Processing PAL (316) is publicly available through a java-based software application that allows users to bulk process activPAL data as well as visualise and summarise data. Processing PAL's validated algorithm (317) isolates valid waking wear data by targeting the identification of time in bed and prolonged wear time. It was originally developed in one hundred and twenty-five 18- to 40-year-olds and then validated against the then usual practice of the monitor-corrected diary method in 741 adults ≥35 years old (317). Since its release, the algorithm/Processing PAL has been used in a wide range of studies for analysing data from diverse populations (for example (318-320)). The software allows users to adjust the algorithm parameter settings that isolate time in bed and prolonged non-wear as well as how the user wants to classify a valid day and file (minimum steps per day, whether to include the first/last days of the measurement period, etc). It also offers the capability to visually review data to ensure the algorithm has performed well on data and make corrections to data if periods of time have been incorrectly coded (for example the incorrect coding of prolonged sedentary time as time in bed). The Processing PAL algorithm has been found to be comparably accurate to the CREA algorithm (available within PAL Technologies Software Suite) for classification of waking wear time; however, the Processing PAL algorithm allows for greater personalisation by the user (321).

In large-scale population studies, for example the 1970 British Cohort Study participants (322), the Processing PAL algorithm has been found to produce good estimates of time in bed compared to participant diaries at group level (323). However, there are potentially still disparities between these methods when estimating these values in individual participants. For example, there are studies demonstrating that as sleep time increased, the agreement between the Processing PAL algorithm results and participant diaries shared less agreement (323). Other, more recent studies have drawn similar conclusions – that the Processing PAL algorithm may still overestimate sleep time by detecting earlier starts and later finishes of time in bed, for example (324). This is because the algorithm was designed to identify time in bed as opposed to sleep. In order to account for this, it is recommended that researchers combine diary and algorithm output data (321).

2.2.3.2 Defining Valid Waking Wear Data with the Processing PAL algorithm

The algorithm used within Processing PAL (detailed in Figure 2 (317)) uses the activPAL "event" files to isolate waking wear time data by separating time in bed and prolonged non-wear time from valid wear time. The activPAL "event" files are created within the PAL Technologies software and have a separate row for each continuous bout of sitting/lying and standing, and for each individual step. The first stage of the algorithm is to identify the longest sitting/lying or standing bout of at least 2 hours along with other sitting/lying or standing bouts of greater than 5 hours within a 24-hour period (midday to midday). These are coded as time in bed or non-wear time. The algorithm also searches either side of these bouts for prolonged periods of sitting/lying or standing that occur after a brief bout of sporadic movement. This allows the algorithm to account for disrupted sleep patterns. If these bouts also meet the defined criteria, they are coded as time in bed or non-wear time.



Red = adaptable threshold

Figure 2 Processing PAL Algorithm

figure courtesy of Dr Charlotte Edwardson

At this point, users can adjust criteria to identify what will constitute a valid day. For the purposes of the analyses in this thesis, a valid waking day was defined as a day with <95% of time spent in any one behaviour (e.g., standing or sitting), ≥500 stepping events (1000 steps) and ≥10 h of waking hours data (317). Participants were required to have at least 3 valid days of data to be included in the analyses (325). Processing PAL then generates heat maps to visually check the processed valid and invalid data (297) (example in Figure 3). The heat maps colour-code activity types (e.g., dark green, MVPA stepping; light green, light stepping; amber/orange, standing; red, sitting/lying) allowing the user to easily perform visual checks to determine where potentially erroneous classifications have occurred. Any instance where the algorithm appears to have incorrectly coded data as valid or invalid, sleep and wake logs can be checked, and adjustments made to the allocations. For example, in a situation where the algorithm appears to have incorrectly coded time as awake when it should be time in bed (example in Figure 4) – the sleep and wake logs can be checked to confirm the participants reported wake time. The Processing PAL "summary file" can then be searched to identify the instance where the mis-coding occurred. This can then be corrected either within the Processing PAL interface or within a "bout corrections file".

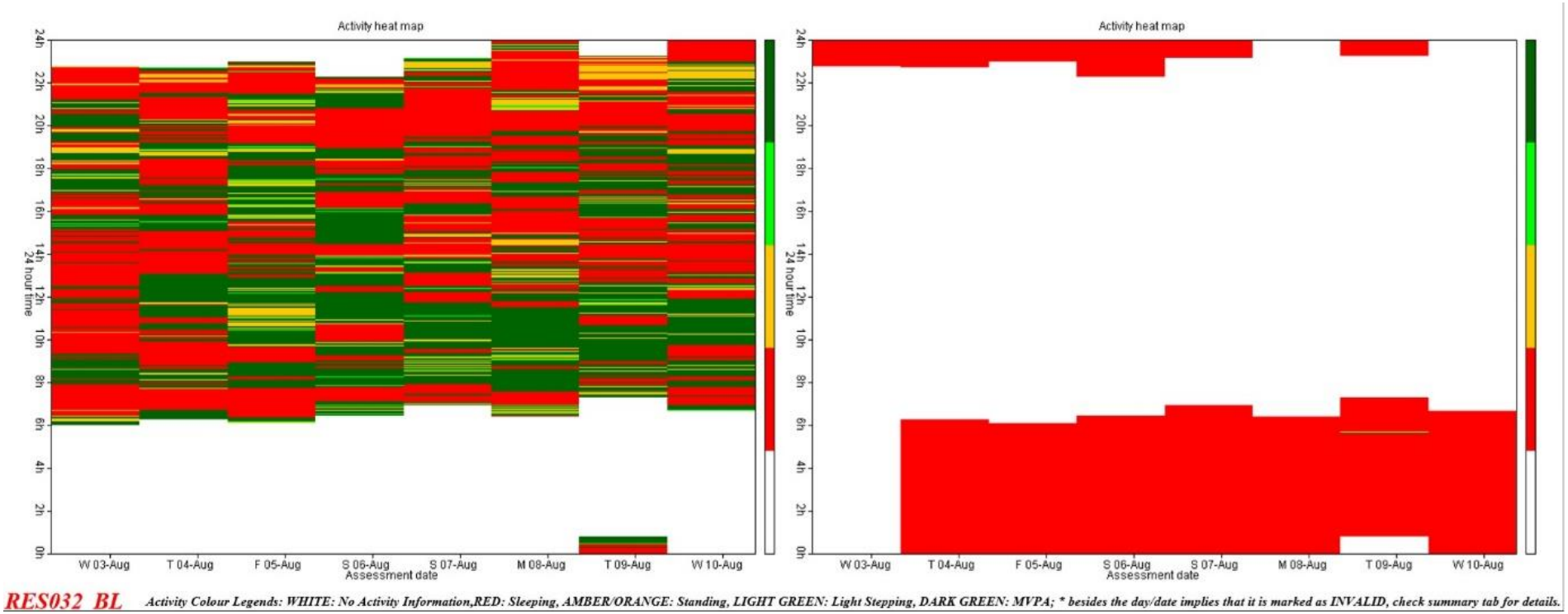


Figure 3 Example of activPAL heatmaps generated through Processing PAL

MVPA: moderate-to-vigorous physical activity

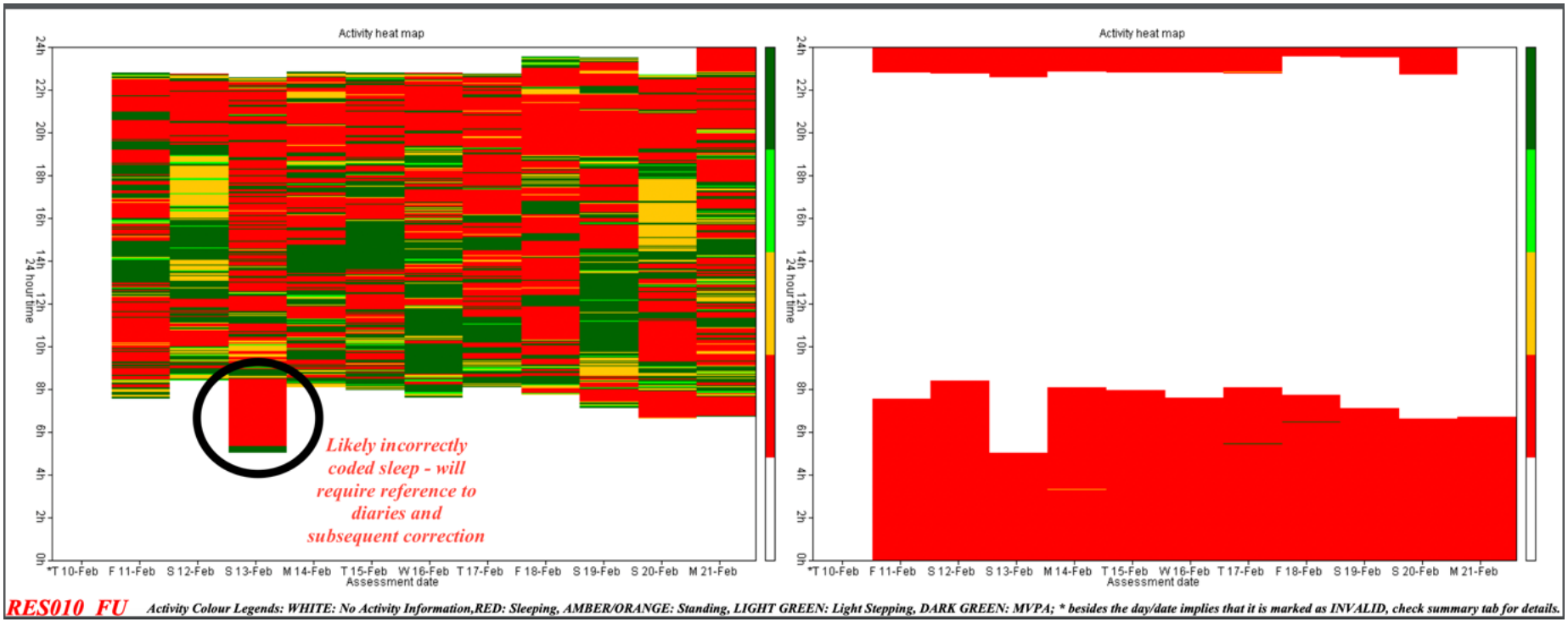


Figure 4 Example of an activPAL heatmap generated through Processing PAL with incorrectly coded sleep time

MVPA: moderate-to-vigorous physical activity

2.2.3.3 Outputs of Interest

Using Processing PAL, it is possible to derive a range of outcomes including, but not limited to, number of steps per day, various bands of step cadence (user defined), number of sit-to-upright transitions, time in different postures, time in different bout lengths of each posture. Details of the outputs of interest included in this thesis are listed below:

Steps/day

The average number of steps taken per day across all valid days.

Brisk and Slow steps/day

The average number of brisk and slow steps taken per day throughout all valid days. This is calculated by using the activPAL "Events" file produced in Processing PAL. The algorithm classifies all steps taken and the duration in which the steps are taken – this allows for a true representation of the cadence of each step (188, 326, 327). The heuristic threshold of 100 steps/min corresponding to absolutely defined ambulatory intensities of ≥3 METs, and therefore being indicative of MVPA has been demonstrated in younger (180), middle-aged (181), and older adults (182). For the analyses contained within this thesis, the number of slow and brisk steps accumulated was derived and the average per day calculated in Processing PAL. Slow steps were bounded at a lower rate of 50 steps/minute and brisk steps, categorised here as steps ≥100 steps/minute, were bounded at an upper rate of 150 steps/minute in order to avoid very slow or fast frequencies of stepping that are unlikely to represent a continuous bout of walking (179)**.**

Brisk steps/day (1-minute bouts)

The average number of brisk steps taken, in bouts of at least 1 minute per day throughout all valid days.

Waking wear time

The average number of hours that were classified as valid waking activPAL wear time, i.e., not "time in bed" or non-wear per day throughout all valid days.

Sitting time and prolonged sitting time

The average number of hours that were classified as sitting time per day throughout all valid days. Prolonged sitting may be broken into categories of: 0-30 minutes, 30-60 minutes, and 60+ minutes.

Standing time and prolonged standing time

The average number of hours that were classified as standing time per day throughout all valid days. Prolonged standing may be broken into categories of: 0-30 minutes, 30+ minutes.

Stepping time and prolonged stepping time

The average number of hours that were classified as stepping time per day throughout all valid days. Prolonged stepping may be assessed in categories of 0-30 minutes.

Peak Step Cadence

Peak step cadence variables were created in STATA by using the activPAL "event files" and then matching the valid waking wear times identified from Processing PAL:
The code (Appendix A1 – A2) generates these peak step cadence variables by:
1) assigning a cadence (step/event interval x 60 x 2) to each individual step taken
2) the step cadence for each individual step is sorted in ascending order
3) the time intervals (not continuous) are collated in accordance with the time period of interest (in this case 1, 10, 30, or 60 minutes)
4) the average step cadence in the time period is identified as the mean

Frequently used techniques report peak step cadence are based on the accumulation of steps over a pre-defined epoch or across a walking event. This has the effect of diluting the true peak by averaging across the epoch or the duration of the event and has been criticised for actually measuring step accumulation as opposed to step cadence. In contrast, by assigning a step cadence to each individual step, we ensure the accurate capture of peak step cadences (188, 190, 328).

Output variables of interest within this chapter included: waking wear time; time spent in postures of sitting, standing, and stepping; steps/day; brisk steps/day; brisk steps/day (1-minute bouts); slow steps/day; 1-minute peak step cadence; 30-minute peak step cadence; and 60-minute peak step cadence.

2.2.4 Descriptive data

Participants were asked to report their date of birth, sex (male or female), ethnicity (participants self-identified to standard census definitions), smoking status, postcode, medical history, and current medications. Two ethnicity groups were created for this analysis, with White British, White Irish, or any other White background being grouped as WE; and Indian, Pakistani, Bangladeshi, or any other South Asian background as SA (38).

Body weight and body composition (Tanita SC-330ST, Tanita, West Drayton, UK), height (Height Measure, Seca, Birmingham, UK), and WC (midpoint between the lower costal margin and iliac crest) were measured to the nearest 0.1kg, 0.1%, and 0.5cm, respectively. Arterial blood pressure was measured in the sitting position (Omron Healthcare, Henfield, UK); three measurements were obtained and the average of the last two used.

2.2.5 Physical function

PF was measured using the STS-60 (329), which has been described in the 'Background' chapter of this thesis (section *1.3.1 Physical Measures of Physical Function*). Briefly, the test was performed on a chair of standard height (~45cm) without arm rests. Participants were instructed to keep their arms stationary by placing hands on their hips. On the command "begin", participants proceeded to stand up and sit back down again as many times as they could within a 60-second period. Participants performed the movements at a self-selected pace and could stop at any time they wished. The number of complete sit-to-stand transitions in a 60-second period was recorded. The STS-60 is considered to be an effective measure of functional exercise performance and is well correlated with other measures of PF such as the 6-minute walk test (330). Previous analysis has also shown the STS-60 to have "excellent" reliability (ICC = 0.927) and offers comparable results to the ISWT, estimated 1-repetition maximum for quadriceps strength, and cardiopulmonary exercise testing (115).

2.2.6 Statistical analysis

Descriptive variables are presented as numbers and percentages for each ethnic group (WE and SA). Descriptive statistics are reported as mean ± SD. Independent samples t-tests were conducted to compare differences between WEs and SAs in descriptive categories.

Differences between ethnic groups in the outcome of interest – STS60 – were explored using generalised linear models (GLMs) with a Poisson distribution and an identity link. Models were adjusted for: 1) age, sex, stature (height and weight) and fat free mass; and 2) model 1 plus brisk stepping and slow stepping. Data are presented as estimated marginal mean (EMM) difference.

GLMs were used to assess whether slow or brisk stepping were associated with PF. Models were stratified by ethnicity and adjusted for age, sex, stature (height and weight), and activPAL valid waking wear time. To account for the confounding effect of PA, models were also adjusted for overall PA category (<7500 or ≥7500 steps/day, based on previous estimates of steps/day in relation to PA recommendations (183)). In addition, models were mutually adjusted whereby slow steps were adjusted for brisk steps and vice versa, to ensure one was not confounding the other. All models were checked for multi-collinearity by examining the relationships between independent variables in the fully adjusted models. Models were initially run on total brisk and slow steps per day as the primary outcome and repeated for brisk steps per day undertaken in at least 1-minute bouts. In order to further explore the association between brisk walking and STS-60 repetitions, the percentage of overall steps undertaken per day at a brisk cadence was calculated (brisk steps/overall steps x 100). The same modelling structure was used to assess the association between STS-60 repetitions and the most active 1-, 30-, and 60-minute peak step cadence metrics. An acyclic diagram showing the statistical model under study can be found in Figure 8.

Interaction terms were explored on the full dataset to assess whether associations with slow or brisk walking were modified by ethnicity. A sensitivity analysis was conducted on associations to investigate whether main effects and interactions were attenuated after adjusting for differences in fat free mass, which was not included in the main model given the potential to act as a mediator between stepping intensity and PF.

For ease of interpretation, the results of the GLM analyses are presented as the unstandardised β coefficients [95% CI] per 1000 steps, per decile of brisk steps as a percentage of overall steps, and per 10 steps/minute for mean peak step cadence. All data were analysed using IBM SPSS Statistics (version 24.0). A p-value of <0.05 was considered statistically significant for the main effects and interactions.

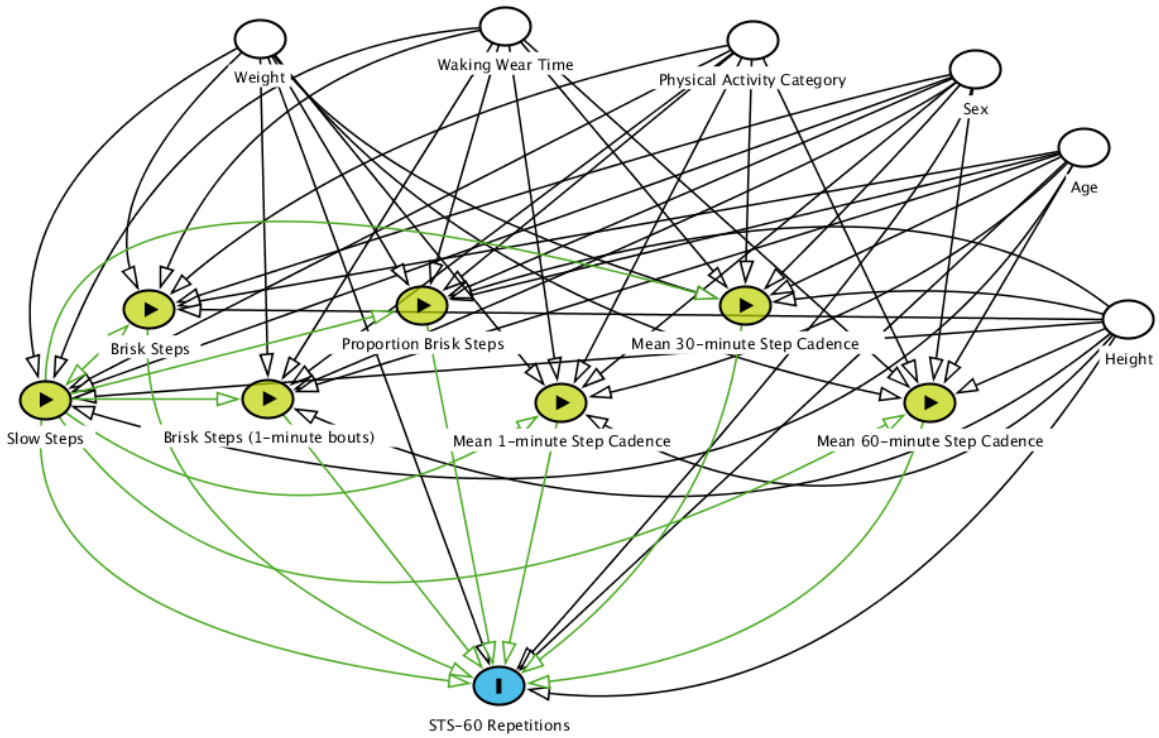


Figure 5 Acyclic Diagram of Statistical Model (Chapter 2)

The blue circle represents the outcome of interest; green circles represent independent variables; white circles represent potential confounders which were adjusted for in the model; black arrows represent the relationships between the confounders and the independent variables/outcome of interest; green arrows represent the relationships between the independent variables and the outcome of interest/other independent variables.

STS-60: sit-to-stand-60

2.3 Results

From the cohort of 108 participants, 4 were excluded due to missing activPAL data or missing STS-60 scores. A total of 104 individuals (age = 72 ± 5; 54% male) were included in the analysis. Within the 104 individuals included, 71 were WE (age = 72 ± 5 years, 54% male) and 33 SA (age = 71 ± 5 years, 55% male). Participant characteristics are displayed in Table 4. Both groups spent similar time sitting (9.0 ± 1.8 vs 9.0 ± 1.5 hours/day for WEs and SAs, respectively) and stepping (1.8 ± 0.6 vs 1.8 ± 0.5 hours/day for WEs and SAs, respectively). However, compared to WEs, SAs had significantly lower levels of overall steps per day (8986 ± 3450 vs 7780 ± 2340 steps/day, $p = 0.040$) and less brisk steps per day (5515 ± 2866 vs 3723 ± 2083 steps/day, $p = 0.001$). Mean peak 30-minute and 60-minute step cadence values also differed by ethnicity, with greater cadences seen in WEs (30-minute, 117.7 ± 10.3 vs 111.8 ± 9.7, $p = 0.009$ and 60-minute, 107.1 ± 11.0 vs 100.8 ± 10.6, $p = 0.009$ steps/minute for WEs and SAs, respectively).

Table 4 Characteristics of *STAND UP* Study Participants

	Population (n = 104)	***WE (n = 71)***	***SA (n = 33)***	***p***
Sex	53.8% male	53.5% male	54.5% male	0.923
Age (years)†	71.7 ± 5.1	72.0 ± 5.1	71.3 ± 5.1	0.526
Weight (kg)	75.1 ± 14.3	77.7 ± 14.3	69.5 ± 12.7	**0.006**
Height (cm)	164.0 ± 9.0	165.7 ± 9.0	160.4 ± 8.0	**0.004**
Body Fat (%)‡	33.0 ± 7.9	32.5 ± 8.2	34.1 ± 7.3	0.344
Fat free mass (kg)	48.0 ± 14.8	50.9 ± 13.5	41.5 ± 15.6	**0.002**
BMI (kg/m^2)	27.8 ± 4.4	28.2 ± 4.6	26.9 ± 3.9	0.156
Waking wear time (hours/day)	15.4 ± 1.0	15.3 ± 1.0	15.7 ± 1.0	0.150
Sitting time (hours/day)	9.0 ± 1.7	9.0 ± 1.8	9.0 ± 1.5	0.935
Standing time (hours/day)	4.7 ± 1.3	4.5 ± 1.4	5.0 ± 1.2	0.116
Stepping time (hours/day)	1.8 ± 0.6	1.8 ± 0.6	1.8 ± 0.5	0.463
activPAL Steps				
Total (steps/day)	8603 ± 3179	8986 ± 3450	7780 ± 2340	**0.040**
Slow (steps/day)	3657 ± 1434	3472 ± 1441	4057 ± 1354	0.052
Brisk (steps/day)	4946 ± 2763	5515 ± 2866	3723 ± 2083	**0.001**
Proportion brisk	0.55 ± 0.18	0.59 ± 0.15	0.45 ± 0.19	**<0.001**
Brisk (1-minute bouts) (steps/day)	2506 ± 2114	2842 ± 2230	1785 ± 1650	**0.008**
activPAL Peak Step Cadence				
Mean 1-minute (steps/minute)‡	156.1 ± 9.6	157.0 ± 9.5	154.0 ± 9.6	0.153
Mean 30-minute (steps/minute)‡	115.9 ± 10.42	117.7 ± 10.3	111.8 ± 9.7	**0.009**
Mean 60-minute (steps/minute)‡	105.2 ± 11.2	107.1 ± 11.0	100.8 ± 10.6	**0.009**

Results are presented as Mean ± Standard Deviation
p < 0.05 values in bold
† n = 103; ‡ n = 100
BMI: body mass index; SA: South Asian; STS-60: sit-to-stand-60; WE: White European

Compared to WEs, SAs scored lower in the STS-60 (23 [95% CI 21.77, 24.06] vs 20 [18.13, 21.40] repetitions, $p = 0.003$) (Figure 6). The difference was largely maintained after adjustment for slow and brisk stepping ($p = 0.045$), with a difference of 2.47 [0.06, 4.88] repetitions remaining between ethnicities (Table 5).

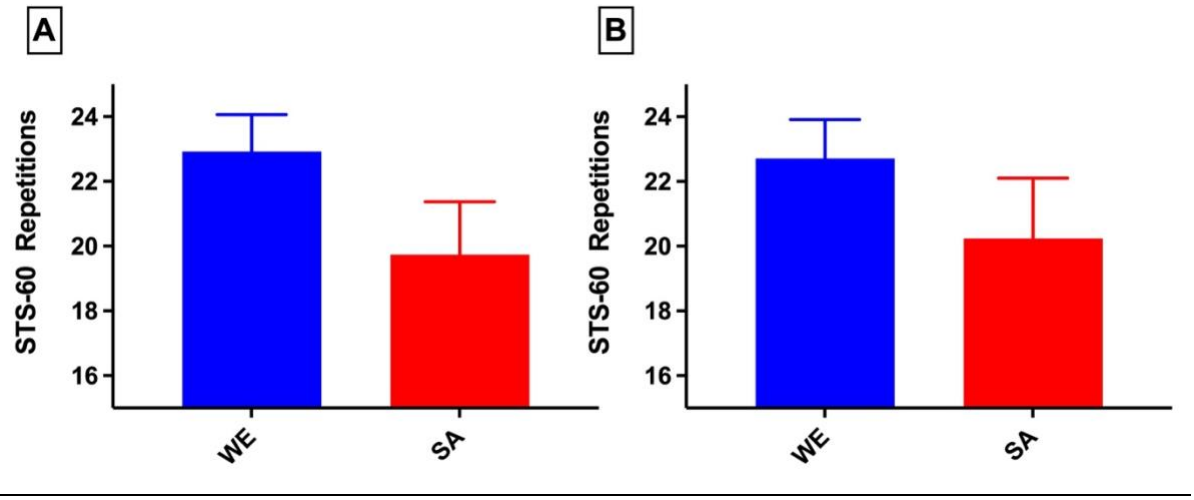


Figure 6 Estimated marginal mean STS-60 repetitions with corresponding upper confidence intervals for White European and South Asian older adults

Model 1 (panel A) adjusted for: age, sex, height, weight, and fat free mass. Model 2 (panel B) adjusted for: age, sex, height, weight, fat free mass, slow stepping, and brisk stepping.
SA: South Asian; STS-60: sit-to-stand-60; WE: White European

Table 5 Estimated marginal mean difference in STS-60 repetitions between White European and South Asian older adults

	WE EMM [95% CI]	***SA EMM [95% CI]***	***Mean Difference [95% CI]***	***p***
Model 1	22.91 [21.77, 24.06]	19.77 [18.13, 21.40]	3.15 [1.09, 5.20]	**0.003**
Model 2	22.71 [21.51, 23.91]	20.24 [18.38, 22.10]	2.47 [0.06, 4.88]	**0.045**

p < 0.05 values in bold
Model 1 adjusted for: age, sex, height, weight, and fat free mass. Model 2 adjusted for: model 1 plus slow stepping and brisk stepping
CI: Confidence Interval; EMM: Estimated Marginal Mean; SA: South Asian; STS-60: sit-to-stand-60; WE: White European

The associations between measures of ambulation intensity and STS-60 are shown in Table 6 and Figure 7.

Table 6 Relationships between step cadence variables and physical function for White European and South Asian older adults

	WE (n = 71)		***SA (n = 33)***		***Interaction p value***
	β [95% CI]	*p*	*β [95% CI]*	*p*	
Slow steps‡†	0.16 [-0.79, 1.11]	0.747	0.01 [-1.51, 1.52]	0.994	0.645
Brisk steps‡†	0.72 [0.05, 1.38]	**0.035**	-1.00 [-2.40, 0.40]	0.160	**<0.001**
Proportion brisk steps§	1.01 [0.19, 1.82]	**0.015**	-0.56 [-1.54, 0.41]	0.265	**<0.001**
Brisk steps (1-minute bouts)‡†	0.99 [0.23, 1.75]	**0.010**	-0.87 [-1.95, 0.20]	0.112	**<0.001**
Mean 1-minute step cadence¶	1.42 [0.12, 2.71]	**0.032**	2.12 [-0.04, 4.28]	0.054	0.377
Mean 30-minute step cadence¶	1.71 [0.22, 3.20]	**0.024**	-2.71 [-5.63, 0.20]	0.068	**0.001**
Mean 60-minute step cadence¶	2.16 [0.62, 3.71]	**0.006**	-2.60 [-5.24, 0.03]	0.053	**<0.001**

p < 0.05 values in bold
Model adjusted for: age, sex, height, weight, physical activity category, and accelerometer waking wear time
† Mutually adjusted for the alternate (slow/brisk) metric
‡ per 1000 steps, § per decile, ¶ per 10 steps/minute
CI: Confidence Interval; SA: South Asian; WE: White European

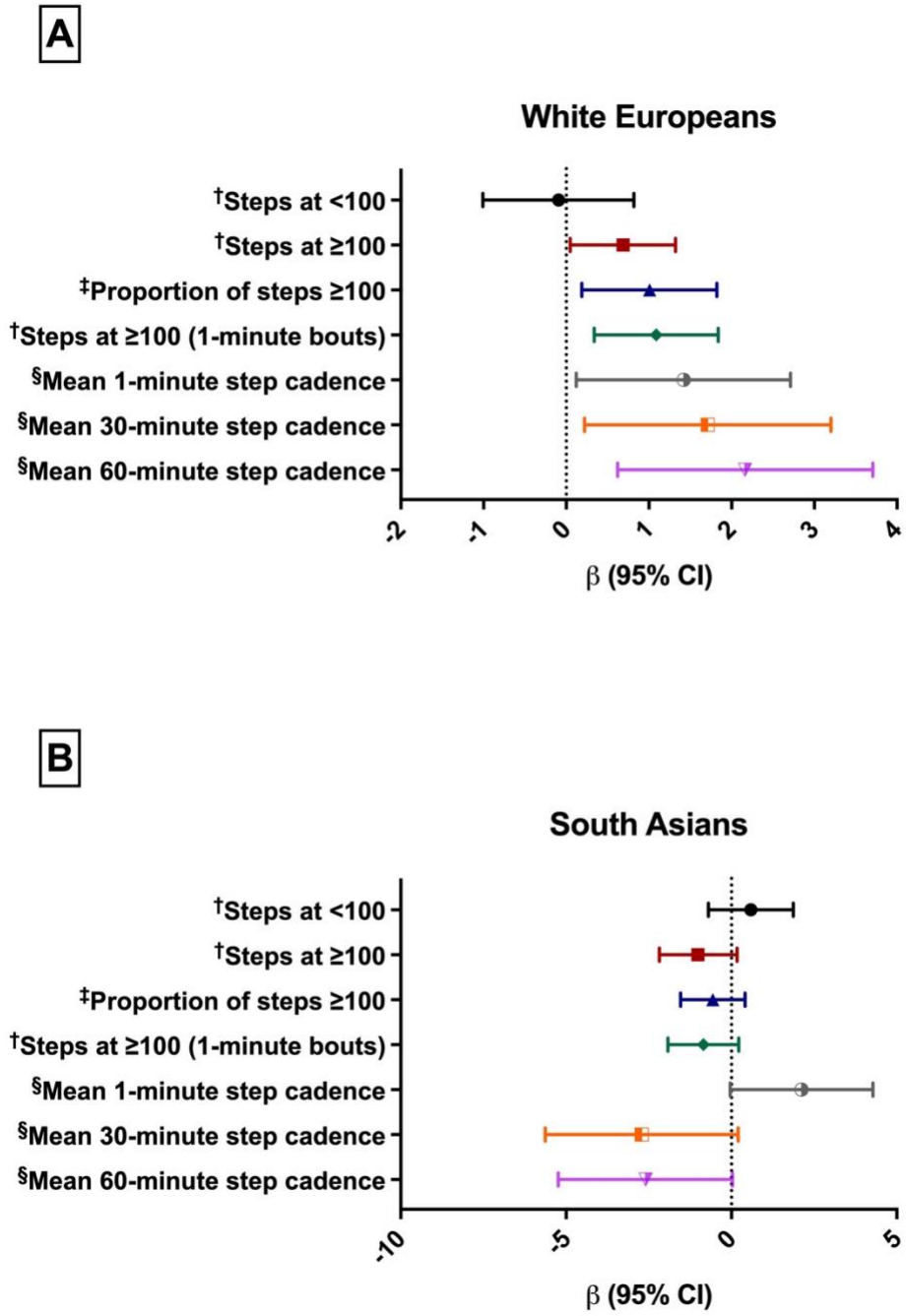


Figure 7 Forest plots of relationships between step cadence variables and STS-60 repetitions for White European and South Asian older adults

Model adjusted for: age, sex, height, weight, physical activity category, and accelerometer waking wear time. Slow/brisk steps mutually adjusted. Panel A represents relationships between directly measured step cadence and performance in the sit-to-stand-60 (STS-60) in White Europeans. Panel B represents relationships between directly measured step cadence and performance in the STS-60 in South Asians. † per 1000 steps, ‡ per decile, § per 10 steps/minute.
CI: confidence interval

In WEs, the number of brisk steps was associated with performance in the STS-60, with every 1000 brisk steps associated with 0.72 [0.05, 1.38] more sit-to-stand repetitions.

Proportion of total steps spent at brisk stepping was also associated, with every 10% higher proportion of brisk steps taken compared to overall steps associated with 1.01 [0.19, 1.82] more sit-stand repetitions.

No associations were observed in SAs. The strength of association was significantly different to WEs ($p < 0.01$ for interaction). This pattern of association was similar in brisk steps accumulated in bouts of at least 1 minute.

In WEs, all step cadence metrics for the most active 1, 30 and 60 minutes were associated with performance in the STS-60, with greater mean peak step cadences being associated with more STS-60 repetitions (mean 1-minute $\beta = 1.42$ [0.12, 2.71], mean 30-minute $\beta = 1.71$ [0.22, 3.20], and mean 60-minute $\beta = 2.16$ [0.62, 3.71]). No associations were observed in SAs, with the strength of association significantly different to WE for the 30-minute and 60-minute data ($p < 0.01$ for interaction).

Associations and interactions remained unchanged before mutual adjustment for slow and brisk steps and when further adjusting for fat free mass (Table 7).

Table 7 Relationships between step cadence variables and physical function for White European and South Asian older adults (alternative models)

	WE (n = 71)		***SA (n = 33)***		***Interaction p value***
	β [95% CI]	*p*	*β [95% CI]*	*p*	
Alternative Model 1					
Slow steps†	-0.09 [-1.01, 0.82]	0.840	0.59 [-0.70, 1.87]	0.371	0.792
Brisk steps†	0.69 [0.05, 1.32]	**0.035**	-1.01 [-2.18, 0.17]	0.093	<**0.001**
Proportion brisk steps‡	1.01 [0.19, 1.82]	**0.015**	-0.56 [-1.54, 0.41]	0.265	<**0.001**
Brisk steps (1-minute bouts)†	1.09 [0.34, 1.84]	**0.004**	-0.85 [-1.92, 0.22]	0.119	<**0.001**
Mean 1-minute step cadence§	1.42 [0.12, 2.71]	**0.032**	2.12 [-0.04, 4.28]	0.054	0.377
Mean 30-minute step cadence§	1.71 [0.22, 3.20]	**0.024**	-2.71 [-5.63, 0.20]	0.068	**0.001**
Mean 60-minute step cadence§	2.16 [0.62, 3.71]	**0.006**	-2.60 [-5.24, 0.03]	0.053	<**0.001**
Alternative Model 2					
Slow steps†‡	0.14 [-0.82, 1.10]	0.770	0.39 [-1.09, 1.87]	0.607	0.277
Brisk steps†‡	0.72 [0.05, 1.38]	**0.034**	-0.96 [-2.35, 0.43]	0.175	<**0.001**
Proportion brisk steps§	1.03 [0.21, 1.86]	**0.014**	-0.82 [-1.78, 0.15]	0.098	<**0.001**
Brisk steps (1-minute bouts)†‡	1.00 [0.23, 1.76]	**0.010**	-1.13 [-2.19, -0.07]	0.037*	<**0.001**
Mean 1-minute step cadence¶	1.42 [0.12, 2.72]	**0.032**	0.62 [-1.77, 3.02]	0.609	0.136
Mean 30-minute step cadence¶	1.75 [0.24, 3.26]	**0.023**	-2.57 [-5.39, 0.25]	0.075	**0.001**
Mean 60-minute step cadence¶	2.20 [0.64, 3.76]	**0.006**	-2.54 [-5.17, 0.09]	0.059	<**0.001**

p < 0.05 values in bold
Alternative Model 1 adjusted for: age, sex, height, weight, physical activity category, and accelerometer waking wear time
Alternative Model 2 adjusted for: age, sex, height, weight, physical activity category, accelerometer waking wear time, and fat free mass
† Mutually adjusted for the alternate (slow/brisk) metric
‡ per 1000 steps, § per decile, ¶ per 10 steps/minute
CI: Confidence Interval; SA: South Asian; WE: White European

2.4 Discussion

This chapter sought to assess the associations between different step cadence metrics describing habitual stepping intensity, and PF assessed by the STS-60 in older adults, and whether these associations differed between SAs and WEs. The results demonstrated that, in WEs, a greater number of brisk steps taken per day, a higher proportion of brisk steps taken per day, or higher peak stepping cadences were associated favourably with PF. In SAs, levels of brisk walking and PF were lower than in WEs and there was no association between these factors, regardless of how stepping intensity or cadence was assessed.

Recent analysis of large cohort studies concluded that although higher intensity of peak 1-minute and peak 30-minute step cadence was associated with lower mortality rates, after adjustment to total steps per day, these associations were largely attenuated (174, 178). However, other research has demonstrated that gait speed can be an important factor in the development of impaired PF in both extremely frail and more robust, largely white, populations (331). Some research has suggested that slower walking speeds are associated with disability, frailty, muscular weakness, falls, and poor performance in step cadence assessments (332, 333). In addition, various functional tasks (particularly those which are characteristic of sit-to-stand/stand-to-sit movements) have also been associated with step cadence in previous research. In particular, hip extension, hip flexion, knee extension, and ankle plantarflexion have all been significantly associated with changes in step cadence (334).

However, these studies have assessed walking pace through laboratory tests. Although this is not the first study to assess the impact of objectively measured habitual stepping intensity and cadence on measures of PF, existing studies have typically focussed on specific clinical populations and have not included formal analysis by ethnicity (335). Whilst habitual stepping intensity was strongly associated with PF in WEs in the analysis, there was no association in SAs. In addition, the lower levels of PF in the SA individuals were independent of differences in brisk and slow stepping activity. These cross-sectional findings are consistent with the wider literature. Whilst the effect of exercise on markers of cardio-metabolic health in SA populations has been positive (336, 337), the effect on measures of fitness, function, and strength have been more equivocal. A systematic review of individuals with T2D identified two studies that assessed functional outcomes, one of which proposed differences compared to control and one of which did not (336). Furthermore, whilst exercise training has been shown to increase muscle strength in SA populations (336), there is evidence that adaptions to strength, in

particular lower body strength, are slower and to a lower magnitude than WEs. In analysis of the responses to a 6-week progressive resistance exercise training programme, WEs were found to have considerably greater responses for lower body muscular strength (338). However, other researchers have demonstrated that SAs respond robustly to resistance exercise, increasing muscle mass and function to a similar extent as WEs (339). Though, it should be noted that in the study by Alkhayl and associates (339), although SAs muscle mass, lowed body strength, and insulin sensitivity responded similarly to WEs after 12 weeks of resistance training, there were lesser responses to body fat, resting carbohydrate and fat metabolism, blood pressure, VO_{2max}, and upper body strength. Taken together, these studies suggest that mechanisms other than lower levels of PA may be needed to explain underlying impairments or differences in muscle physiology, PF, and fitness in SA populations. Genetic, epigenetic, and foetal programming are all possible candidates that have been identified previously and require future research (340). The cultural context for why individuals engage in walking may also be important; for example, brisk walking for exercise may be more strongly linked to recreation and leisure in WE populations, whereas it may be less culturally appropriate for SA populations. Recent qualitative analysis of SAs views of PA suggested that many who were not meeting national PA guidelines believed that they were sufficiently active (341). The study also highlighted SA females' perceptions of restrictive social and cultural norms that discouraged the uptake of exercise (341). Similar investigations that have specifically investigated views towards PA in SA women have identified similar themes, with cultural and structural factors being barriers, and faith and educational factors acting as facilitators (342). Consequently, where brisk walking is undertaken in SA populations, it may be more likely to take place in non-leisure or non-recreational contexts. Differences in contexts may in turn influence associations with health (343).

Another potential factor contributing to the comparatively low levels of PF in SA participants could be the inherently lower levels of lean mass. Indeed, body composition analysis within this chapter revealed that the mean percentage of fat free mass was ~5 centiles lower in the SAs than in the WEs. Body composition analyses in SA men and women from other studies have also consistently shown lower levels of lean mass in SAs than in WEs (344). Previous research has also indicated significantly lower levels of muscular strength, muscular perfusion, and muscular oxidative capacity in SAs compared to WEs, which remained constant even after control for various cardiometabolic factors – including prevalence of T2D (306, 307). However, in the analysis within this chapter, differences between ethnicities in STS-60

remained independent of fat-free mass, as did ethnic differences in the association between stepping intensities and STS-60.

The results highlighting the importance of brisk stepping for WEs in this chapter are potentially clinically meaningful. For example, two repetitions have been reported as the MCID in results from the STS-60 (345). Based on the results of this analysis, walking an additional 2777 brisk steps per day relates to a difference of two STS-60 repetitions. This equates to approximately 28 minutes of brisk walking per day, which is consistent with the minimum PA recommendations for health (346). Alternatively, a difference of 20% in the proportion of overall steps undertaken at a brisk cadence (e.g., moving from 50% to 70% of total steps at a brisk cadence) was also related to approximately two STS-60 repetitions, independent of overall PA levels. Finally, increasing mean peak 1-minute step cadence by 15 steps/minute; mean peak 30-minute step cadence by 12 steps/minute; or mean peak 60-minute step cadence by 9 steps/minute are all associated with a difference of two STS-60 repetitions.

2.4.1 Strengths and Limitations

A strength of this analysis is the use of the activPAL device to measure step cadence. The activPAL has previously been found to be highly accurate in determining step cadence at speeds ≥0.5 m/s (301). The analysis is potentially limited by PF being assessed by only one measure; the STS-60 test. However, this test has been shown to have good measurement properties, is an established measure of overall functional ability, and has been associated with other measures of PF – including walk tests, 1-repetition maximum testing, and cardiopulmonary exercise testing (115, 330, 345). The *STAND UP* cohort of ~100 older adults from two major cities with high densities of SAs and WEs, is a relatively small sample and consists of a small number of SAs compared to WEs. The nature of the cohort, which only included healthy volunteers, may not be generalisable to a typical older adult population. Finally, as the analysis detailed in this chapter is observational in nature – results could be explained by unmeasured confounders; and causality, including direction of causality, cannot be tested.

2.4.2 Conclusion

In conclusion, these results highlight that, compared to WEs, SAs have lower levels of ambulatory activity, lower PF, fewer steps taken at a brisk pace, and lower mean peak step cadence for a range of time thresholds. In WEs only, this analysis demonstrated that brisk

walking, but not slow walking, is associated with PF. This may have important implications for future intervention design in this area. By continuing to explore this topic further, researchers will be better equipped to tailor interventions to appropriately address the health issues of different clinical and ethnic groups.

The results of this chapter have demonstrated the associations between step cadence and PF in healthy, older adults, with data measured at one timepoint. The subsequent chapter will build on this by examining change data to explore associations between step cadence and cardiometabolic health in people with prediabetes.

Chapter 3: Associations between change in step cadence and change in cardiometabolic health over 4 years in people with prediabetes

Chapter Overview

This chapter reports on an analysis of data from the *PROPELS* study – a 4-year RCT aimed at improving walking behaviour. The actual trial was unsuccessful in increasing stepping over 4 years; however, the use of such a dataset with measurements at three timepoints over a 4-year period allowed for a very interesting investigation into change data. This analysis looks into the associations between change in a number of step cadence variables and change in cardiometabolic health in people with prediabetes and explores potential interactions with sex and ethnicity. The chapter concludes with a discussion into how the findings fit within the current research landscape and what the implications may be for future studies investigating step cadence and cardiometabolic health in people with prediabetes.

Key Findings

In people with prediabetes:

- Increases in overall steps/day over a 4-year period are associated with:
    - Decreased BMI (-0.10 kg/m^2 per 1000 steps/day [95% CI -0.14, -0.06])
    - Decreased WC (-0.27 cm per 1000 steps/day [-0.41, -0.12])
    - Increased HDL-C (0.013 mmol/L per 1000 steps/day [0.008, 0.019])
    - Decreased HbA1c (-0.008% per 1000 steps/day [-0.015, -0.000])
- Increases in brisk steps/day over a 4-year period are associated with:
    - Decreased BMI (-0.09 kg/m^2 per 1000 steps/day [-0.15, -0.04])
    - Decreased WC (-0.25 cm per 1000 steps/day [-0.43, -0.06])
    - Increased HDL-C (0.015 mmol/L per 1000 steps/day [0.008, 0.021])
    - Decreased HbA1c (-0.010% per 1000 steps/day [-0.019, -0.001])
- Increases in slow steps/day over a 4-year period are associated with:
    - Decreased BMI (-0.16 kg/m^2 per 1000 steps/day [-0.28, -0.05])
- Increases in 10-minute peak step cadence over a 4-year period are associated with:
    - Decreased BMI (-0.02 kg/m^2 per 1000 steps/day [-0.04, -0.00])
    - Decreased WC (-0.09 cm per 10 steps/minute [-0.16, -0.03])
    - Increased HDL-C (0.004mmol/L per 10 steps/minute [0.002, 0.006])

In SA but ***not*** in WE people with prediabetes:

    - Increases in 10-minute peak step cadence over a 4-year period are associated with:
        - Decreased BMI (-0.08 kg/m^2 per 10 steps/minute [-0.11, -0.05])

In WE but ***not*** in SA people with prediabetes:

- Increases in overall steps/day over a 4-year period are associated with:
    - Decreased HbA1c (-0.010% per 1000 steps/day [-0.018, -0.002])
- Increases in brisk steps/day over a 4-year period are associated with:
    - Decreased HbA1c (-0.013% per 1000 steps/day [-0.023, -0.002])
- Increases in 10-minute peak step cadence over a 4-year period are associated with:
    - Decreased HbA1c (-0.003% per 10 steps/minute [-0.006, 0.000])

Publications and Conference Presentations

The original work relating to this chapter was published in Medicine and Science in Sport and Exercise:

McBride P, Henson J, Edwardson C, Maylor B, Dempsey PC, Rowlands AV, Davies MJ, Khunti K, Yates T (2023). Four-Year Increase in Step Cadence Is Associated with Improved Cardiometabolic Health in People with a History of Prediabetes. *Medicine and Science in Sports and Exercise*. doi: 10.1249/MSS.0000000000003180. Epub ahead of print. PMID: 37005498 (347).

The original work was also presented at:
International Conference on Ambulatory Measurement of Physical Activity and Movement (ICAMPAM) 2022, June 2022, Keystone, CO, USA.

Author Contribution

This was a secondary data analysis and all the data collection had been completed by researchers at University of Leicester and University of Cambridge prior to the commencement of my PhD project. The main activPAL data had already been cleaned and processed by Dr Charlotte Edwardson. However, I received training in the generation of the peak step cadence metrics, ran the code to produce the metrics, and ran checks to make sure that data were lined up to the correct participants. Prof. Thomas Yates designed the statistical analysis methods and trained me in their execution. I performed the statistical analyses. I wrote the first draft of the

manuscript with the assistance of Dr Joseph Henson and addressed reviewer and co-author comments prior to publication.

3.1 Introduction

Having investigated associations between step cadence and PF in Chapter 2, it is also important to investigate how stepping behaviours are associated with cardiometabolic health. Recent large studies have suggested associations between step cadence and mortality are partially or fully mediated by controlling for overall steps per day (172, 174, 178), whereas other studies have shown cross-sectional associations with markers of cardiometabolic health (for example, (191, 192)). However, these studies have largely focused on typically healthy individuals with stepping measured at one time point. Further, there is sparse data in general investigating associations between change in stepping behaviour and change in cardiometabolic health outcomes. Therefore, the potential associations between step cadence, health status, and the potential health impacts of changing walking behaviour, particularly in high-risk populations such as those with a history of prediabetes, remains unclear. This chapter aims to investigate the degree to which changes in step cadence over a 4-year period are associated with various cardiometabolic risk markers in people with a history of prediabetes recruited from primary care.

3.2 Methods

3.2.1 Design and procedure

The analysis included data from the *PRomotion Of Physical activity through structured Education with differing Levels of ongoing Support for people at high risk of type 2 diabetes (PROPELS)* study. The study protocol and methods have been published in detail elsewhere (348). Briefly, this multicentre (Leicester and Cambridge, UK) RCT investigated the effectiveness of an intervention to support PA change and maintenance, delivered at two intervention levels against a control condition, over a 4-year period, with measures taken at baseline, 1-year, and 4-years. Participants were randomised to either: a control group who received a detailed advice leaflet; an intervention group who received the advice leaflet plus a structured educational programme followed by annual group maintenance sessions; or an intervention group who received the same package as the first intervention group plus a highly tailored text and phone call service designed to support behaviour change and pedometer use. The interventions did not result in sustained changes to behaviour at 4-years (349).

3.2.2 Participants

Participants were identified as having had reported HbA1c (6.0 – 6.4% or 42 – 47.9mmol/mol); fasting glucose (5.5 – 6.9mmol/L); or 2-hour post-challenge blood glucose (7.8 – 11.1mmol/L), defined as having a history of prediabetes within the last 5 years documented in their primary care records, and confirmation was sought that they had not been diagnosed with T2D (348). Other inclusion criteria included being able to communicate in verbal and written English, being free from any condition or limitation that would render participants unable to participate in the study, and the provision of written informed consent. The trial was sponsored by University of Leicester, United Kingdom and ethics approval was granted by NHS National Research Ethics Service, East Midlands Committee (12/EM/0151).

3.2.3 Device-assessed physical activity and sedentary behaviour

In this study, participants were asked to wear the activPAL3™ device (PAL Technologies, Ltd., Glasgow, UK) 24 h/day for 7 days on the midline anterior aspect of the right thigh. The activPAL device has already been discussed in the 'Background' chapter of this thesis (section *1.8.1 The activPAL*). The processing of the data has been discussed in Chapter 2 of this thesis (sections *2.2.3.1 Processing PAL, 2.2.3.2 Defining Valid Waking Wear Data with the Processing PAL algorithm, and 2.2.3.3 Outputs of Interest*). Output variables of

interest within this chapter included: waking wear time; steps/day; brisk steps/day; slow steps/day; and 10-minute peak step cadence.

3.2.4 Descriptive data

Participants were asked to report their date of birth, sex (male or female), ethnicity (participants self-identified to standard census definitions), smoking status, postcode, medical history, and current medications. Three ethnicity groups were created for this analysis, with White British, White Irish, or any other White background being grouped as WE; and Indian, Pakistani, Bangladeshi, or any other South Asian background as SA (38). All other ethnicities were categorised as "Other".

3.2.5 Markers of cardiometabolic health

Markers of cardiometabolic health were measured at baseline, and after 1 year and 4 years. Full details of measurements have been detailed previously (348). Briefly, HbA1c and lipid profile (triglycerides, HDL-C, and LDL-C) were assessed by venous sampling. Collection and sampling were standardised across research sites. Body weight and body composition (Tanita SC-330ST, Tanita, West Drayton, UK), height (Height Measure, Seca, Birmingham, UK), and WC (midpoint between the lower costal margin and iliac crest) were measured to the nearest 0.1kg, 0.1%, and 0.5cm, respectively. Arterial blood pressure was measured in the sitting position (Omron Healthcare, Henfield, UK); three measurements were obtained and the average of the last two used. Postcode (in order to calculate the Index of Multiple Deprivation (IMD)), alcohol intake, and smoking status were assessed through researcher- and self-administered questionnaires. Use of relevant medications (such as blood pressure medication, lipid lowering substances, and metformin) were determined by reviewing a list or packets of currently prescribed medications that participants were asked to bring to each study assessment and were recorded in a consultation with a member of the study team.

3.2.6 Statistical analysis

Given that there was no difference between groups in PA at 4-years (349), the *PROPELS* data was analysed as a single cohort for the purposes of this chapter. The flow of participants in this analysis is shown in Figure 8.

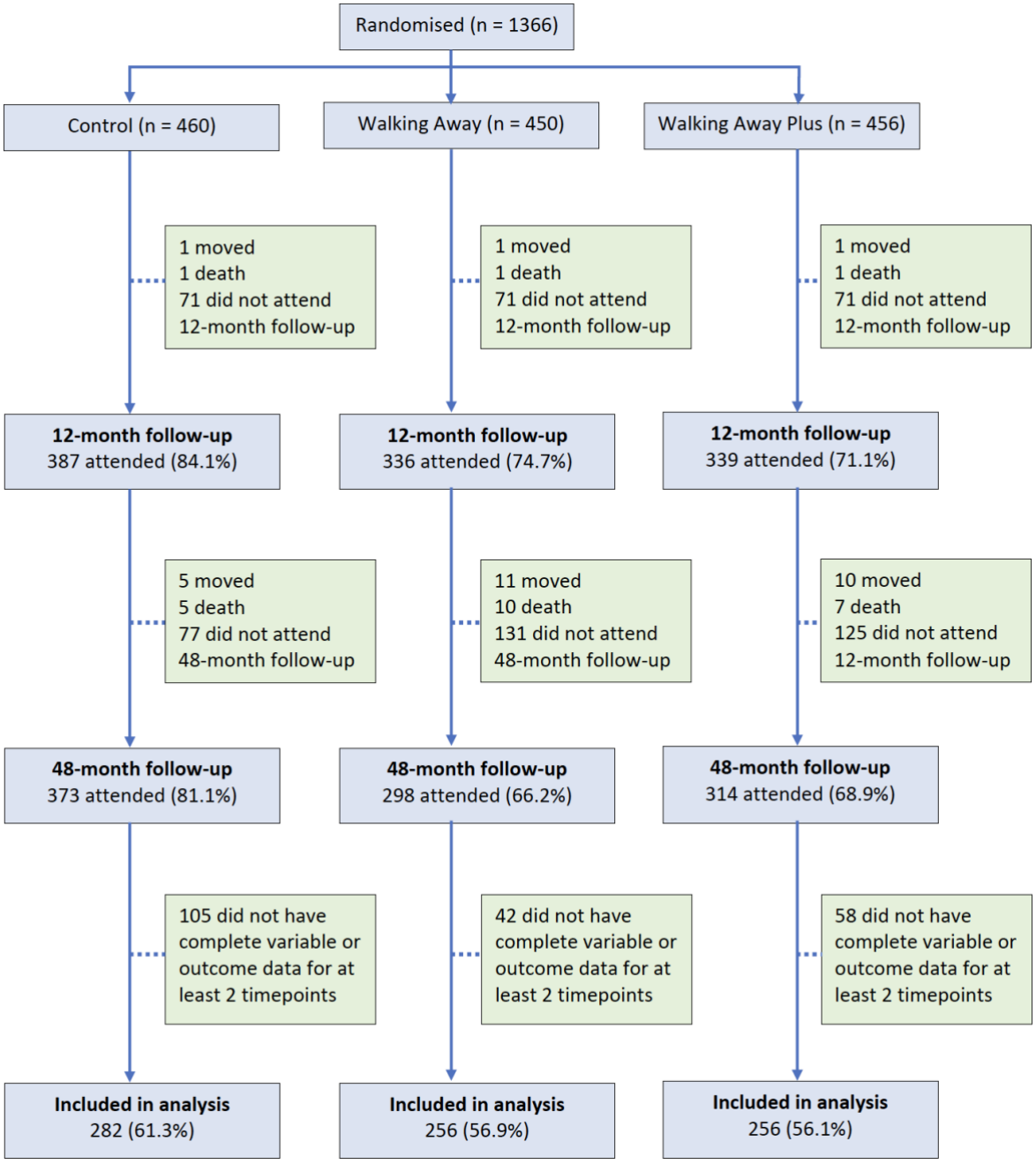


Figure 8 *PROPELS* Study Participant Flow

Associations between change in the step cadence (exposure) variables and change in the markers of cardiometabolic health (outcome) variables were explored using generalised estimating equations (GEE), accounting for repeated measures using an exchangeable correlation matrix. Models were conducted across two levels (baseline to 1 year and 1 year to 4 years), allowing all change values to be included in the analysis over the 4-year period. Models were restricted to complete case analysis, meaning only participants with complete data for all variables were included. Interaction terms for measurement period were tested in

the models described below to confirm associations of interest were consistent across the different measurement periods and suitable for pooling within a repeated measures analysis. Coefficients can therefore be interpreted as the association between change in exposure and outcome variables within the 4-year study period. Models were adjusted for baseline values of each level for both the outcome and exposure variable, change in wear time, randomisation group, age, sex, ethnicity (White European, South Asian, other), employment status (employed, part-time employed, retired, other), IMD, and time varying covariates, smoking status (smoker, previous smoker, never smoked), alcohol consumption (units per day), history of previous CVD (yes/no), blood pressure medication (yes/no), and lipid lowering medication (yes/no). In addition, models were mutually adjusted for change in number of slow steps/day (when brisk steps/day and peak 10-minute are the exposure variable) or change in number of brisk steps/day (when slow steps/day is the exposure variable) in order to assess their independent associations. An acyclic diagram showing the statistical model under study can be found in Figure 9. Further adjustment for overall steps/day was not attempted due to multicollinearity between change in total steps/day with brisk steps/day or slow steps/day within this population ($r > 0.50$). However, to provide additional context for the results on stepping intensity, we also repeated the analysis for total steps/day without adjustment for brisk or slow steps. Supplementary models were also run without mutual adjustment for brisk and slow steps/day and for the main model plus change in WC to investigate whether associations were independent of changes to adiposity. For descriptive purposes, change in brisk steps/day from baseline were also categorised as high increasers (>1000 steps/day increase), moderate increasers (1-1000 steps/day increase), moderate decreasers (1-1000 steps/day decrease), and high decreasers (>1000 steps/day decrease), which broadly reflected quartiles with data split at the 27th, 52nd, and 75th percentiles. For context, 1000 brisk steps equates to around 10 minutes of brisk walking (183).

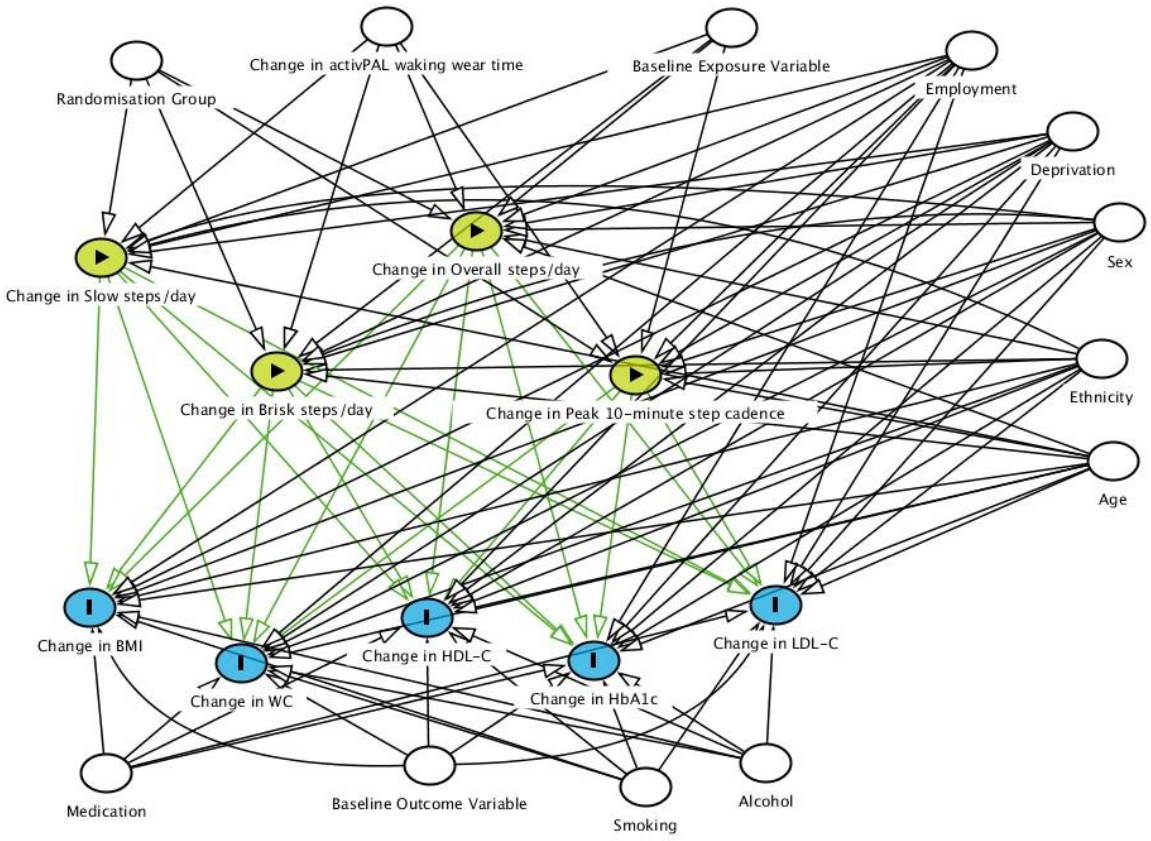


Figure 9 Acyclic Diagram of Statistical Model (Chapter 3)

The blue circles represent the outcomes of interest; green circles represent independent variables; white circles represent potential confounders which were adjusted for in the model; black arrows represent the relationships between the confounders and the independent variables/outcome of interest; green arrows represent the relationships between the independent variables and the outcome of interest/other independent variables.

BMI: body mass index; HbA1c: glycated haemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; WC: waist circumference

Interaction terms were explored to assess whether associations with slow or brisk steps/day were modified by ethnicity or sex. Significant interactions were then stratified by categories. For interactions and stratification by ethnicity, participants with "Other" ethnicities were excluded due to low numbers, meaning data could not be fitted to the models.

An additional sensitivity analysis was conducted where missing data were replaced with multiple imputations across 5 datasets. Missing data were imputed using the fully conditional specification (FCS) method, an iterative Markov chain Monte Carlo method for when the pattern of missing data is arbitrary. FCS is a flexible alternative to the joint modelling approach to multiple imputation, which is less appropriate for imputing categorical variables as it involves specifying a multivariate distribution for the missing data, assuming both linearity and normality of all variables. FCS multiple imputation fits a univariate model for each variable

with missing data, using all other available variables in the model as predictors, allowing an appropriate regression model to be selected for each variable and the capture of complex relationships between variables (350).

To aid interpretation, results are presented as both standardised and non-standardised β coefficients [95% CI] per 1000 steps/day for slow and brisk steps/day and per 10 steps/min for peak step cadence. All data were analysed using IBM SPSS Statistics (version 24.0). A *p*-value of <0.05 was considered statistically significant for the main effects and interactions.

3.3 Results

From a total of 1366 participants recruited to the study, 794 participants (age = 60 ± 9 years; 51.3% male; 72.9% WE, 21.9% SA, 5.2% other ethnicities) had valid activPAL data at baseline and at least one follow-up period (1-year and 4-year) and were included in this analysis. Models therefore analysed participants who had data at all timepoints alongside participants who had data at baseline and 1-year follow-up (but not 4-year), and participants with baseline and 4-year follow-up (but not 1-year). Participant characteristics at each measurement period (baseline, 1-year, and 4-years) are displayed in Table 8 and baseline characteristics stratified by treatment group in Appendix B Table B1. Participants averaged 15.8 ± 1.2 hours per day of valid waking wear time, 8445 ± 3364 steps/day, of which 4794 ± 2865 were brisk steps/day. There were no substantial differences between characteristics of participants included and excluded due to missing data (data shown in Appendix B Table B2).

Table 8 Characteristics of *PROPELS* study participants

	Baseline (n = 794)	***1-year (n = 791)***	***4-year (n = 749)***
Fixed variables			
	***n* [%] of participants**		
Ethnicity			
White European	579 [72.9%]	574 [72.6%]	556 [74.2%]
South Asian	174 [21.9%]	171 [21.6%]	149 [19.9%]
Other Ethnicities	41 [5.2%]	46 [5.8%]	44 [5.9%]
Sex			
Male	407 [51.3%]	409 [51.7%]	386 [51.5%]
Female	387 [48.7%]	382 [48.3%]	363 [48.5%]
History of Cardiovascular disease	100 [12.6%]	128 [16.2%]	121 [16.1%]
Employment			
Full-time	288 [36.3%]	270 [34.1%]	208 [27.8%]

Part-time Retired Unemployed or other	146 [18.4%] 275 [34.6%] 85 [10.7%]	140 [17.7%] 320 [40.5%] 61 [7.7%]	123 [16.4%] 363 [48.4%] 55 [7.4%]
	Mean ± SD		
Social Deprivation (IMD decile)	5.8 ± 3.0	5.8 ± 2.9	5.8 ± 2.8
Time varying variables			
	***n* [%] of participants**		
Lipid Lowering Substances	237 [29.9%]	246 [31.1%]	286 [38.2%]
Blood Pressure Medication	295 [37.2%]	308 [38.9%]	305 [40.7%]
Smoking Status Non-smokers Ex-smokers Current smokers	 443 [55.8%] 288 [36.3%] 62 [7.8%]	 448 [56.6%] 287 [36.3%] 56 [7.1%]	 404 [53.9%] 257 [34.3%] 47 [6.3%]
	Mean ± SD		
Alcohol (units per day)	3.7 ± 5.9	3.8 ± 5.5	3.7 ± 5.8
Weight (kg)	81.0 ± 17.3	81.1 ± 17.7	80.0 ± 18.1
BMI (kg/m^2)	29.0 ± 5.4	29.0 ± 5.5	28.8 ± 5.6
Waist Circumference (cm)	98.3 ± 13.9	98.2 ± 13.9	99.6 ± 14.0
HDL-C (mmol/L)	1.5 ± 0.4	1.5 ± 0.5	1.5 ± 0.5
LDL-C (mmol/L)	3.0 ± 0.9	2.9 ± 0.9	2.7 ± 0.9
Triglycerides (mmol/L)	1.6 ± 1.1	1.6 ± 1.1	1.6 ± 0.9
HbA1c (%) [mmol/mol]	5.8 ± 0.3 [40.7 ± 3.5]	5.9 ± 0.3 [41.3 ± 3.4]	6.0 ± 0.4 [41.6 ± 4.7]
activPAL valid waking wear time (hours/day)	15.8 ± 1.2	15.4 ± 2.6	15.4 ± 2.5
Steps/day	8445 ± 3364	8626 ± 3798	8422 ± 3962
Slow Steps/day	2401 ± 1286	2408 ± 1334	2386 ± 1312
Brisk Steps/day	4794 ± 2865	5018 ± 3126	4900 ± 3286
Peak 10-minute step cadence (steps/minute)	127.8 ± 10.1	128.0 ± 10.6	127.1 ± 10.5
Peak 10-minute step cadence (steps/minute)	127.8 ± 10.1	128.0 ± 10.6	127.1 ± 10.5

BMI: body mass index; HbA1c: glycated haemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; IMD: index of multiple deprivation; LDL-C: low-density lipoprotein cholesterol; SD: Standard Deviation

3.3.1 Slow and brisk steps

Associations between change in overall, slow, and brisk steps/day with change in markers of cardiometabolic health are presented in Table 9. Change in total steps/day were associated with change in BMI, WC, HDL-C, and HbA1c. However, when separated by and mutually adjusted for stepping intensity, associations were largely only maintained for change in brisk steps where every 1000 step/day change was associated with a change in BMI (-0.09 kg/m2 [95% CI -0.15, -0.04], WC (-0.25 cm [-0.43, -0.06]; HDL-C (0.015 mmol/L [0.008, 0.021]; and HbA1c (-0.010% [-0.019, -0.001] (Table 9). Standardised associations are displayed in Figure 10. Further adjustment of markers of cardiometabolic health for change in WC did not change the overall pattern of results, with associations persisting; nor did the removal of mutual adjustment for brisk and slow steps/day (Table 10). In contrast slow steps were only associated with change in BMI (-0.16 kg/m2 per 1000 steps/day [-0.28, -0.05].

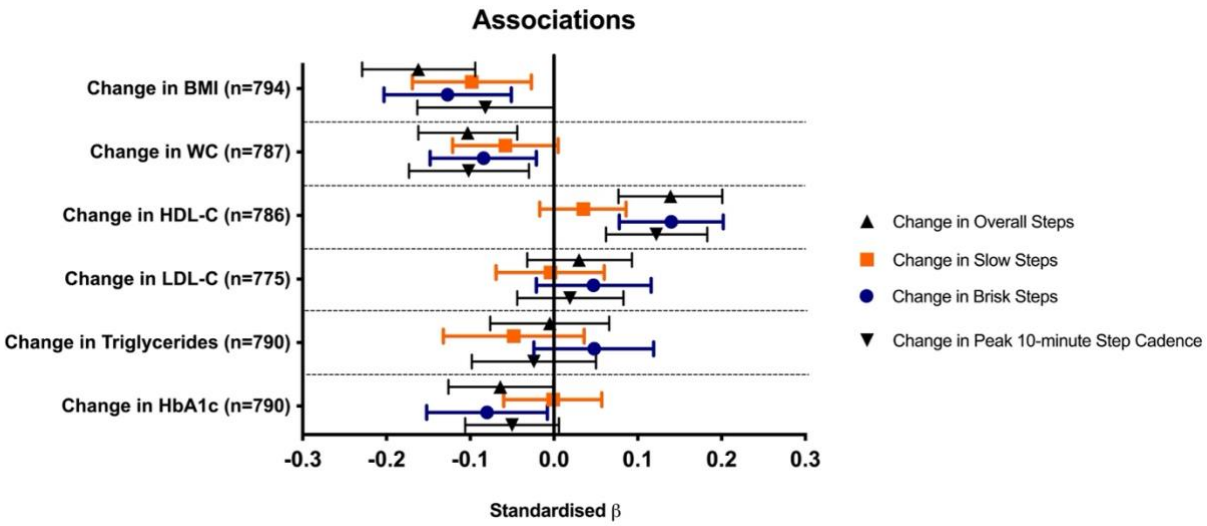


Figure 10 Standardised associations between change in step cadence markers and change in cardiometabolic health outcomes

Data adjusted for baseline value for both the dependant and exposure variable, change in activPAL waking wear time, group, age, sex, ethnicity (White European, South Asian, other), deprivation, employment (employed, part-time employed, retired, other), smoking, alcohol (drinks per week), previous cardiovascular (yes/no), blood pressure medication (yes/no), lipid lowering medication (yes/no), mutual adjustment for baseline and change in slow steps/day (when brisk steps/day or peak 10-minute step cadence is the exposure variable) or baseline and change in brisk steps/day (when slow steps/day is the exposure variable).
Data shown as standardised difference (per standard deviation) in the outcome per 1000 step/day change in slow and brisk steps/day and per 10 steps/minute change in peak 10-minute step cadence.
BMI: body mass index; HbA1c: glycated haemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; WC: waist circumference

Table 9 Non-standardised associations between 4-year change in step cadence variables and 4-year change in markers of cardiometabolic health in people with prediabetes

	Change in BMI (kg/m^2), n = 794		***Change in waist circumference (cm), n = 787***		***Change in HDL-C (mmol/l), n = 786***		***Change in LDL-C (mmol/l), n = 775***		***Change in triglycerides (mmol/l), n = 790***		***Change in HbA1c (%) [mmol/mol], n = 790***	
	β [95% CI]	*p*	*β [95% CI]*	*p*	*β [95% CI]*	*p*	*β [95% CI]*	*p*	*β [95% CI]*	*p*	*β [95% CI]*	*p*
Change in Overall steps/day (per 1000 steps)	-0.10 [-0.14, -0.06]	**<0.001**	-0.27 (-0.41, -0.12)	**<0.001**	0.013 (0.008, 0.019)	**<0.001**	0.009 (-0.006, 0.025)	0.241	0.00 (-0.02, 0.03)	0.711	-0.008 (-0.015, 0.00) [-0.08 (-0.16, -0.01)]	**0.031**
Change in Slow steps/day (per 1000 steps)	-0.16 [-0.28, -0.05]	**0.007**	-0.38 (-0.80, 0.04)	0.073	0.008 (-0.004, 0.021)	0.188	-0.003 (-0.047, 0.041)	0.895	-0.046 (-0.125, 0.034)	0.260	-0.002 (-0.018, 0.013) [-0.02 (-0.18, 0.15)]	0.846
Change in Brisk steps/day (per 1000 steps)	-0.09 [-0.15, -0.04]	**0.001**	-0.25 (-0.43, -0.06)	**0.009**	0.015 (0.008, 0.021)	**<0.001**	0.014 (-0.006, 0.035)	0.175	0.020 (-0.010, 0.050)	0.190	-0.010 (-0.019, -0.001) [-0.11 (-0.21, -0.01)]	**0.029**
Change in Peak 10-minute Step Cadence (per 10 steps)	-0.02 [-0.04, 0.00]	**0.049**	-0.09 (-0.16, -0.03)	**0.005**	0.004 (0.002, 0.006)	**<0.001**	0.002 (-0.004, 0.008)	0.547	-0.003 (-0.013, 0.007)	0.527	-0.002 (-0.004, 0.000) [-0.02 (-0.05, 0.00)]	0.080

Data displayed as non-standardised beta coefficients [95% CI]

p < 0.05 values in bold

Adjusted for baseline value for both the outcome and exposure variable, change in activPAL valid waking wear time, group, age, sex, ethnicity (White European, South Asian, other), deprivation, employment (employed, part-time employed, retired, other), smoking, alcohol (drinks per day), previous cardiovascular disease (yes/no), blood pressure medication (yes/no), lipid lowering medication (yes/no), plus mutual adjustment for baseline and change in slow steps/day (when brisk steps/day or peak 10-minute step cadence is the exposure variable) or baseline and change in brisk steps/day (when slow steps/day is the exposure variable.

BMI: body mass index; CI: confidence interval; HbA1c: glycated haemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

Table 10 Non-standardised associations between 4-year change in step cadence variables and 4-year change in markers of cardiometabolic health in people with prediabetes

	Change in BMI (kg/m^2)		***Change in waist circumference (cm)***		***Change in HDL-C (mmol/L)***		***Change in LDL-C (mmol/L)***		***Change in triglycerides (mmol/L)***		***Change in HbA1c (%) {mmol/mol}***	
Participants contributing data, *n*	794		787		786		775		790		790	
	β [95% CI]	*p*	*β [95% CI]*	*p*	*β [95% CI]*	*p*	*β [95% CI]*	*p*	*β [95% CI]*	*p*	*β [95% CI]*	*p*
Alternative Model 1												
Change in Slow steps/day	-0.19 [-0.30, -0.07]	**0.001**	-0.41 [-0.82, 0.01]	0.053	0.010 [-0.002, 0.023]	0.106	0.000 [-0.044, 0.043]	0.983	-0.039 [-0.116, 0.039]	0.328	-0.004 [-0.019, 0.011] {-0.04 [-0.20, 0.13]}	0.662
Change in Brisk steps/day	-0.10 [-0.15, -0.04]	**<0.001**	-0.26 [-0.44, -0.08]	**0.005**	0.015 [0.009, 0.022]	**<0.001**	0.014 [-0.006, 0.034]	0.178	0.018 [-0.011, 0.048]	0.225	-0.010 [-0.019, -0.001] {-0.11 [-0.20, -0.01]}	**0.033**
Change in Peak 10-minute step Cadence	-0.02 [-0.04, -0.01]	**0.037**	-0.10 [-0.17, -0.03]	**0.003**	0.004 [0.002, 0.006]	**<0.001**	0.002 [-0.004, 0.008]	0.586	-0.003 [-0.013, 0.006]	0.507	-0.002 [-0.004, 0.000] {-0.02 [-0.04, 0.00]}	0.093

Alternative Model 2									
Change in Overall Steps/day		0.011 [0.005, 0.017]	**<0.001**	0.006 [-0.010, 0.022]	0.450	0.006 [-0.020, 0.033]	0.642	-0.005 [-0.011, 0.002] {-0.05 [-0.12, 0.02]}	0.170
Change in Slow steps/day		0.006 [-0.006, 0.019]	0.321	-0.004 [-0.047, 0.040]	0.873	-0.028 [-0.106, 0.050]	0.477	0.002 [-0.013, 0.017] {0.03 [-0.12, 0.19]}	0.682
Change in Brisk steps/day		0.013 [0.007, 0.020]	**<0.001**	0.010 [-0.011, 0.031]	0.339	0.018 [-0.013, 0.049]	0.255	-0.007 [-0.016, 0.002] {-0.08 [-0.17, 0.01]}	0.094
Change in Peak 10-minute step cadence		0.004 [0.002, 0.006]	**<0.001**	0.001 [-0.005, 0.007]	0.729	-0.002 [-0.011, 0.008]	0.749	-0.001 [-0.003, 0.001] {-0.01 [-0.03, 0.02]}	0.475

Data displayed as non-standardised beta coefficients [95% CI]
p < 0.05 values in bold
Alternative Model 1: adjusted for baseline value for both the outcome and exposure variable, change in activPAL valid waking wear time, group, age, sex, ethnicity (White European, South Asian, other), deprivation, employment (employed, part-time employed, retired, other), smoking, alcohol (drinks per day), previous cardiovascular disease (yes/no), blood pressure medication (yes/no), lipid lowering medication (yes/no).
Alternative Model 2: adjusted for Alternative Model 1, plus mutual adjustment for baseline and change in slow steps/day (when brisk steps/day or 10-minute peak step cadence is the exposure variable) or baseline and change in brisk steps/day (when slow steps/day is the exposure variable) and baseline and change in waist circumference.
BMI: body mass index; CI: confidence interval; HbA1c: glycated haemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol

When analysed categorically, change in brisk steps/day showed broadly dose-related associations with change in markers of cardiometabolic health. Compared to high decreasers, high increasers had 0.29 kg/m2 [0.03, 0.55] lower BMI (Figure 11; Panel A) and 0.06 mmol/L (-0.09, -0.02) lower HDL-C (Figure 11; Panel C). HbA1c increased in all groups, but the largest increase occurs in the high decreasers, 0.11% (0.07, 0.15), being 0.04% (0.01, 0.08) different to high increasers (Figure 11; Panel D).

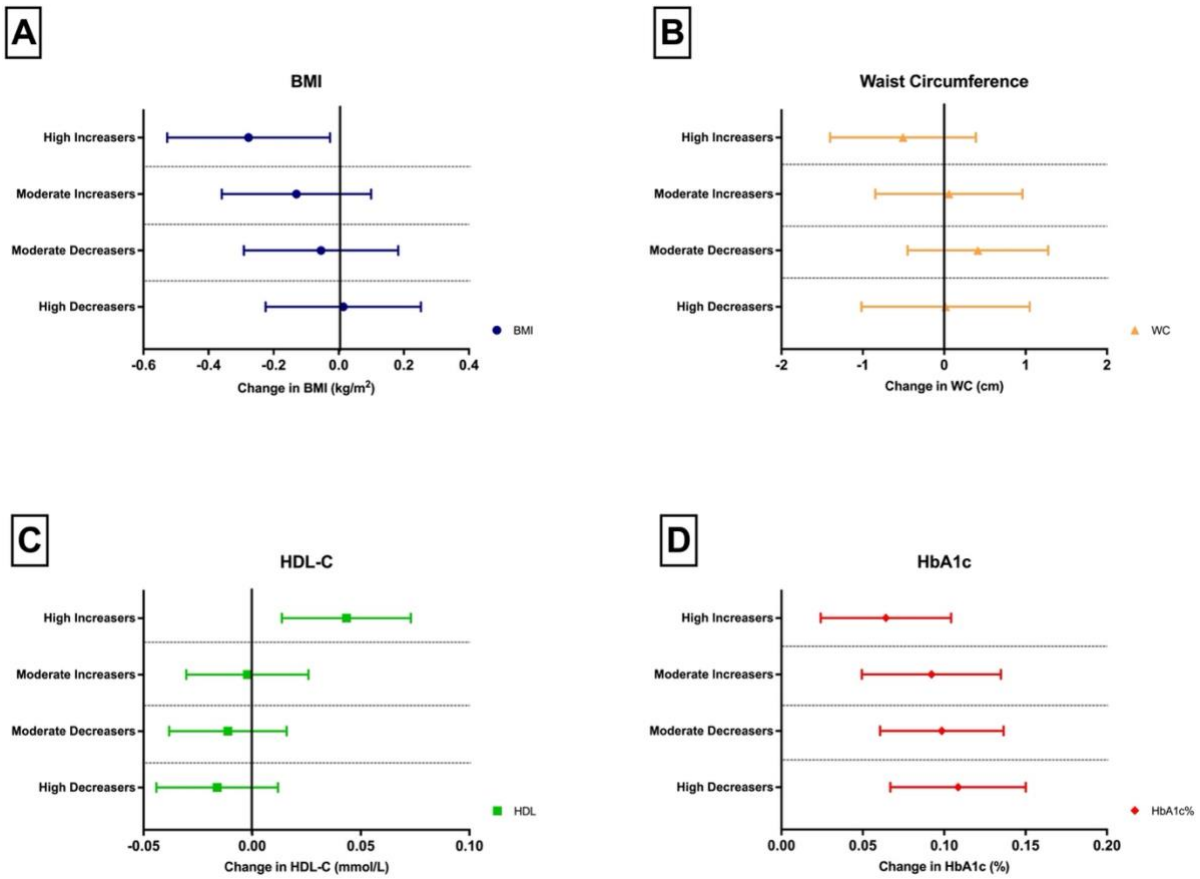


Figure 11 Group difference in change in markers of cardiometabolic health and change in brisk steps/day

Data points represent mean change [95% CI].
Adjusted for baseline value for both the dependant and exposure variable, change in activPAL waking wear time, group, age, sex, ethnicity (White European, South Asian, other), deprivation, employment (employed, part-time employed, retired, other), smoking, alcohol (drinks per week), previous cardiovascular disease (yes/no), blood pressure medication (yes/no), lipid lowering medication (yes/no), and mutual adjustment for baseline and change in slow steps/day.
High Increasers >1000 brisk steps/day increase
Moderate Increasers 0-999 brisk steps/day increase
Moderate Decreasers 1-999 brisk steps/day decrease
High Decreasers >1000 brisk steps/day decrease
BMI: body mass index; CI: confidence interval; HbA1c: glycated haemoglobin A1c; HDL-C: high-density lipoprotein cholesterol; WC: waist circumference

3.3.2 Peak step cadence

Associations between change in peak stepping cadence variables and change in markers of cardiometabolic health are presented in Figure 10 (non-standardised coefficients shown in

Table 9). In the whole cohort, there were associations between change in 10-minute peak step cadence variables and change in BMI (-0.02 kg/m^2 per 10 steps [-0.04, 0.00]), WC (-0.09 cm per 10 steps [-0.16, -0.03]), and HDL-C (0.004mmol/L per 10 steps [0.002, 0.006]). Further adjustment of markers of cardiometabolic health for change in WC did not change the overall pattern of results, with association persisting; nor did the removal of mutual adjustment for brisk and slow steps/day (Table 10).

3.3.3 Ethnicity and sex interactions

Interaction analyses suggested some differences between ethnicities (Appendix B Table B3) for brisk steps. Stratified results are presented in Figure 12 (non-standardised coefficients shown in Appendix B Table B4). Associations in SAs were observed between change in 10-minute peak step cadence and change in BMI (-0.08 kg/m2 per 10 steps [-0.11, -0.05]). No associations were observed in WEs.

A significant association was found for change in overall steps/day (-0.010% per 1000 steps [-0.018, -0.002]), brisk steps/day (-0.013% per 100 steps [-0.023, -0.002]) and change in peak 10-minute step cadence (-0.003% per 10 steps [-0.006, 0.000]) with change in HbA1c in WEs, but not in SAs.

Results revealed a significant association between change in brisk steps/day and change in LDL-C for males (0.029mmol/L per 1000 steps [0.002, 0.057]) but not females (see Appendix B Table B5).

Multiple imputations for missing data did not change the overall interpretation of BMI, WC, HDL-C, LDL-C, triglycerides, or HbA1c (Appendix B Table B6).

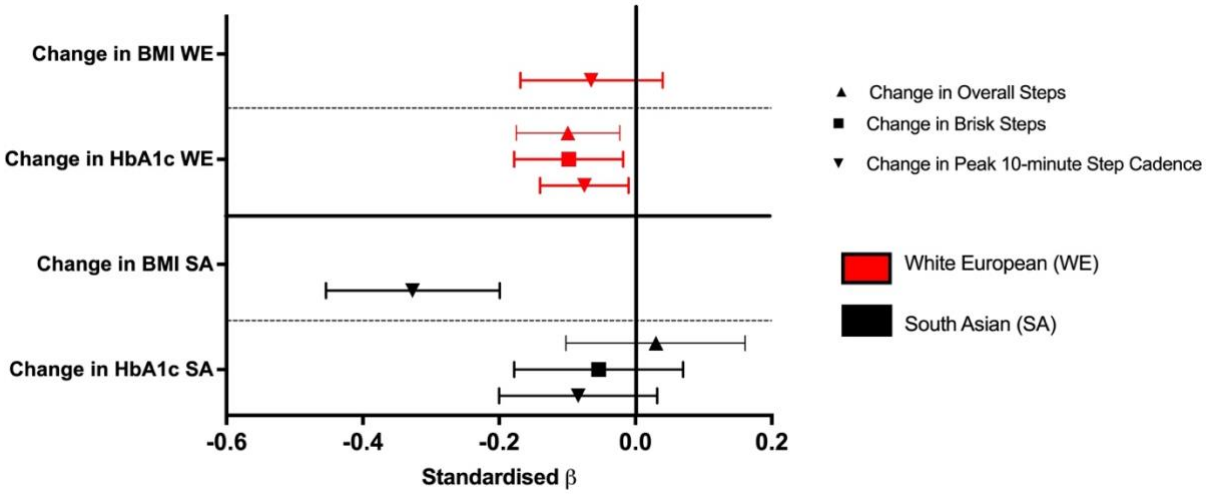


Figure 12 Standardised associations between change in brisk steps/day and peak step cadence variables and change in cardiometabolic health outcomes stratified by ethnicity

Adjusted for baseline value for both the dependant and exposure variable, change in wear time, group, age, sex, deprivation, employment (employed, part-time employed, retired, other), smoking, alcohol (drinks per week), previous cardiovascular disease (yes/no), blood pressure medication (yes/no), lipid lowering medication (yes/no), plus mutual adjustment for baseline and change in slow steps/day. Data shown as standardised difference (per standard deviation) in the outcome per 1000 step/day change in brisk steps/day and per 10 steps/minute change in peak 10-minute step cadence with corresponding confidence intervals.

BMI: body mass index; HbA1c: glycated haemoglobin A1c

3.4 Discussion

To my knowledge, this analysis is the first to investigate the associations between change in stepping behaviours and change in markers of cardiometabolic health in people with prediabetes. The analysis has shown that whilst increases in overall stepping over a 4-year period had a beneficial association with adiposity, HDL-C, and HbA1c in people with a history of prediabetes, these associations were only maintained for brisk steps when analysed by and mutually adjusted for stepping intensity. Additionally, increases in average steps/minute for 10-minute peak step cadence was associated with improvements in adiposity and HDL-C. Changes in slow steps/day were not associated with changes to markers of cardiometabolic health, apart from BMI. When results were stratified by ethnicity, a stronger association was seen between 10-minute peak step cadence and adiposity in SAs than in WEs. Conversely, a stronger association between increase in brisk steps/day and 10-minute peak step cadence and change in HbA1c was seen in WEs compared to SAs.

This analysis, using accelerometer measured stepping behaviour, provides new prospective evidence in support of the importance of brisk stepping for cardiometabolic health. Previous evidence using self-reported measures has found faster habitual walking pace to be a stronger predictor of survival and longer telomere length than overall PA volume or other lifestyle factors (179, 351-353). However, recent studies using objectively measured stepping cadence at a single time point within the general population have been more equivocal, with some or all of the associations of brisk stepping with health outcomes attenuated after adjustment for overall stepping volume (172, 174, 178), emphasising the need for further research. This analysis shows that a stronger, more consistent pattern of health benefits is observed with 4-year changes to brisk steps/day than for slow steps/day in those with a history of prediabetes. This finding supports the continued emphasis on MVPA within recent updated PA guidelines in the USA (354), UK (355), and internationally (203).

The associations between 4-year change in brisk steps/day and change in HDL-C were consistent across the different metrics of walking intensity employed. Early intervention studies investigating how the introduction of a brisk walking programme influences lipid profiles showed beneficial changes to HDL-C after 12 weeks of increased brisk walking (356). More recently, a 1-year lifestyle intervention aimed at increasing overall and brisk stepping demonstrated that brisk walking lasting ≥10 minutes was significantly associated with an increase in HDL-C (357). The results of the present analysis support these findings and provide

new evidence that longer-term changes to brisk walking may be beneficial for improving lipid profile. The analysis detailed in this chapter exhibited that difference in change in HDL-C between those that decreased their brisk steps/day by over 1000 steps/day vs those that increased by over 1000 steps/day was 0.06 mmol/L [0.02, 0.09]. Previous research has suggested that 0.05 mmol/L equates to the MCID in HDL-C (358), with a difference of 0.06 mmol/L shown to be associated with a 3-6% difference in the relative risk of CVD mortality in women and men (359).

This analysis also identified an association between a 4-year change in brisk steps/day and reduction in HbA1c. This supports data from the NHANES cohort which reported an association between PA and HbA1c in people at risk for T2D which was stronger when a higher percentage of overall activity came from MVPA (360). Similarly, the present analysis identified associations between 4-year change in several step cadence variables and change in BMI and WC, which extends observations from previous cross-sectional associations (361). However, changes in HbA1c and adiposity between those that increased and decreased their brisk steps/day were relatively modest and below the threshold for clinical significance (362). Nonetheless, there was a dose-related association between categorical change in brisk steps/day and change in HbA1c; and in this high-risk population, any action to reverse or slow the trajectory of worsening cardiometabolic health over time could have important public health benefits.

When the data were stratified by ethnicity, an increase in brisk steps/day and average peak step cadence for 10-minutes resulted in a reduction in HbA1c in WEs, but not in SAs. Conversely, there were stronger associations between peak 10-minutes step cadence and adiposity in SAs than in WEs. Previous, cross-sectional analysis of the *PROPELS* cohort highlighted that SAs engaged in less MVPA and took fewer steps per day at baseline than WEs (285). Different patterns of baseline activity, fitness, and relative intensity of PA may help explain differences in the health benefits of increasing brisk steps/day. However, it is notable that the results for HbA1c are in contrast to previous experimental research showing reductions in insulin resistance in response to acute exercise sessions are greater in SAs than in WEs (337). Similarly, acute responses of postprandial insulin to breaking up prolonged sitting with bouts of walking have previously been reported as being greater in SAs than in WEs (38). This suggests that further research is required to determine how acute and chronic adaptions to PA may differ by, or be optimised in, different ethnic groups. This is particularly important for

walking, which is one of the most universally popular forms of PA across different ethnicities and cultures (363).

3.4.1 Strengths and Limitations

There are several notable strengths of this chapter. To the best of my knowledge, this is the first analysis to investigate the associations between change in metrics for stepping activity and change in markers of cardiometabolic health in people with a history of prediabetes. Further, the inclusion of a population that was predominantly recruited from primary care with coded HbA1c or glucose values highlighting a history of prediabetes makes these results reflective of people currently being referred to T2D prevention programmes. A further strength of this analysis is the use of the activPAL device to calculate step cadence. The activPAL has previously been found to be highly accurate in determining step cadence at speeds ≥0.5 m/s (301). Additionally, it is important to note the high proportion of study participants representing ethnic minority groups, specifically SAs. However, the chapter is also limited by various factors. This is secondary data analysis of a trial that was designed for a different research question. The duration and requirements of the original trial may have deterred some people from taking part. For example, both the overall (8445 steps/day) and brisk steps (4794 steps/day) at baseline were relatively high. Therefore, the generalisability of the findings to less active populations requires further research. There was also loss of data due to reduced capacity for activPAL placement within the study or through participant drop-out. However, multiple imputation did not result in meaningful change to the overall pattern of results. Furthermore, as the *PROPELS* intervention did not elicit meaningful change to stepping behaviour after 4 years (349), the cohort was combined and analysed as an observational study. Therefore, causation between change in stepping behaviour and change in cardiometabolic health cannot be established and residual or unmeasured confounding cannot be discounted.

3.4.2 Conclusion

This chapter concludes that when change in total steps over a 4-year period was split out by intensity (brisk steps/day and slow steps/day), only increases in brisk steps/day were associated with beneficial changes to a range of cardiometabolic health markers in people with a history of prediabetes. These findings highlight the need to further explore the benefits of promoting brisk stepping as part of a healthy lifestyle. Further to this, the differences in the strength of associations between WEs and SAs for changes in brisk steps/day and peak stepping

cadence and changes in adiposity and HbA1c suggest that behavioural interventions may need to be tailored to suit responses of different ethnic groups.

The results of this chapter have demonstrated the associations between change in step cadence and change in markers of cardiometabolic health in people with a history of prediabetes, over 4 years. The following chapter will build on this data and the results of Chapter 2 by discussing the implementation of an intervention designed to reduce sitting time by breaking up SB with periods of walking and light resistance activity.

Chapter 4: Reducing sitting time in people with type 2 diabetes through personalised intervention

Chapter Overview

This chapter reports on the *RESPONSE* Study. I originally designed this study as a RCT (see Appendix C1). However, due to COVID-19 restrictions, I had to redesign the methods and overall study aims in order to proceed in the resulting unprecedented times. The study was therefore restructured into a before and after design. The chapter presents a personalised intervention designed to reduce sitting time through regular and targeted PA breaks in SB. The chapter concludes with a discussion around the preliminary efficacy of the intervention, the potential for expansion, the impact the research may have on informing future studies, and the potential reasons for the successes and failures within the intervention.

Key Findings

- The *RESPONSE* intervention appeared to:
    - Reduce sitting time (-0.61 hours [95% CI -1.21, -0.00])
    - Improve PF
        - STS-60 (4.47 reps [3.22, 5.72])
        - SPPB (1.63 points [1.08, 2.18])
        - 4-MGST (-0.33 seconds [-0.50, -0.15]

Author Contribution

I wrote the original RCT protocol alongside a fellow PhD student conducting a similar study in people with peripheral arterial disease (PAD) – Jemma Perks. We wrote the original protocol under the supervision of Prof Thomas Yates, Prof Robert Sayers, Dr Charlotte Edwardson, and Dr Joseph Henson. The amended (COVID-19-safe) protocol was written by me under the supervision of Prof Thomas Yates and Dr Joseph Henson. The intervention was designed by myself and Dr Charlotte Edwardson. The study set up and recruitment was all completed by me. I took all participants through baseline and follow-up measurement sessions, conducted all weekly coaching calls with participants, helped them to design and adhere to personalised plans to break up time spent engaging in SB, and analysed the data (including all CGM, activPAL, and secondary data). GENEActiv data were cleaned and processed by Dr Tatiana Plekhanova.

I was responsible for:

- Writing, alongside another PhD student, the original full study protocol (see Appendix C1)
- Preparing documents for sponsor review
- Responding to sponsor comments
- Preparing and submitting the ethics application to the Research Ethics Committee (REC), responding to comments and queries, and attending the REC meeting to discuss the study.
- Liaising with Sponsor to ensure procedures were being followed and that data were being managed appropriately.
- Preparing documents for amendments
    - Three amendments were required – two non-substantial to extend the study end date, and one substantial to allow for protocol revisions. This substantial amendment was needed to restructure the protocol from a RCT to a single-arm before and after study.
- Working with the National Institute for Health Research (NIHR) Clinical Research Network (CRN) to recruit primary care practices to the study as participant identification centres (PICs) and aid in meeting recruitment targets.
- Liaising with PICs to discuss practice capability.
- Ordering and preparing recruitment packs to be sent to the PICs before being forwarded to potential participants.
- Responding to reply slips sent by potential participants.
- Conducting screening to identify which potential participants would be eligible to take part in the study.
- Discussing the study with potential participants and taking interested parties through the informed consent procedures.
- Arranging with eligible participants an appropriate time to conduct baseline and follow-up measurements, ensuring that materials and resources were ready for them, and conducting all necessary measurements.
- Tracking participant progress through the intervention to ensure that all elements were delivered at the correct times.
- Working with participants to design a personalised plan to break up their sitting time based on CGM data, accelerometer data, and their perceived barriers.

- Distributing educational materials, measurement devices, and sedentary time reminder devices to participants.
- Conducting weekly coaching calls with participants.
- Extracting and processing CGM data
- For activPAL data pertaining to this study, I was responsible for: setting up the activPAL device for each participant; waterproofing the device; ordering and preparing pre-paid envelopes to return devices; fitting the device to the participant's leg and giving them instructions on how to change the dressing if required; giving instructions on how to record wake and sleep times on the diaries provided; downloading and storing the data after the device had been returned; creating 'event files' from PAL Batch (within PAL Technologies Software Suite); processing the 'event files' through Processing PAL; and visually checking the heatmaps generated in Processing PAL before checking these against the wake and sleep logs to ensure they were accurate. Where they were not, I manually made corrections using the "Corrections" page in Processing PAL. This involved identifying the event within the "Summary" document where Processing PAL had incorrectly coded the bout and inputting the correction into Processing PAL.
- Arranging for the processing, data cleaning, and quality checking of GENEActiv data.
- Organising the data for analysis and ensuring that all data is easily accessible for future research.
- Conducting all analyses of the data in SPSS.
- Planning the process evaluation and collecting relevant data from participants about the pros and cons of the intervention.

4.1 Introduction

The interplay between T2D and impaired PF has already been discussed in the Background to this thesis. Briefly, people with T2D have been reported to be at greater risk of developing impairments to PF (65), have greater risk of presenting with factors associated with impaired PF (92), and are more likely to experience impairments at an earlier age (91). The need to develop strategies for people with T2D to improve their cardiometabolic health has also already been established. Chapters 2 and 3 of this thesis demonstrated the associations between PA with improved PF and cardiometabolic health; though did not address another factor highlighted in the Background to this thesis – SB.

The successes and challenges associated with previous SB change interventions, such as *SMArT Work, SMART Work and Life,* and *Stand and Move at Work* have been discussed in the Background to this thesis. A possible strategy to increase the impact of SB change interventions on markers of cardiometabolic health may lie in the personalisation. For example, recent meta-analysis of eight RCTs suggested that PA conducted after a meal was more effective than PA conducted before a meal or remaining sedentary (364). Additionally, there was a moderating influence of time between meal and PA, suggesting that PA taken as soon as possible after a meal may have a greater impact on postprandial glucose control compared to waiting a longer interval after meals (364). Experimental examples of this can be seen in the study by Reynolds et al. (156) which investigated specifically targeting PA after participants' meals. For a period of 2 weeks, participants were either advised to walk 30 minutes per day or to walk 10 minutes after each main meal (three per day) – iAUC improved by 0.88 [95% CI 0.78, 0.99] in the group that walked 10 minutes after each main meal, compared to the group that walked 30 minutes in one bout during the day (156). Another study specifically looked at timing *Salat* – an obligatory Islamic prayer which is "similar to other aerobic exercises, such as tai chi and yoga" – before and after meals (365). When *Salat* (typically 10-20 minutes in duration) was performed within 5-10 minutes of finishing a meal, participants saw a 3.3kg [95% CI 2.32, 4.27] greater reduction in bodyweight and a 3.63% [2.60, 4.65] greater reduction in bodyfat percentage compared to participants who performed *Salat* before meals. However, personalised strategies have not been effective in all populations – such as the *SIT LESS* intervention in people with coronary artery disease (366). The intervention involved three face-to-face education and motivational interviewing/goal setting sessions with trained research nurses, a self-monitoring device connected to a smartphone application in which participants and research nurses could track adherence and adjust goals, and regular (weekly during weeks

1-6 and bi-weekly during weeks 7-12) calls from research nurses to offer supportive coaching. Although the participants in the study who received the personalised intervention decreased their sitting time by 1.6 hours per day, this was not significantly different to participants in the control group who decreased by 1.2 hours per day. Further, although the participants who received the *SIT LESS* intervention saw beneficial changes to quality of life and 10-year risk of recurrent cardiovascular events, this did not differ from the control group. It is not clear, however, how the responses from a T2D or prediabetes population may differ compared to the cardiac rehabilitation cohort recruited to the *SIT LESS* study.

Based on this information detailing the health benefits associated with targeting PA and SB breaks and the results detailed in Chapters 2 and 3 of this thesis demonstrating the associations between step cadence with PF and cardiometabolic health, there appears to be a need to investigate the merits of an intervention that uses a personalised approach to reduce sitting time and uses PA breaks in SB to increase PA through stepping and light resistance exercise with an aim to improve glucose control and PF in people with T2D or prediabetes. Therefore, the aims of this chapter were to test the potential of a 4-week personalised intervention to reduce sitting time in people with T2D or prediabetes and assess the potential impact upon glucose control. Secondary aims included assessing the changes to PF – a key secondary outcome – as well as sleep duration and quality, quality of life, muscular pain and function, anxiety and depression, fatigue, breathlessness, and disability. In addition to these, a further secondary aim was to investigate how baseline and follow-up values in the primary and key secondary outcomes within the trial population compare to those observed within a healthy control population, and whether the intervention brings participants closer to normal values.

4.2 Methods

4.2.1 Design and procedure

RESPONSE was a single arm before and after study conducted over 4 weeks in both male and female participants with T2D or prediabetes. The overall study design is shown in Figure 13. Healthy control volunteers free of T2D, obesity, hypertension, or prevalent CVD were also recruited, for a baseline case-control comparison. The healthy control group did not participate in the intervention, nor did they complete follow-up measurements – their data were used to make comparisons with the T2D/prediabetes group pre- and post- intervention to assess if, and how well, the intervention brought the intervention participants back to normal levels post-intervention. Recruitment and study procedures were conducted between August 2021 and October 2022. This study was approved by the London – Surrey Research Ethics Committee (20/LO/1102) (Appendix C2). All participants provided written informed consent (Appendix C3). The study was coordinated within the Leicester Biomedical Research Centre, hosted within the Leicester Diabetes Centre, at Leicester General Hospital.

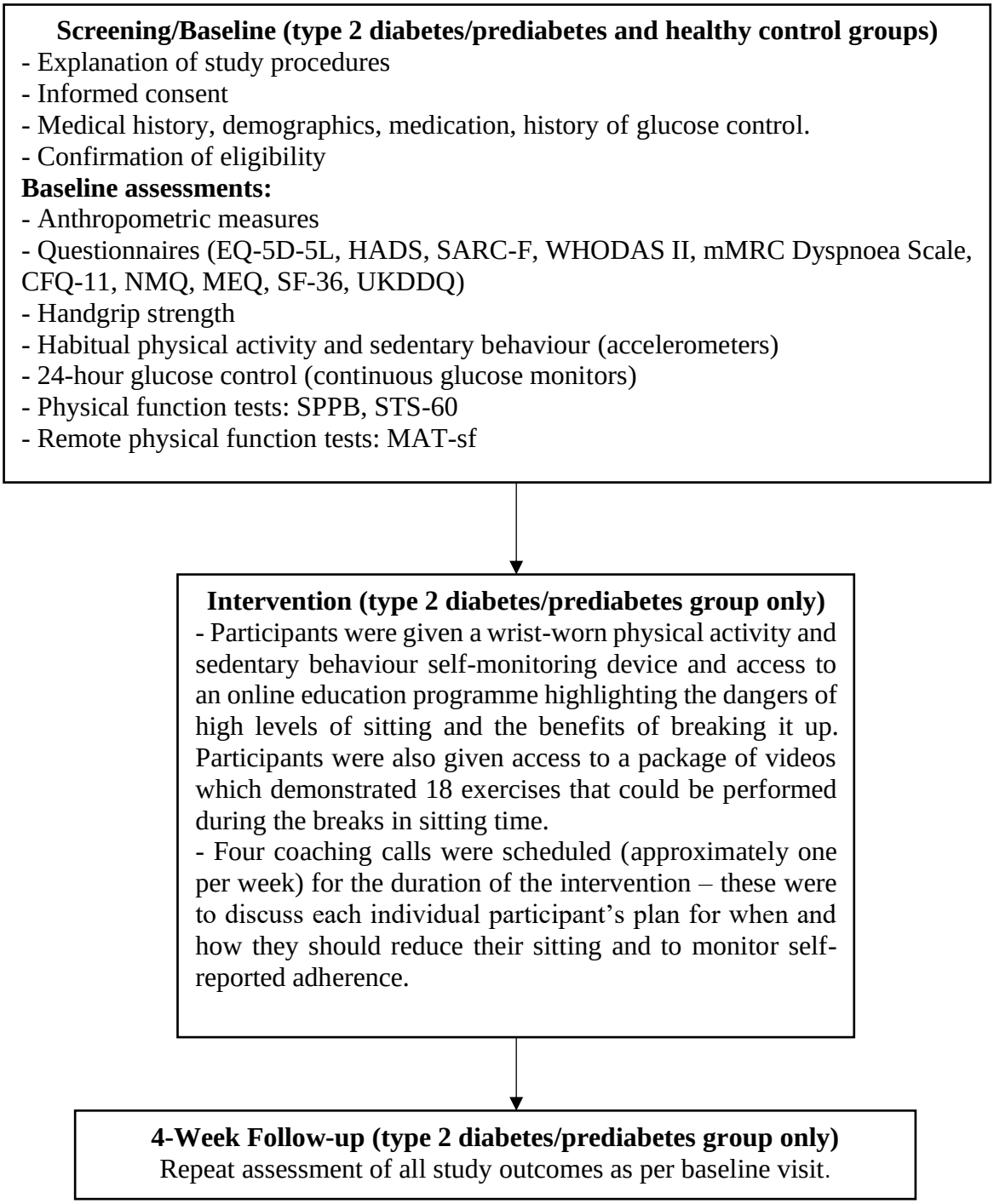


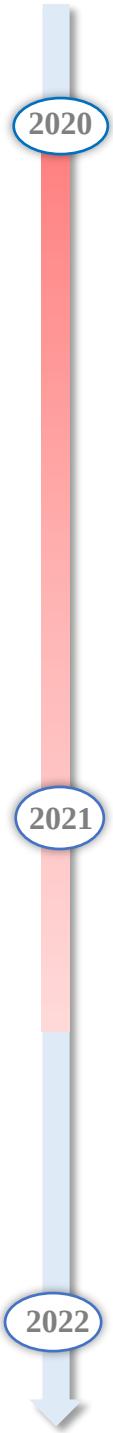
Figure 13 *RESPONSE* study design

CFQ-11: Chalder fatigue questionnaire; HADS: hospital anxiety and depression scale; MAT-sf: mobility assessment tool – short form; MEQ: morningness-eveningness questionnaire; NMQ: Nordic musculoskeletal questionnaire; SF-36: short form-36; SPPB: short physical performance battery; STS-60: sit-to-stand-60; UKDDQ: UK diabetes and diet questionnaire; WHODAS II: World Health Organization disability assessment schedule

4.2.2 COVID-19 Adaptations

Originally, the plan for the *RESPONSE* study was to devise and conduct a RCT investigating a 4-week personalised coaching programme to reduce time spent sitting (see

Appendix C1). Initial study development began in October 2019 and was given Sponsor green light in March 2021 (see Figure 14). A substantial amendment was required to allow for uncertain COVID-19 restrictions – this received Sponsor approval in August 2021. Due to the uncertainty surrounding COVID-19 restrictions at the time, it was decided to include two avenues of data collection – in person and remote. Additionally, the study went through considerable restructuring to be changed to a single-arm before and after design. It is also at this point that the decision was made to include a healthy control group (free of any cardiometabolic conditions), who would not take part in the intervention but would provide a reference point to demonstrate how well the intervention might bring people with T2D or prediabetes back to normal values.



October-February	Literature review and study protocol drafting *(protocol originally written as a combined submission with a similar PAD project)*
March-April	Protocols separated and redesigned as two individual RCTs ☼ **March 23rd first national lockdown**
April	Preparation of all documentation in accordance with UoL Sponsor and UHL trust standard SOPs
April-May	LDC quality check
June-July	UoL Sponsor documentation review ☼ **July 4th first local lockdown in Leicester**
August-September	Study documentation preparation and submission to HRA/REC
November	HRA/REC approval granted ☼ **November 5th second national lockdown** ☼ **January 6th third national lockdown**
March	Sponsor green light issued
April-June	Amendments in response to the ongoing uncertainty around the COVID-19 pandemic: restructure into single-arm before and after study with option for remote delivery, and inclusion of healthy control *(substantial amendment to restructure the study)* Approval for participants to attend LDC
June	COVID-19 amendments: approved by sponsor, submitted to HRA/REC
August	COVID-19 amendment: Sponsor green light issued.
August	Recruitment started
September	Recruitment ended
October	Study end

Figure 14 *RESPONSE* study timeline

Blue shading represents time pre-/post-national restrictions related to COVID-19. Red shading represents time under national/local restrictions related to COVID-19.

HRA: Health Research Authority; LDC: Leicester Diabetes Centre; PAD: peripheral arterial disease; RCT: randomised controlled trial; REC: research ethics committee; University Hospitals Leicester; UoL: University of Leicester; SOP: Standard Operating Procedure

4.2.3 Participants

Participants were recruited through three pathways: primary care; existing Leicester Diabetes Centre study databases of consenting individuals; and through referral from promotional study materials posted in various community locations. GP practices were contacted through the Clinical Research Network, requesting support and identifying potentially eligible participants. Each practice that agreed to take part was given the inclusion and exclusion criteria so that they could search for eligible patients. Practices were sent recruitment packs (containing a Participant Information Sheet (PIS) (Appendix C4), a reply slip, and a freepost envelope to return their details to the study team) to forward on to patients (using stamped envelopes provided). In total, 703 recruitment packs were sent to potential participants. For database recruitment, participants from previous studies within the Leicester Diabetes Centre who had consented to be contacted about future research were screened using the inclusion and exclusion criteria. Those who were identified as eligible were sent a recruitment pack containing the same documents as those sent out by GP practices. Referral recruitment involved potential participants contacting the study team to highlight their interest – these people were screened for eligibility and sent the same recruitment pack. Potential participants who registered interest in taking part in the study were screened for the following inclusion (Table 11) and exclusion criteria (Table 12). The upper age limit of 75 was primarily selected to limit risk associated with exposure to COVID-19. Risk of COVID-19-related mortality in people aged over 75 was significantly higher than those in younger age categories (367).

Table 11 Inclusion criteria for the *RESPONSE* Study

Type 2 diabetes Group	***Healthy Control Group***
- Aged between 40 and 75 years, inclusive - Diagnosed with type 2 diabetes or prediabetes within the last 10 years - Diabetes controlled by diet alone, or receiving mono- or dual-therapy - No changes to glucose lowering medication regime within the preceding 3 months - HbA1c levels 6.5-9% - Able and willing to give informed consent - Able to understand spoken and written English - Able to undertake light physical activity	- Aged between 40 and 75 years, inclusive - Able and willing to give informed consent - Able to understand spoken and written English - Able to undertake light physical activity - Weight stable (≤ 3kg weight change in preceding 3 months) - BMI ≤ 45 kg/m^2

- Weight stable (≤ 3kg weight change in preceding 3 months) - BMI ≤ 45 kg/m^2	

BMI: body mass index; HbA1c: glycated haemoglobin A1c

Table 12 Exclusion Criteria for the *RESPONSE* Study

Type 2 diabetes Group	***Healthy Control Group***
- Current diagnosis of type 1, gestational, or monogenic diabetes mellitus - Receiving insulin therapy - Hospital admission in preceding 3 months - Current or planned pregnancy or breast feeding; any contra-indications to exercise - Participation in another research study with investigational medical product in the preceding 3 months - Current participation in a structured exercise programme - Serious illness with life expectancy < 1 year - History of chronic pancreatitis - Previous major amputation - Recent cardiovascular event (within 12 months) - Steroid use - Current diabetic foot ulcers - Recent diagnosis or treatment for cancer (within 12 months).	Identical to type 2 diabetes Group

4.2.4 Sample Calculations

The original RCT was powered to detect at least a 10% (0.8 mmol/L) difference in average (CGM defined) glucose levels between groups, assuming an average 24-hour blood glucose level of 8 mmol/L (368), a standard deviation of 0.8 mmol/L, a 5% level of significance and 90% power. Based on these criteria, 21 individuals per group were required to complete the trial. The sample size of 21 was retained for the before and after design. This allowed for the detection of a moderate effect size (0.5) for a before and after design, assuming an intra-individual correlation in repeated measures of 0.7, a power of 80% and a significance level of 0.05. Adjustment was not made for assigning co-primary outcomes (average glucose and sitting) given the hypothesis generating nature of the revised trial protocol.

4.2.5 Intervention

Overall Intervention Structure

The principal aim of the intervention was to have participants reduce their daily sitting time by 30 minutes per day, in addition to targeting breaks in sitting time around habitual spikes in blood glucose and periods of extended sitting – based on baseline data. The intervention – personalised to reduce sitting time based on each participant's activity and glucose profile – consisted of an online education programme (adapted from the *SMART Work and Life* online education programme (267)), a wrist worn PA and SB self-monitoring device, and weekly coaching calls with a researcher.

Online Education Programme

Participants receiving the intervention were sent a link to an online education programme adapted from the version used in the *SMART Work & Life* intervention (267). The programme was developed with input from various stakeholders and other similar programmes from published research (e.g., *Stand Up Victoria* (369) and *SMarT Work* (260)). The online education programme which came from the *SMART Work & Life* intervention is grounded in several behaviour change theories (Social Cognitive Theory (370), Self-Regulation Theory (371), and Relapse Prevention Theory (372).

The online education programme included:

- A background on the shift in PA and SB that has occurred recently with respect to transport, leisure time, and work
- An overview of a typical day in an adult's life, estimating how much time is typically spent watching television, eating, driving, working, and engaging in PA
- A worksheet where participants could log their activities to estimate daily sitting time
- A snapshot of recent news headlines that have highlighted the dangers of sitting
- Basic information on the impact that sitting time can have on blood glucose, CVD, mortality, depression and anxiety, cancer, WC, circulation, musculoskeletal health, cognitive function, muscle wasting, tiredness, and quality of life
- An animation highlighting the importance of achieving the right balance of PA and SB, and a description of different intensities of PA
- A quiz where participants could test their knowledge of the points covered in the session
- An animation highlighting the benefits of reducing sitting time
- An overview of evidence around breaking up sitting time with standing, LPA or MPA walking, or basic resistance training exercises and the impacts on health outcomes
- A review of the key messages from the online education programme

- An activity encouraging participants to think about when and how they could break up/reduce their sitting time
- An overview of the importance of self-monitoring and prompts
- Details of mobile phone apps, computer software, and wearable devices that could be used to self-monitor sitting time
- A guide to setting goals around sitting time reduction
- A worksheet encouraging participants to make a plan about when and how they could break up and reduce their sitting time, potential barriers that might get in the way, and how they could overcome these
- A final summary of key points from the online education programme
- A list of resources discussed in the programme and links to these
- Details of what the next steps in the intervention would entail

Participants were asked to complete the online education programme before their first coaching call (typically within 3-5 days of being sent the link).

Videos

Participants were sent video links to example activities that they could use to break up their sitting time – these were created by, and featured myself as a demonstrator. All participants were sent links to the same videos at the time of their first coaching call. Activities shown in videos were: step-up, walking, heel tap, wall press-up, biceps curl, squat/half-squat, chest stretch, back stretch, hamstring stretch, calf stretch, single-leg balance, side leg lift, rear leg lift, reverse lunge, arm circles, chair squat, and tip-toe balance.

Self-monitoring Tools

Each participant was provided with a *Hama Fit Watch 4900* smartwatch (Hama UK Ltd., Basingstoke, UK). The devices were set up by a researcher via the Hama app and posted, along with a USB charger, to participants before their first coaching call. Devices were configured to give reminders to break up sitting between the hours of 9am and 9pm if the device recorded 30-60 minutes of uninterrupted sedentary time (based on participant and researcher agreement). Additionally, through the online education programme, participants were referred to three smartphone applications (*Sitting Timer, Stand Up!,* and *Chairless*) as well as four desktop applications (*Outstanding, Break Timer, Workrave,* and *Time Out*) which were recommended for use at work and at home.

Coaching Calls

After the participants had completed the online education programme and received the self-monitoring device, they joined their first coaching call with a researcher to discuss their personalised plan (typically 30-45 minutes in duration). The first coaching call included a discussion about their baseline CGM and activPAL data, identifying times in the day where they were consistently sedentary or were seeing significant glucose spikes; the structuring of a plan about how to reduce sitting time, potential barriers and how to address them, and an opportunity for the participant to ask any questions. Coaching calls were repeated once per week throughout the intervention period to ensure that participants were adhering to the intervention, make changes to the plan where required, and address any issues. Coaching calls were conducted either over the phone or via video call software, depending on participant preference and capability. Coaching calls were semi-structured, ensuring that key points were covered (Coaching Call Guidance can be seen in Appendix C5). In order to increase uniformity of coaching, all calls were conducted by myself – I have worked professionally as a strength and conditioning coach for over 10 years, specialising in the delivery of exercise and behaviour change for people with chronic disease (including T2D).

Intervention Personalisation

The intervention recommendations given to participants were personalised to each participant based on their baseline CGM and activPAL data. Prior to calls, data from CGM and activPAL were extracted and reviewed to identify patterns where reductions in sitting time would be particularly beneficial. An example of this can be seen in Figure 15 and Figure 16 (baseline CGM and activPAL from the same participant). On Tuesday 22nd March (circled on each figure in blue), the participant was largely inactive after midday which corresponds with spikes in glucose around meal times. Whereas on Sunday 20th March (circled on each figure in black), the participant was largely active around the same time period and had much more stable glucose levels. These figures would have been used to demonstrate to the participant the importance of activity around meal times and to help them target their PA and breaks in sitting time accordingly.

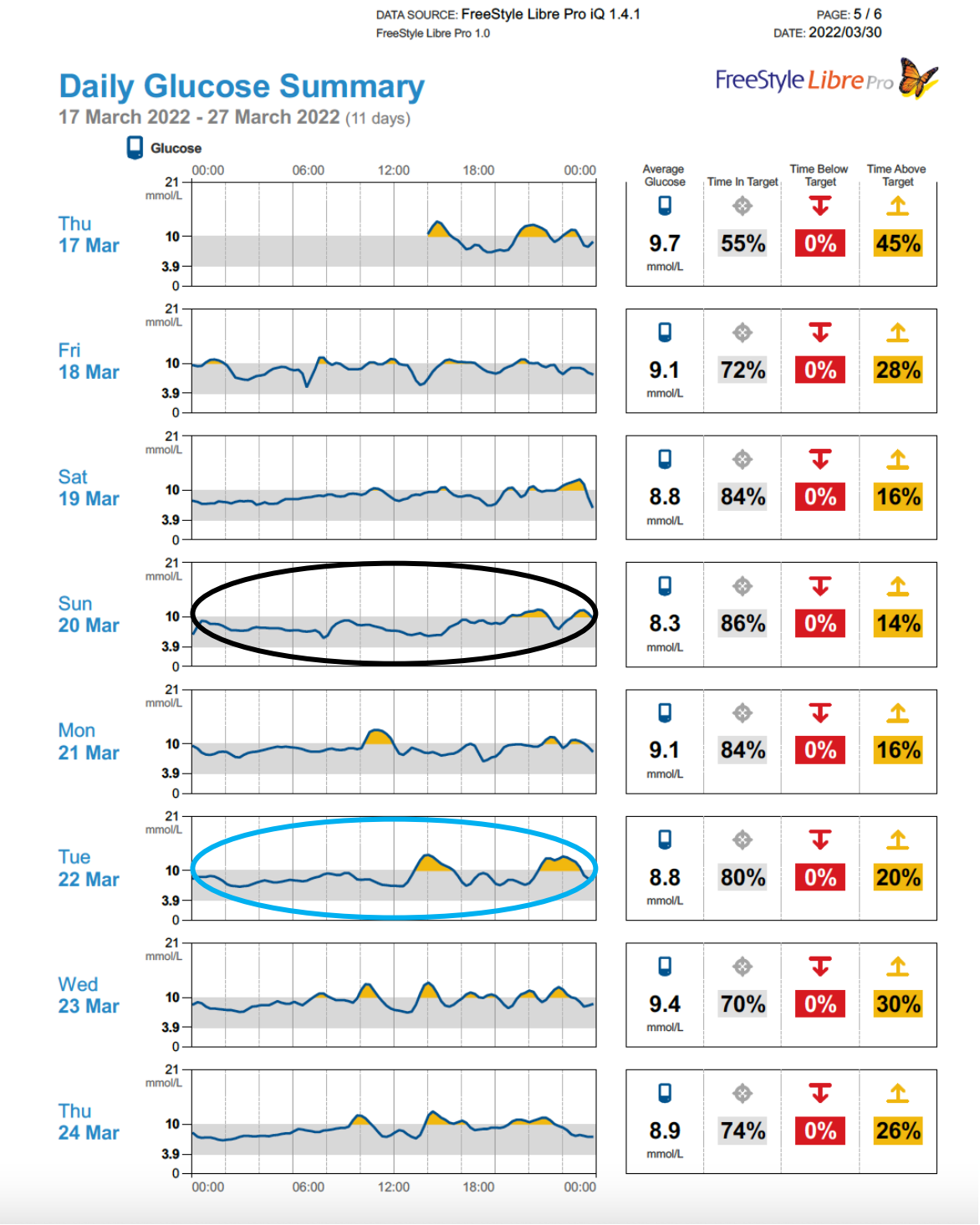


Figure 15 Example continuous glucose monitor output from a RESPONSE participant

Blue circle highlights a day when the participant was largely inactive after midday which corresponds with spikes in glucose around meal times. The black circle highlights a day when the participant was largely active around the same time period and had much more stable glucose levels

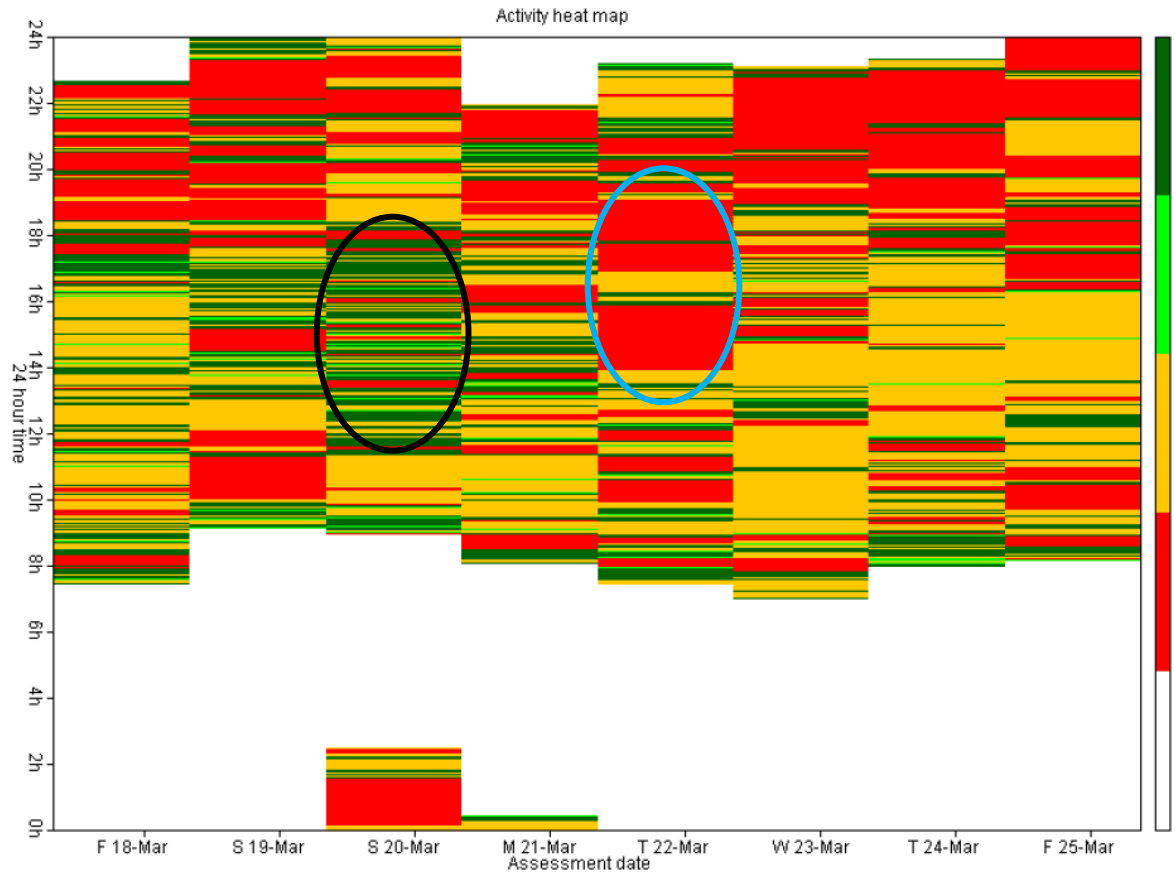


Figure 16 Example activPAL output from a RESPONSE participant
(WHITE: No activity information; RED: Sitting/Lying; AMBER: Standing; LIGHT GREEN: Light Stepping; DARK GREEN: moderate-to-vigorous physical activity)
Blue circle highlights a day when the participant was largely inactive after midday which corresponds with spikes in glucose around meal times. The black circle highlights a day when the participant was largely active around the same time period and had much more stable glucose levels

4.2.6 Outcomes

I defined 2 primary outcomes a priori: habitual sitting time and average weekly blood glucose. Secondary outcomes included: various domains of habitual PA and sitting (detailed in the below 'Habitual Sitting Time and Physical Activity' sub-section), overall glucose control (detailed in the below 'Continuous Glucose Monitor Data' sub-section), various measures of PF (detailed in the below 'Physical Function' sub-section), anthropometric and demographic data, and data on sleep, muscular pain and function, anxiety and depression, fatigue, breathlessness, and disability levels.

Habitual Sitting Time and Physical Activity

In this study, two devices were used concurrently for the measurement of habitual sitting time and PA. The use of two devices allows for more accurate measurement of behaviour

and allows for measurement at different locations and for designation of sitting time using both acceleration and inclination (297, 373).

Participants were asked to wear the activPAL3™ device (PAL Technologies, Ltd., Glasgow, UK) 24 h/day for 8 days on the midline anterior aspect of the right thigh. The activPAL device has already been discussed in the 'Background' chapter of this thesis (section *1.8.1 The activPAL*). The processing of the data has been discussed in Chapter 2 of this thesis (sections *2.2.3.1 Processing PAL, 2.2.3.2 Defining Valid Waking Wear Data with the Processing PAL algorithm, and 2.2.3.3 Outputs of Interest*). Output variables of interest within this chapter included: sitting time; prolonged sitting (at least 30-minutes); waking wear time; time spent standing and stepping; steps/day; brisk steps/day; slow steps/day; and sit-to-stand transitions

Participants also wore the GENEActiv Original (Activinsights Ltd, Kimbolton, UK) 24 h/day for 8 days during baseline and follow-up, on their non-dominant wrist. The GENEActiv has previously been found to provide a valid measure of sedentary time and PA during free living conditions in adults (374). The outcomes of interest from the GENEActiv were mean minutes (overall and in 1-minute bouts) of MVPA, average daily acceleration (*m*g), peak step cadence, and sleep duration. Measuring sleep duration is an important part of understanding changes in 24-hour movement behaviours, and changes in sleep patterns can have a marked impact on health outcomes in people with T2D (375).

Alongside this, the participants completed a wake and sleep log for the days they wore the devices. Both devices were fitted in-person by a researcher on the day of their measurement appointment for baseline and again prior to the final week of the intervention. Participants were provided with prepaid envelopes to return devices.

Continuous Glucose Monitor Data

Following baseline measures, participants were fitted with a blinded professional sensor-based CGM system on the upper arm for continuous glucose data analysis (FreeStyle® Libre Pro IQ™; Abbott Diabetes Care, Witney Oxon, UK). One of the key benefits of the blinded "Pro" version of the FreeStyle® Libre, and the reason for its use here, is that it automatically takes readings at predefined points (every 15 minutes) and does not require the participant to scan the device with a reader or smartphone in order to store glucose data. This

was selected as a primary measure over PF because, although they are both key measures of health and wellbeing in people with T2D, the NHS Long Term Plan is more centred around reducing incidence and rates of T2D through lowering glucose levels (376). The sensor is calibrated by the supplier and does not require any participant, healthcare provider, or researcher intervention prior to initialisation or during the measurement period. The sensor measures interstitial glucose and automatically stores glucose data every 15 minutes (96 glucose readings per day). At the end of the 8-day monitoring period, the participants removed the monitor themselves and returned it to the research team – either in person or by using a freepost envelope, provided. A follow-up period sensor was fitted before the final week of the intervention, at the same time as the activPAL and GENEActiv. Upon receipt, scanning the sensor with the FreeStyle reader transfers the data, in preparation for analysis. The FreeStyle Libre software allows for the generation of summary glucose reports. The raw data were also extracted and processed through custom code in RStudio (Appendix C6 – C7) which generates an output showing: mean glucose, HbA1c, time in range (TIR, 3.9-10.0 mmol/L), time above (TAR1, above 10.0 mmol/L and TAR2, above 13.9 mmol/L) and below (TBR1, below 3.9 mmol/L and TBR2, below 3.0 mmol/L) range at various thresholds, high (HBGI) and low blood glucose index (LBGI), number of hyper- hypoglycaemic events, and AUC. The code removes the first and last measurement day so that only full 24-hour days are analysed.

Physical Function

PF was a key secondary outcome in this study due to the interplay between T2D and impaired PF (discussed in the Background to this thesis). Multiple measures of PF were selected to incorporate various aspects of functional capacity. In order to minimise the learned effects of these PF measurements, participants were given a 'trial run' of each assessment before baseline measures were collected and then allowed to rest for 30 minutes (while other measures were collected), following which the actual measurements were taken. As per the protocol, participants were given the option to complete these assessments on-site with a researcher, or to complete them remotely with a researcher providing instructions over video call – with the same measurement method used at baseline and follow-up.

Participants were asked to complete the STS-60, standing from and returning to a standardised position as many times as possible in 60 seconds while keeping arms across their chest. The test – which is a strong predictor of PF as well as muscular endurance – has already been discussed in the Background to this thesis.

Participants were then taken through the SPPB, which has been detailed in the Background to this thesis. The test consists of a balance test, gait speed test, and chair stand test. Balance tests required participants to complete a) side-by-side stand, b) semi-tandem stand, and c) tandem stand, each lasting for 10 seconds (or as long as is possible for the participant) – one attempt was given for each stance. The gait speed test measured the time taken to walk 4m at a self-selected "normal pace" – two attempts were allowed and the faster was scored. The third part of the assessment required participants to rise from a chair with their arms across their chest five times – one attempt was allowed. Total SPPB score was calculated by summing the scores for the 3 individual elements (ranging from 0 – unable to complete the test – to 4). Cut points for individual test scores of 1 to 4 were based on previously established quartiles of timed performance (for walking speed and 5-second sit-to-stand test) or established time criteria (for balance test), according to Guralnik et al (95). These were summed for an overall score range of 0 to 12, with 0 indicating the lowest PF.

Self-reported PF was assessed using the mobility assessment tool–short form (MAT-sf) – a 10-item computer-based assessment using animated video clips. The items cover a range of lifestyle PF measures including walking on level ground, a slow jog, outdoor walking on uneven terrain, walking up a ramp with and without a handrail, stepping over hurdles, ascending and descending stairs with and without a handrail, and climbing stairs carrying shopping bags. The test has been validated against the SPPB and the 400m walk test (377).

HGS was determined using a handheld dynamometer, calibrated prior to first measurement. Participants were seated on a standard height chair without armrests and positioned with the shoulder adducted and neutrally rotated, elbow flexed at 90°, and forearm in a neutral position. The grip handle was adjusted based on the participants hand size. Three measurements were taken on each hand with the highest value being taken as their maximum grip strength.

4.2.7 Descriptive data

Anthropometric and Demographic Variables

Body weight (Tanita SC-330ST, Tanita, West Drayton, UK), height, and WC were measured to the nearest 0.1kg, 0.5cm, and 0.1cm, respectively. WC was measured using a soft tape mid-way between the lowest rib and the iliac crest. Three measurements were taken and

the average of the last two used. Information on date of birth, sex, ethnicity, medication history, medical history, family history of disease from first degree relatives, smoking status, and alcohol consumption were obtained from self-report.

Sleep

Participants self-reported usual sleep patterns using the Morningness-Eveningness Questionnaire (MEQ). This validated questionnaire consists of 19 items on sleep habits and fatigue and assesses individual differences in the degree to which respondents are active and alert at certain times of day. The scale item responses determine preferences in sleep and waking times, and subjective 'peak' times at which respondents feel their best. Individuals were classified as either; evening type (score of ≤52), intermediate type (53-64) or morning type (≥65) (378).

Physical Disability

Participants self-reported physical disability using the World Health Organisation – Disability Assessment Schedule (WHO-DAS) which is a short, well established measure of functional health and disability (379).

Sarcopenia

Participants self-reported symptoms of sarcopenia using the SARC-F. The SARC-F includes five components: strength, assistance walking, rise from a chair, climb stairs, and falls (380).

Anxiety and Depression

Participants self-reported symptoms of anxiety and depression using the Hospital Anxiety and Depression Scale (HADS) which is a frequently used and well validated measure of anxiety and depression in a range of populations (381).

Breathlessness

Participants self-reported symptoms of dyspnoea using the Modified Medical Research Council (mMRC) Dyspnoea Scale, a single item questionnaire which can also be used to assess breathlessness (382).

Usual Dietary Habits

Participants self-reported usual eating patterns using the UK Diabetes and Diet Questionnaire (UKDDQ). Answers from each of the questionnaire items were re-coded into numerical values by applying the following codes: A=5, B=4, C=3, D=2, E=1, F=0. The mean UKDDQ score, based on the total number of questions answered (in case of incomplete questionnaires) for each individual was then calculated from all questionnaire scores, giving a final score ranging from 0 to 5 (383).

Quality of Life

Participants self-reported quality of life using the EQ-5D-5L – a widely used patient reported outcome questionnaire assessing health across mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (384).

Fatigue

Participants self-reported fatigue using the Chalder Fatigue Questionnaire (CFQ-11) – an 11-point measure for assessing physical and mental fatigue (385).

Muscular Pain and Function

Participants self-reported muscular pain and function using the Nordic Musculoskeletal Questionnaire (NMQ). The NMQ incorporates questions about pain and dysfunction felt by individuals in the previous 12 months and 7 days across upper limbs, lower limbs, upper back, and lower back (386).

4.2.8 Process Evaluation and Post-intervention questionnaires

To track the success of recruitment and retention, number of recruitment packs sent out, number of reply slips, and number of subsequent eligible participants was recorded along with the number of participants who completed follow-up. Further to this, throughout the study, attendance to and duration of all study visits and coaching calls was monitored. Participants' experiences and adherence to other aspects of the intervention were assessed through the end-of-study questionnaires (Appendix C8). Two questionnaires were given to participants at their follow-up appointment, along with a freepost return envelope, to be taken home, completed, and returned to the study team. One focussed on the online education programme and asked participants about how much of the online education programme they completed, how useful they found each section, the appropriateness of each section, and the key messages they took

away. The second questionnaire asked participants to rate the self-monitoring device they were given for various aspects such as ease of use, obtrusiveness, and encouragement. During every coaching call, participants were asked about their reduction in sitting time, including if and when they failed to stand when the self-monitoring device instructed them to, what activities they used to break up their sitting, and what barriers they experienced to breaking up their sitting.

4.2.9 Safety

Safety of the intervention was assessed by considering adverse events (AE) and serious adverse events (SAE) that were related to the intervention or study procedures.

4.2.10 Statistical analysis

Descriptive analyses, in terms of medians, interquartile ranges (IQR), and percentages were conducted for the variables investigated. To test differences between the T2D/Prediabetes and healthy control group, EMMs from GLMs were explored – adjusted for age and sex. GEEs were used to compare measurements before and after the intervention. Poisson loglinear models were used for count data in both GLMs and GEEs.

All tests were conducted using IBM SPSS Statistics (version 28.0). A p-value of <0.05 was considered statistically significant for the main effects.

4.3 Results

4.3.1 Participant Recruitment and Characteristics

Recruitment pathways for the *RESPONSE* study are shown in Figure 17 (T2D/Prediabetes) and Figure 18 (healthy control). For the T2D/prediabetes group, a total of 37 potential participants were screened and 12 were deemed ineligible for participation. For the healthy control group, 28 potential participants were screened and none were deemed ineligible. Reasons behind potential participants being ineligible to take part in the study varied, but prevailing factors were age and participation in structured exercise programmes. Prior to baseline data collection in the T2D/prediabetes group, four participants withdrew from the study; and a further two dropped out after completion of baseline data collection. From the healthy control group, three participants withdrew from the study before baseline data collection. The most frequently cited reason for participant drop-out was the time commitment. There were 19 T2D (age = 61.4 ± 7.2, BMI 29.31 ± 4.22, 47.4% female, 73.7% WE) and 25 healthy control (age = 51.6 ± 9.3, BMI 26.55 ± 3.26, 64.0% female, 64.0% WE) participants included in the analysis. No participants with prediabetes were recruited.

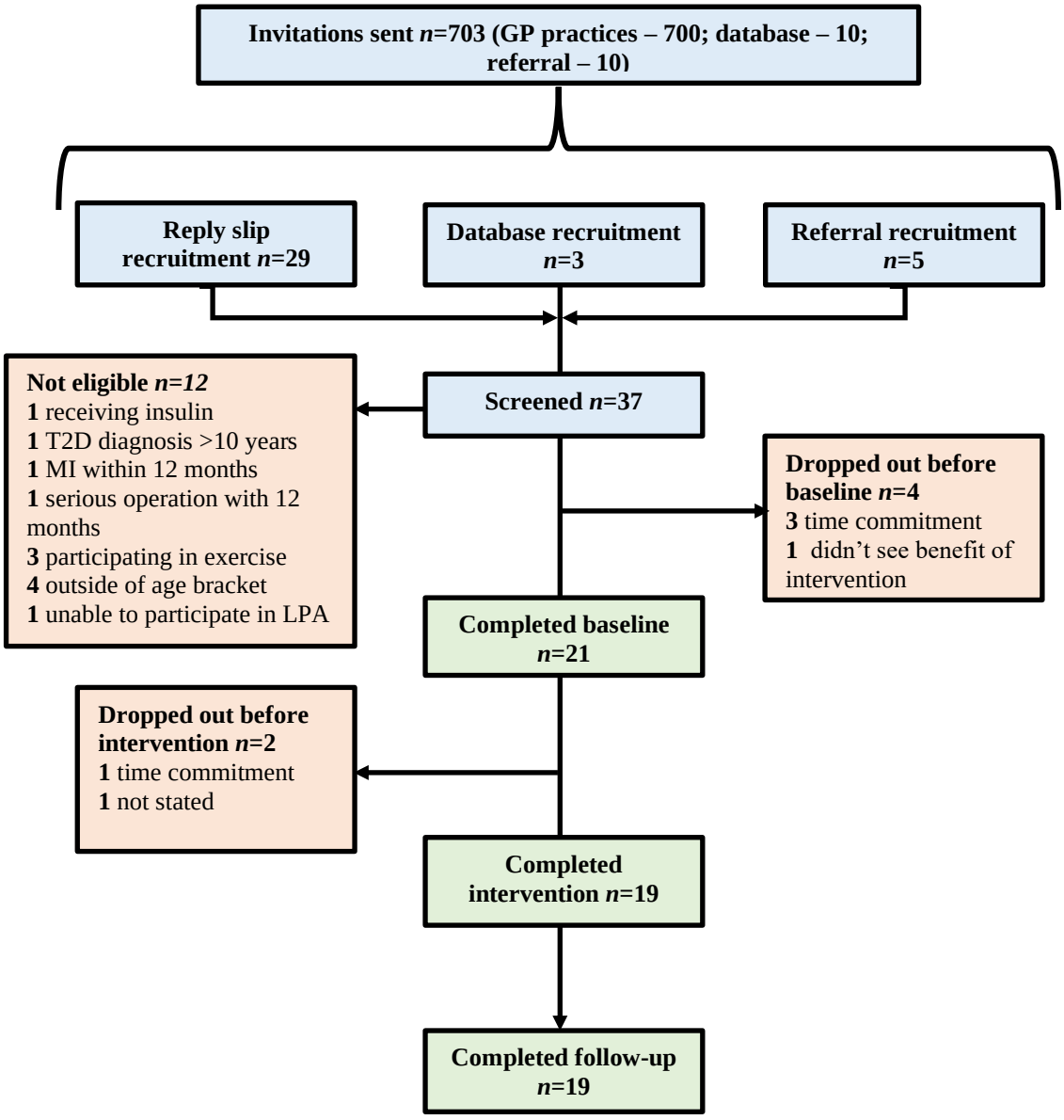


Figure 17 Recruitment pathway for type 2 diabetes/prediabetes participants in the *RESPONSE* study

GP: general practitioner; LPA: light-intensity physical activity; MI: myocardial infarction; T2D: type 2 diabetes

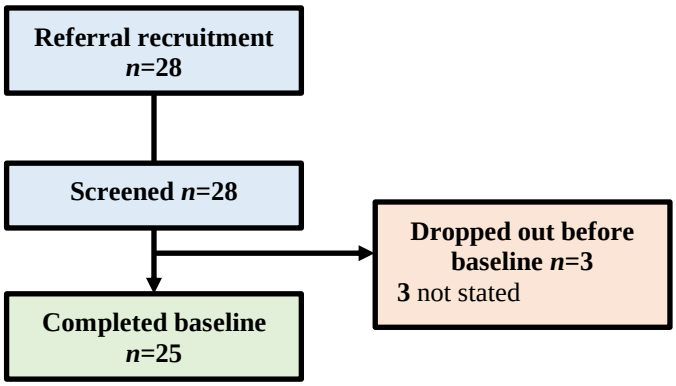


Figure 18 Recruitment pathway for healthy control participants in the *RESPONSE* study

Baseline descriptive data for both groups can be seen in Table 13. Median and IQR data for participants with T2D at baseline and follow-up and healthy control participants at baseline can be seen in Table 14 A-F. Those who dropped out of the study after completion of baseline measurements (2 participants) were aged 63.0 ± 8.5, BMI 28.2 ± 1.2, 100% female, 100% SA. Their baseline measures did not differ markedly from the baseline measures of participants who remained in the intervention.

Table 13 Characteristics of *RESPONSE* study participants

	Type 2 diabetes (n = 19)		***Healthy Control (n = 25)***	
	Mean/Frequency	SD/%	Mean/Frequency	SD/%
Age (mean)	61.4	7.2	51.6	9.3
Sex				
Male	10	52.6	9	36.0
Female	9	47.4	16	64.0
Ethnicity				
White European	14	73.7	16	64.0
South Asian	5	26.3	8	32.0
Black	0	0	1	4.0
Smoking Status				
Non-Smoker	10	52.6	21	84.0
Ex-Smoker	5	26.3	4	16.0
Current Smoker	4	21.1	0	0
Alcohol units per week (mean)	4.7	6.0	3.0	4.8
Employment				
Employed	8	42.1	18	75.0
Unemployed	2	10.5	1	4.2
Retired	9	47.4	5	20.8
Medication				
Metformin	12	63.2	0	0
Lipid Lowering Substances	12	63.2	3	12.0
Blood Pressure Medication	12	63.2	3	12.0

SD: standard deviation

Table 14A Primary outcome descriptive data for *RESPONSE* study participants

	Type 2 diabetes Baseline				***Type 2 diabetes Follow-up***				***Healthy Control***			
	n	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR
Sitting Time (hours/day)	*19*	8.84	10.11	12.03	*19*	7.33	9.46	11.51	*25*	8.40	9.35	10.42
Average Daily Glucose (mmol/L)	*19*	6.30	7.59	8.68	*19*	6.35	7.36	8.55	*24*	4.78	5.09	5.55
IQR: interquartile range												

Table 14B Physical function outcome descriptive data for *RESPONSE* study participants

	Type 2 diabetes Baseline				***Type 2 diabetes Follow-up***				***Healthy Control***			
	n	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR
MAT-sf (points)	*19*	57.22	68.99	70.31	*19*	65.79	68.99	70.31	*25*	68.99	71.13	73.13
STS-60 (reps)	*19*	17	21	22	*19*	21	26	28	*25*	22	26	31
4-MGST (sec)	*19*	2.37	2.69	3.22	*19*	2.19	2.31	2.59	*25*	2.30	2.55	3.16
L-HGS (kg)	*18*	20.00	27.00	35.00	*18*	21.75	25.50	33.00	*24*	22.00	29.50	38.00
R-HGS (kg)	*18*	23.75	30.00	36.50	*18*	23.75	29.50	39.50	*24*	24.00	30.00	35.00
SPPB (cumulative score)	*19*	9	11	11	*19*	12	12	12	*24*	11	12	12
4-MGST: 4-meter gait speed test; IQR: interquartile range; L-HGS: left handgrip strength; MAT-sf: mobility assessment tool – short form; R-HGS: right handgrip strength; SPPB: short physical performance battery; STS-60: sit-to-stand-60												

Table 14C activPAL outcome descriptive data for *RESPONSE* study participants

	Type 2 diabetes Baseline				***Type 2 diabetes Follow-up***				***Healthy Control***			
	n	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR
Waking Wear Time (hours)	*19*	14.81	15.34	16.60	*19*	14.78	15.36	15.93	*25*	15.09	15.65	16.22
Prolonged Sitting Time (30+ min bouts) (hours)	*19*	4.24	5.91	7.86	*19*	3.40	5.14	7.85	*25*	3.82	5.26	6.16
Prolonged Sitting Bouts/day (30+ min bouts)	*19*	4	5	7	*19*	3	5	7	*25*	3	4	6
% waking wear time sitting	*19*	55.21	64.64	76.56	*19*	49.62	65.91	76.82	*25*	55.09	60.48	67.04
% waking wear time prolonged sitting (30+ min bouts)	*19*	25.93	39.01	48.83	*19*	23.06	33.81	50.49	*25*	24.11	33.44	41.91
Stepping Time (hours)	*19*	1.08	1.65	2.12	*19*	1.34	1.61	2.35	*25*	1.57	1.98	2.55
Steps/day	*19*	5224	7810	10338	*19*	6046	8372	10472	*25*	7042	10086	12728
Brisk Stepping Time (hours)	*19*	0.51	0.73	1.15	*19*	0.48	0.72	1.08	*25*	0.64	0.90	1.33

Brisk Steps/day	*19*	3524	4792	8018	*19*	3308	4896	7640	*25*	4299	6308	9146
Brisk Stepping Time (1-min bouts) (hours)	*19*	0.11	0.28	0.56	*19*	0.07	0.23	0.58	*25*	0.19	0.33	0.57
Brisk Steps/day (1-min bouts)	*19*	724	1920	4034	*19*	456	1610	4000	*25*	1471	2202	4146
% waking wear time stepping	*19*	6.94	9.73	13.30	*19*	7.33	9.46	11.51	*25*	10.09	13.65	16.50
Standing Time (hours)	*19*	2.58	4.08	4.64	*19*	2.49	3.75	5.01	*25*	3.25	4.08	5.34
% waking wear time standing	*19*	16.12	26.47	29.42	*19*	15.95	23.84	35.60	*25*	21.33	26.05	34.80
Sit to Stand Transitions	*19*	33	49	53	*19*	38	41	50	*25*	34	48	57
IQR: interquartile range												

Table 14D GENEActiv outcome descriptive data for *RESPONSE* study participants

	Type 2 diabetes Baseline				***Type 2 diabetes Follow-up***				***Healthy Control***			
	n	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR
Sedentary Time (mins/day)	*18*	509.90	605.30	653.55	*18*	588.15	645.9	677.65	*25*	468.45	558.1	613.03
Average Acceleration (mg/day)	*18*	17.48	20.30	24.55	*18*	18.30	22.30	26.10	*25*	22.15	27.40	37.05
Intensity Gradient	*18*	-2.90	-2.75	-2.60	*18*	-2.85	-2.70	-2.60	*25*	-2.70	-2.60	-2.42
MVPA Time (mins/day)	*18*	47.10	92.70	140.48	*18*	46.67	70.94	103.64	*25*	72.08	97.88	142.56
MVPA Time (1-min bouts) (mins/day)	*18*	13.95	27.60	50.08	*18*	12.05	28.20	44.00	*25*	28.17	44.35	71.13
LPA (mins/day)	*18*	233.90	605.30	653.55	*18*	198.60	233.50	280.15	*25*	249.15	318.70	374.28
Peak 10-minute Step Cadence (continuous) (mg)	*18*	103.78	187.33	217.50	*18*	102.35	127.30	179.65	*25*	155.48	183.50	257.30
Peak 10-minute Step Cadence (total) (mg)	*18*	157.18	264.85	329.20	*18*	161.46	198.53	240.38	*25*	213.28	245.78	330.95
Peak 30-minute Step Cadence (continuous) (mg)	*18*	82.78	130.09	157.23	*18*	80.50	93.50	135.40	*25*	116.33	138.30	182.63
Peak 30-minute Step Cadence (total) (mg)	*18*	116.77	120.85	175.15	*18*	115.65	146.66	165.79	*25*	149.95	174.62	237.63
Sleep Duration (hours/day)	*18*	6.38	7.10	7.78	*18*	6.00	7.00	7.35	*25*	6.13	6.60	7.60
IQR: interquartile range; LPA: light-intensity physical activity; MVPA: moderate-to-vigorous physical activity												

Table 14E Continuous glucose monitor outcome descriptive data for *REPOSNSE* study participants

	Type 2 diabetes Baseline				***Type 2 diabetes Follow-up***				***Healthy Control***			
	n	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR
HbA1c (%)	*19*	5.59	6.40	7.09	*19*	5.62	6.26	7.01	*24*	4.64	4.83	5.12
Variability SD	*19*	1.45	1.64	1.99	*19*	1.51	1.73	2.13	*24*	0.83	0.86	0.96

Variability %CV	*19*	0.19	0.23	0.26	*19*	0.21	0.22	0.26	*24*	0.15	0.17	0.21
TAR 1 (% of day)	*19*	0.00	0.00	0.52	*19*	0.00	0.00	7.81	*24*	0.00	0.00	0.00
TAR 2 (% of day)	*19*	2.83	10.24	24.10	*19*	3.36	7.99	30.02	*24*	0.00	0.00	0.10
TIR (% of day)	*19*	75.90	89.43	94.66	*19*	55.59	92.01	94.97	*24*	88.18	96.93	99.72
TBR 1 (% of day)	*19*	0.00	0.00	0.74	*19*	0.00	0.17	1.89	*24*	0.28	2.81	10.78
TBR 2 (% of day)	*19*	0.00	0.00	0.13	*19*	0.00	0.00	0.00	*24*	0.00	0.00	0.55
LBGI	*19*	0.07	0.17	1.18	*19*	0.04	0.35	0.94	*24*	1.14	2.78	3.87
HBGI	*19*	1.18	2.44	5.31	*19*	0.96	2.08	8.30	*24*	0.03	0.10	0.18
Hypoglycaemic Events	*19*	0	0	7	*19*	0	0	12	*24*	0	13	27
Severe Hypoglycaemic Events	*19*	0	0	0	*19*	0	0	0	*24*	0	0	8
Hyperglycaemic Events	*19*	4	16	27	*19*	6	14	30	*24*	0	0	0
Severe Hyperglycaemic Events	*19*	0	0	0	*19*	0	0	0	*24*	0	0	0
AUC	*19*	1090.75	1208.22	1671.28	*19*	1032.54	1276.34	1663.74	*24*	655.27	976.30	1088.62

AUC: area under the curve; HbA1c: glycated haemoglobin A1c; HBGI: high blood glucose index; IQR: interquartile range; LBGI: low blood glucose index; SD: standard deviation; TAR: time above range; TBR: time below range; TIR: time in range

Table 14F Clinical and questionnaire outcome descriptive data for *RESPONSE* study participants

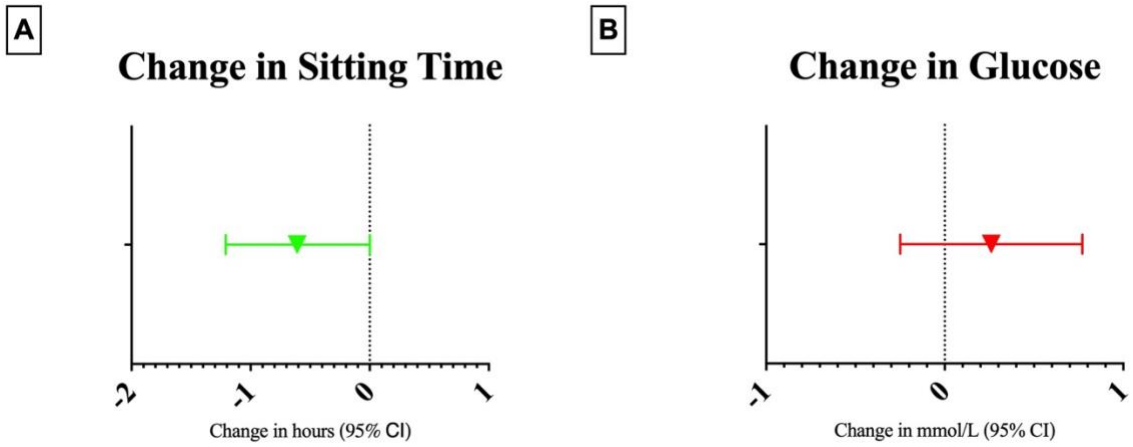
	Type 2 diabetes Baseline				***Type 2 diabetes Follow-up***				***Healthy Control***			
	n	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR	*n*	25 IQR	Median	75 IQR
Weight (kg)	*18*	69.88	76.50	89.03	*18*	68.35	76.65	89.60	*21*	59.05	64.40	89.00
WC (cm)	*19*	94.0	101.9	111.2	*19*	94.0	96.2	104.0	*25*	82.6	91.2	97.6
BMI (kg/m^2)	*18*	25.90	28.14	33.07	*18*	25.38	27.84	33.04	*21*	24.32	26.70	28.11
Sarcopenia (SARC-F)	*18*	0.00	0.00	0.25	*18*	0.00	0.00	1.00	*22*	0.00	0.00	0.00
Depression (HADS-D)	*18*	1.00	4.50	8.00	*18*	1.00	3.50	8.50	*22*	0.00	1.00	4.25
Anxiety (HADS-A)	*18*	3.50	6.50	9.25	*18*	2.75	5.00	10.25	*22*	2.00	4.50	8.25
Breathlessness (mMRC Dyspnoea Scale)	*18*	0.0	1.0	1.0	*18*	0.0	0.5	1.0	*22*	0.0	0.0	0.0
Fatigue (CFQ-11)	*18*	11	12	15	*18*	9	11	15	*22*	5	11	13
Usual Diet (UKDDQ)	*18*	3.09	3.50	3.96	*18*	3.17	3.62	4.00	*22*	3.14	3.62	3.91
Sleep (MEQ)	*18*	48.75	58.50	63.00	*18*	52.50	60.00	63.25	*23*	51.00	59.00	65.00
Muscular Pain and Function (NMQ)	*17*	30.0	33.0	41.0	*17*	32.0	35.0	41.0	*21*	29.5	33.0	36.5
Physical Disability (WHO-DAS)	*18*	3.50	13.50	33.50	*18*	1.00	10.50	40.25	*22*	0.00	1.00	6.25
Quality of Life (EQ-5D-5L VAS)	*18*	57.50	82.50	91.25	*18*	70.00	80.00	91.25	*22*	70.00	90.00	95.00

SARC-F: cumulative score ranges from 0 (low risk of sarcopenia) to 10 (high risk of sarcopenia); HADS: each domain is scored from 0-21 (0-7 normal, 8-10 borderline abnormal, 11-21 abnormal); mMRC Dyspnoea Scale: score ranges from 0 (no breathlessness) to 4 (severe breathlessness); CFQ-11: global score ranges from 0 (no fatigue) to 33 (severe fatigue); UKDDQ: aggregate score ranges from 0 (very poor diet) to 5 (very

healthy diet); MEQ: scores 16-41 indicate "evening types", 42-58 indicate "intermediate types", and 59-86 indicate "morning types"; NMQ: cumulative score ranges from 27 (no musculoskeletal pain) to 68 (regular musculoskeletal pain); WHO-DAS: summary score ranges from 0 (no disability) to 100 (severe disability); EQ-5D-5L VAS ranges from 0 (worst imaginable health) to 100 (best imaginable health) BMI: body mass index; IQR: interquartile range; WC: waist circumference

4.3.2 Primary Outcomes

Post-intervention, participants decreased their overall activPAL derived sitting time by 0.61 hours [95% CI 0.00, 1.21] (Figure 19, Panel A). There was no significant change in glucose, though results do appear to trend upwards (0.26 [-0.25, 0.77]) (Figure 19, Panel B). Note, the difference in direction of change is likely due to two outliers who raised the group mean without severe impact on median values.



**Cohen's D: Change in sitting time = 0.246; change in glucose = 0.145*

Figure 19 Change in primary outcomes after the *RESPONSE* study intervention
CI: confidence interval

These findings appear to be supported by the change in the difference between the healthy control group compared to the T2D group at baseline and follow-up. Table 15 shows the difference between baseline data for the T2D group and baseline data for the healthy control group, alongside the difference between follow-up data for the T2D group and baseline data for the healthy control group.

Table 15 Differences between primary outcomes between type 2 diabetes and health control *RESPONSE* study participants

	Difference (T2D-BL vs Healthy Control-BL)	***95% CI***	***p***	***Difference (T2D-FU vs Healthy Control-BL)***	***95%CI***	***p***
Sitting Time (hours)	0.63	-0.56, 1.81	0.300	-0.22	-1.42, 0.98	0.722
Glucose (mmol/L)	2.36	1.63, 3.09	**<0.001**	2.70	1.74, 3.66	**<0.001**

p < 0.05 values in bold
Model adjusted for age and sex

BL: baseline; CI: confidence interval; FU: follow-up; T2D: type 2 diabetes

4.3.3 Secondary Outcomes

PF and PA

After the intervention, participants saw improvements to PF measures: 4-MGST decreased by 0.33 seconds [0.15, 0.50]; overall SPPB increased by 1.63 points [1.08, 2.18]; and STS-60 reps increased by 4.47 [3.22, 5.72] (Table 16A). MAT-sf score and HGS also increased, though these did not reach statistical significance (1.55 [-0.36, 3.46] points and 1.28 [0.68, 3.24] kilograms, respectively).

Table 16A Change in physical function outcomes after the *RESPONSE* study intervention

	Change	***95% CI***	***p***
MAT-sf (points)	1.55	-0.36, 3.46	0.111
STS-60 (repetitions)	4.47	3.22, 5.72	**<0.001**
4-MGST (sec)	-0.33	-0.50, -0.15	**<0.001**
L-HGS (kg)	0.22	-0.29, 2.74	0.862
R-HGS (kg)	1.28	-0.68, 3.24	0.201
SPPB (cumulative score)	1.63	1.08, 2.18	**<0.001**

p < 0.05 values in bold
4-MGST: 4-meter gait speed test; CI: confidence interval; L-HGS: left handgrip strength; MAT-sf: mobility assessment tool – short form; R-HGS: right handgrip strength; SPPB: short physical performance battery; STS-60: sit-to-stand-60

These changes are reflected in the change in the difference between the healthy control group compared to the T2D group at baseline and follow-up (Table 16B). For example, whilst those with T2D took over 6 repetitions less than healthy controls at baseline (p<0.001), the difference had reduced to 2 repetitions at follow-up (p=0.289).

Table 16B Differences between physical function outcomes between T2D and health control *RESPONSE* study participants

	Difference (T2D-BL vs Healthy Control-BL)	***95% CI***	***p***	***Difference (T2D-FU vs Healthy Control-BL)***	***95%CI***	***p***
MAT-sf (points)	-5.63	-9.41, -1.85	**0.004**	-4.20	-7.36, -1.03	**0.009**
STS-60 (repetitions)	-6.16	-9.71, -2.62	**<0.001**	-2.05	-5.84, 1.74	0.289
4-MGST (sec)	-0.00	-0.35, 0.35	0.994	-0.32	-0.63, 0.00	0.052
L-HGS (kg)	-3.20	-7.02, 0.62	0.101	-2.97	-7.59, 1.65	0.208
R-HGS (kg)	-1.92	-5.64, 1.80	0.311	-1.62	-5.66, 2.43	0.434
SPPB (cumulative Score)	-0.81	-1.71, 0.09	0.079	0.94	0.34, 1.55	**0.003**

p < 0.05 values in bold
Model adjusted for age and sex
4-MGST: 4-meter gait speed test; BL: baseline; CI: confidence interval; FU: follow-up; L-HGS: left handgrip strength; MAT-sf: mobility assessment tool – short form; R-HGS: right handgrip strength; SPPB: short physical performance battery; STS-60: sit-to-stand-60; T2D: type 2 diabetes

Aside from overall sitting time, there were no other statistically significant changes to activPAL outcomes (Table 17A). However, there were non-significant reductions in prolonged sitting (-0.40 hours [-0.87, 0.06]) as well as increases in overall steps/day (473 steps [-571, 1517]) and brisk steps/day (306 steps [-615, 1228]). There was also a reduction in the proportion of time spent sitting (-1.98% [-4.98, 1.03]). The reduction in proportion of time spent sitting was accompanied by an increase in the proportion of time spent standing (1.01% [-1.39, 3.41]) and stepping (0.97% [-0.20, 2.13]).

Table 17A Change in activPAL outcomes after the *RESPONSE* study intervention

	Change	***95% CI***	***p***
Waking Wear Time (hours)	-0.45	-1.03, 0.13	0.125
Prolonged Sitting Time (30+ min bouts) (hours)	-0.40	-0.87, 0.06	0.089
Prolonged Sitting Bouts (30+ min bouts)	-0.47	-1.08, 0.13	0.127
% waking wear time sitting	-1.98	-4.98, 1.03	0.197
% waking wear time prolonged sitting (30+ min bouts)	-1.25	-4.82, 2.32	0.493
Stepping Time (hours)	0.09	-0.09, 0.27	0.306
Steps/day	472.63	-571.24, 1516.50	0.375
Brisk Stepping Time (hours)	0.04	-0.09, 0.17	0.559
Brisk Steps/day	306.32	-615.06, 1227.69	0.515
Brisk Stepping Time (1-min bouts) (hours)	0.02	-0.12, 0.15	0.790
Brisk Steps/day (1-min bouts)	165.47	-786.00, 1116.95	0.733
% waking wear time stepping	0.97	-0.20, 2.13	0.104
Standing Time (hours)	0.06	-0.34, 0.47	0.761
% waking wear time standing	1.01	-1.39, 3.41	0.408
Sit to Stand Transitions	-0.53	-4.26, 3.21	0.783

p < 0.05 values in bold
CI: confidence interval

Comparison to the healthy control group at both time points (Table 17B) also showed that, after the intervention, participants in the T2D group had brought their markers of stepping and brisk stepping closer to those in the healthy control group.

Table 17B Differences between activPAL outcomes between type 2 diabetes and health control *RESPONSE* study participants

	Difference (T2D-BL vs Healthy Control-BL)	***95% CI***	***p***	***Difference (T2D-FU vs Healthy Control-BL)***	***95%CI***	***p***
Waking Wear Time (hours)	0.38	-0.42, 1.19	0.348	-0.21	-1.01, 0.59	0.608
Prolonged Sitting Time (30+ min bouts) (hours)	-0.03	-1.23, 1.16	0.953	-0.57	-1.73, 0.60	0.339

Prolonged Sitting Bouts (30+ min bouts)	0.27	-0.82, 1.37	0.626	-0.38	-1.55, 0.78	0.520
% waking wear time sitting	2.47	-4.79, 9.73	0.505	-0.11	-8.10, 7.88	0.979
% waking wear time prolonged sitting (30+ min bouts)	-1.48	-8.78, 5.83	0.692	-2.78	-10.65, 5.09	0.489
Stepping Time (hours)	-0.61	-1.03, -0.20	**0.004**	-0.47	-0.88, -0.07	**0.021**
Steps/day	-3131	-5526, -736	**0.010**	-2422	-4793, -51	**0.045**
Brisk Stepping Time (hours)	-0.26	-0.59, 0.07	0.125	-0.19	-0.54, 0.15	0.265
Brisk Steps/day	-1818	-4119, 483	0.122	-1333	-3704, 1058	0.276
Brisk Stepping Time (1-min bouts) (hours)	-0.20	-0.50, 0.09	0.174	-0.18	-0.50, 0.14	0.280
Brisk Steps/day (1-min bouts)	-1386	-3407, 635	0.179	-1151	-3371, 1068	0.309
% waking wear time stepping	-4.37	-6.90, -1.85	**<0.001**	-3.10	-5.66, -0.54	**0.018**
Standing Time (hours)	0.37	-0.62, 1.36	0.461	0.48	-0.60, 1.56	0.382
% waking wear time standing	1.90	-4.22, 8.01	0.543	3.21	-3.48, 9.90	0.347
Sit to Stand Transitions	-1.60	-6.35, 3.15	0.508	-3.57	-11.91, 4.77	0.402

p < 0.05 values in bold
Model adjusted for age and sex
BL: baseline; CI: confidence interval; FU: follow-up; T2D: type 2 diabetes

Average acceleration and intensity gradient appeared to increase post-intervention, but only intensity gradient reached statistical significance (1.38 [-0.39, 3.14] and 0.07 [0.02, 0.13], respectively) (Table 18A). There was a significant decrease in LPA and sleep duration (-40.65 [-63.09, -18.21] minutes and -0.43 [-0.69, -0.18] hours, respectively). No other GENEActiv variables had statistically significant results; however, the direction of change in MVPA and step cadence variables indicated a beneficial effect between baseline and follow-up.

Table 18A Change in GENEActiv outcomes after the *RESPONSE* study intervention

	Change	*95% CI*	*p*
Acceleration (mg)	1.38	-0.39, 3.14	0.126
Intensity Gradient	0.07	0.02, 0.13	**0.007**
MVPA Time (1-min bouts) (mins)	1.28	-6.09, 8.65	0.734
MVPA Time (mins)	4.35	-5.77, 14.47	0.400
Peak 30-minute Step Cadence (continuous) (mg)	8.73	-6.49, 23.95	0.261
Peak 30-minute Step Cadence (total) (mg)	8.50	-2.29, 19.28	0.122
Peak 10-minute Step Cadence (continuous) (mg)	15.39	-3.30, 34.07	0.106
Peak 10-minute Step Cadence (total) (mg)	17.18	-0.89, 35.24	0.062
LPA (mins)	-40.65	-63.09, -18.21	**<0.001**
Sedentary Time (mins)	26.93	-14.86, 68.73	0.207
Sleep Duration (hours)	-0.43	-0.69, -0.18	**<0.001**

p < 0.05 values in bold
CI: confidence interval; LPA: light-intensity physical activity; MVPA: moderate-to-vigorous physical activity

Comparisons to the healthy control group are shown in Table 18B.

Table 18B Differences between GENEActiv outcomes between type 2 diabetes and health control *RESPONSE* study participants

	Difference (T2D-BL vs Healthy Control-BL)	***95% CI***	***p***	***Difference (T2D-FU vs Healthy Control-BL)***	***95%CI***	***p***
Acceleration (mg)	-8.25	-14.66, -1.85	**0.012**	-6.52	-12.81, -0.23	**0.042**
Intensity Gradient	-0.17	-0.37, 0.04	0.105	-0.09	-0.30, 0.11	0.363
MVPA Time (1-min bouts) (mins)	-29.17	-48.66, -9.68	**0.003**	-27.59	-48.15, -7.03	**0.009**
MVPA Time (mins)	-46.03	-74.35, -17.70	**0.001**	-39.54	-69.21, -9.86	**0.009**
Peak 30-minute Step Cadence (continuous) (mg)	-57.81	-169.28, 53.67	0.309	-48.81	-161.08, 63.46	0.394
Peak 30-minute Step Cadence (total) (mg)	-58.53	-163.58, 46.52	0.275	-47.83	-153.48, 57.83	0.375
Peak 10-minute Step Cadence (continuous) (mg)	-69.79	-183.20, 43.63	0.228	-53.51	-168.84, 61.81	0.363
Peak 10-minute Step Cadence (total) (mg)	-85.06	-202.59, 32.59	0.156	-71.24	-189.98, 47.51	0.240
LPA (mins)	-44.23	-105.16, 16.69	0.155	-79.98	-138.05, -21.92	**0.007**
Sedentary Time (mins)	59.61	-10.52, 129.74	0.096	71.05	2.98, 139.11	**0.041**
Sleep Duration (hours)	0.19	-0.64, 1.02	0.650	-0.15	-0.89, 0.60	0.703

p < 0.05 values in bold
Model adjusted for age and sex
BL: baseline; CI: confidence interval; FU: follow-up; LPA: light-intensity physical activity; MVPA: moderate-to-vigorous physical activity; T2D: type 2 diabetes

Other Glucose Outcomes

The only statistically significant change to other glucose variables from CGM data was an increase in TAR1 (2.17 % [0.02, 4.32]) (Data in Table 19A).

Table 19A Change in continuous glucose monitor outcomes after the *RESPONSE* study intervention

	Change	***95% CI***	***p***
HbA1c (%)	0.17	-0.16, 0.49	0.311
Variability SD	0.09	-0.06, 0.23	0.228
Variability %CV	0.01	-0.01, 0.03	0.420
TAR 1 (% of day)	2.17	0.02, 4.32	**0.048**
TAR 2 (% of day)	4.97	-2.20, 12.14	0.174
TIR (% of day)	-4.79	-11.84, 2.27	0.184
TBR 1 (% of day)	0.10	-0.75, 0.94	0.826
TBR 2 (% of day)	-0.20	-0.54, 0.15	0.263
LBGI	-0.06	-0.36, 0.24	0.676
HBGI	0.92	-0.34, 2.18	0.154
Hypoglycaemic Events	0.79	-4.90, 6.48	0.786
Severe Hypoglycaemic Events	-1.53	-3.45, 0.40	0.120
Hyperglycaemic Events	-0.58	-6.01, 4.85	0.835
Severe Hyperglycaemic Events	2.84	-2.58, 8.26	0.304
AUC	72.61	-192.84, 338.05	0.592

p < 0.05 values in bold
AUC: area under the curve; CI: confidence interval; HbA1c: glycated haemoglobin A1c; HBGI: high blood glucose index; IQR: interquartile range; LBGI: low blood glucose index; SD: standard deviation; TAR: time above range; TBR: time below range; TIR: time in range

The comparisons to the healthy control group are shown in Table 19B. Of note, compared to the healthy control group, incidents of hypoglycaemic events and severe hypoglycaemic events were lower in the T2D group at both baseline (-9.51 [-11.80, -7.23 events and -2.76 [-3.90, -1.62] events, respectively) and follow-up (-8.36 [-10.54, -6.18] events and -3.01 [-3.93, -2.09] events, respectively) (Table 19B). In the T2D group, TBR 1 at baseline was also significantly -7.63% [-14.40, -0.86] lower than in the healthy control group.

Table 19B Differences between continuous glucose monitor outcomes between type 2 diabetes and health control *RESPONSE* study participants

	Difference (T2D-BL vs Healthy Control-BL)	***95% CI***	***p***	***Difference (T2D-FU vs Healthy Control-BL)***	***95%CI***	***p***
HbA1c (%)	1.49	1.02, 1.95	<**0.001**	1.54	0.94, 2.14	<**0.001**
Variability SD	0.75	0.33, 1.17	<**0.001**	1.10	0.59, 1.61	<**0.001**

Variability %CV	0.04	-0.02, 0.09	0.162	0.08	0.02, 0.14	**0.009**
TAR 1 (% of day)	1.33	-0.59, 3.24	0.174	3.49	-0.15, 7.14	0.060
TAR 2 (% of day)	14.18	7.03, 21.33	**<0.001**	17.84	5.64, 30.04	**0.004**
TIR (% of day)	-6.76	-16.63, 3.11	0.179	-11.40	-25.36, 2.56	0.109
TBR 1 (% of day)	-7.63	-14.40, -0.86	**0.027**	-6.44	-13.26, 0.38	0.064
TBR 2 (% of day)	-0.31	-1.12, 0.51	0.458	-0.29	-1.04, 0.47	0.459
LBGI	-2.20	-3.30, -1.10	**<0.001**	-2.02	-3.10, -0.95	**<0.001**
HBGI	3.12	1.64, 4.61	**<0.001**	3.85	1.47, 6.23	**0.002**
Hypoglycaemic Events	-9.51	-11.80, -7.23	**<0.001**	-8.36	-10.54, -6.18	**<0.001**
Severe Hypoglycaemic Events	-2.76	-3.90, -1.62	**<0.001**	-3.01	-3.93, -2.09	**<0.001**
Hyperglycaemic Events	18.45	15.91, 20.99	**<0.001**	14.26	11.88, 16.64	**<0.001**
Severe Hyperglycaemic Events	1.60	0.81, 2.39	**<0.001**	1.25	0.55, 1.95	**<0.001**
AUC	325.25	35.91, 614.59	**0.028**	401.85	72.26, 731.44	**0.017**

p < 0.05 values in bold
Model adjusted for age and sex
AUC: area under the curve; BL: baseline; CI: confidence interval; FU: follow-up; HbA1c: glycated haemoglobin A1c; HBGI: high blood glucose index; IQR: interquartile range; LBGI: low blood glucose index; SD: standard deviation; T2D: type 2 diabetes; TAR: time above range; TBR: time below range; TIR: time in range

Clinical and Questionnaire Outcomes

There was a significant decrease in weight (-0.93 kg [-1.78, -0.09]) and BMI (-0.32 kg/m^2 [-0.61, -0.03]) following the intervention (Table 20). Several other markers which did not reach statistical significance are also trending in a beneficial direction (WC -1.08 cm [-2.87, 0.71]; depression -0.50 [-1.69, 0.69] HADS-D; anxiety -0.63 [-1.82, 0.56] HADS-A; fatigue -0.97 [-2.42, 0.48] CFQ-11; muscular pain and function -0.69 [-3.20, 11.06] NMQ; and EQ-VAS 3.93 [-3.20, 11.06]). There were no notable changes to sarcopenia (SARC-F 0.14 [-0.12, 0.40]), breathlessness (mMRC Dyspnoea Scale 0.05 [-0.21, 0.30]), usual diet (UKDDQ 0.09 [-0.04, 0.22]), or sleep (MEQ 0.47 [-1.20, 2.13]).

Table 20 Change in clinical and questionnaire outcomes after the *RESPONSE* study intervention

	Change	***95% CI***	***p***
Weight (kg)	-0.93	-1.78, -0.09	**0.031**

WC (cm)	-1.08	-2.87, 0.71	0.237
BMI (kg/m^2)	-0.32	-0.61, -0.03	**0.029**
Sarcopenia (SARC-F)	0.14	-0.12, 0.40	0.303
Depression (HADS-D)	-0.50	-1.69, 0.69	0.411
Anxiety (HADS-A)	-0.63	-1.82, 0.56	0.298
Breathlessness (mMRC Dyspnoea Scale)	0.05	-0.21, 0.30	0.714
Fatigue (CFQ-11)	-0.97	-2.42, 0.48	0.190
Usual Diet (UKDDQ)	0.09	-0.04, 0.22	0.162
Sleep (MEQ)	0.47	-1.20, 2.13	0.581
Muscular Pain and Function (NMQ)	-0.69	-2.85, 1.47	0.532
Physical Disability (WHO-DAS)	3.93	-3.20, 11.06	0.280

$p < 0.05$ values in bold
BMI: body mass index; CI: confidence interval; WC: waist circumference

4.3.4 Remote Testing

Participants were given the option to complete assessments remotely. However, only one participant opted for this. It is therefore not possible to conduct any formal statistical testing on the differences between testing modalities. Informal analysis however revealed no notable differences in their results compared to the group average.

4.3.5 Recruitment and Retention

The overall response rate from the 703 invitations sent for participation in the intervention was 5.26%. Of note is that this study was conducted in Leicestershire, UK – an area which was subject to various local lockdowns in addition to the national lockdowns, due to large numbers of people in the county testing positive for COVID-19 (387). The study did not succeed in recruiting the planned 21 participants required to achieve 90% power. The study did complete baseline measures with 21 participants; however, 2 participants withdrew from the study before the start of the intervention. All 19 participants who began the intervention completed follow-up at 4 weeks. Based on the sample size calculations conducted during initial study design, post-hoc power calculation revealed that by having 19 participants complete the intervention, my analysis was able to detect a reduction in glucose from baseline of 0.8 mmol/L with 86.9% power.

4.3.6 Online Education Programme

Participants were asked to complete questionnaires after follow-up measures to better understand their experiences of different aspects of the intervention (Tables 21-23).

In questionnaires, participants were asked to present their opinions of various other aspects of the intervention and its success. Of the participants who returned completed process

evaluation questionnaires (n = 11; 52.4% of the total sample), three stated they had partially completed the online education programme and eight stated that they had completed the programme in full; however, the "case studies" section appears to have been less well adhered to (Table 21). The online education programme scored highly for increasing participants' awareness of the health consequences associated with excessive sitting (4.0 ± 1.10 on a scale of 1 to 5, with 5 being the most favourable rating). The lowest rating for the online education programme came from participant's opinions on the duration – scoring 3.64 ± 1.03.

As a result of the online education programme, participants reported a wide range of strategies that they implemented, including: "stand while watching TV"; "use the watch as a prompt"; "when making a drink at night, do exercises"; "walk after breakfast and before dinner"; "use stairs at work"; "walk to see people rather than phone"; "avoid using car for journeys less than a mile"; "standing at computer". They also reported a number of barriers to them breaking up their time spent engaging in SB, such as; "being out with friends"; "tiredness"; "television"; "motivation"; "lifestyle has become increasingly sedentary"; "apps not compatible"; and "knees find walking hard work".

Table 21 Participant responses to the post-follow-up questionnaire – online education programme

Aspects of the online education programme	***Number of participants who completed programme (% of questionnaire responses)***	***Mean usefulness (1-5; not at all useful – extremely useful)***	***SD***
Sitting time worksheet	10 (90.9%)	3.90	0.99
Goal setting worksheet	9 (81.8%)	3.78	1.20
Top tips worksheet	9 (81.8%)	4.22	0.67
Animations	10 (90.9%)	3.60	1.08
Case studies	6 (54.6%)	4.00	1.10
Overall review of the online education programme		***Mean agreement (1-5; strongly disagree – strongly agree)***	***SD***
The level of the programme was appropriate		3.82	1.08
The length of the programme was appropriate		3.64	1.03
The programme increased my awareness of the health consequences of sitting too much		4.00	1.10
The health consequences covered in the programme motivated me to make a change to the time I spend sitting		3.64	1.12

The health benefits of reducing and breaking up sitting motivated me to make a change to the time I spend sitting		3.73	1.10
Overall, the programme motivated me to make a change to the time I spend sitting		3.73	1.10
SD: standard deviation			

In free-text sections of the questionnaires, several participants reported that the programme encouraged them to "break up sitting time more"; "become less sedentary"; and "to stand more often". They also reported that the programme highlighted "the importance of moving to help with diabetes"; "a little exercise frequently helps diabetes"; and "more healthy eating and some exercise benefit your health and reduce blood sugar levels".

4.3.7 Self-monitoring Device

As part of the questionnaires, participants were asked to A: rate the self-monitoring device for various qualities based on its ease of use and how much they felt it helped them (Table 22). All participants who returned questionnaires (n = 11; 52.4% of the total sample) stated they had used the self-monitoring device. Five indicated that they planned to purchase something similar in the future. Participants rated the *Hama Fit Watch 4900* smartwatch self-monitoring device highly for various qualities with the exception of obtrusiveness; scores suggest that they may have found it mildly obtrusive. Participants did not report using any of the other self-monitoring tools detailed in the online education programme.

Table 22 Participant responses to the post-follow-up questionnaire – self-monitoring device

Watch qualities rated 1-5 for the following:	***Mean score (1-5; lowest – highest)***	***SD***
Battery life	4.27	1.27
Ease of charging	4.40	0.97
Ease of use	4.46	1.04
Obtrusiveness	2.82	1.60
Usefulness	4.70	0.48
Encouragement	4.10	1.20
SD: standard deviation		

4.3.8 Coaching Calls

Coaching calls were fairly well attended – 84%, 79%, 74%, and 100% of participants attended Coaching Calls 1, 2, 3, and 4, respectively (Table 23). The prevailing reasons for participants not attending coaching calls were the participants not responding to researcher

calls or the participant reporting feeling unwell (Table 24). At the end of each coaching call, participants were asked to rate their feelings on a scale of 1 to 10 about the week ahead based on two questions: 1. "how important is it for you to break up your sitting?" and 2. "how confident are you that you will be able to break up your sitting?". Responses to both were fairly high, with the lowest average response for Q1 coming in Coaching Call 2 (8.87 ± 0.99) and the lowest response for Q2 coming in Coaching Call 1 (9.31 ± 0.79) (Table 23).

Table 23 RESPONSE study coaching call attendance

	Baseline	***Coaching Call 1***	***Coaching Call 2***	***Coaching Call 3***	***Coaching Call 4***	***Follow-up***
Number of participants who attended (% of total sample)	21 (100%)	16 (76.2%)	15 (71.4%)	14 (66.7%)	19 (90.5%)	19 (90.5%)
Duration (mean minutes per call)	37.33	19.67	13.00	11.43	10.84	30.53

	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*	*Mean*	*SD*
Q1: How important is it for you to break up your sitting? (1-10; very unimportant – very important)	9.31	0.95	8.87	0.99	9.21	0.98	8.90	0.81
Q2: How confident are you that you will be able to break up your sitting? (1-10; not at all confident – completely confident)	9.31	0.79	9.47	0.64	9.64	0.50	9.47	0.70

SD: standard deviation

Table 24 Reasons for coaching call non-attendance during the RESPONSE study

Coaching Call non-attendance Reasons across all four calls	
No response	5
No call scheduled	1
Participant unwell	3
Participant had to work	1

4.3.9 Safety

There were no adverse intervention-related outcomes reported during the study.

4.4 Discussion

The aim of this chapter was to report on a 4-week personalised intervention designed to reduce sitting time through PA breaks in SB in people with T2D or prediabetes, and assess the potential impact upon glucose control and markers of PF and cardiometabolic health. The results demonstrated that although activPAL derived sitting time was reduced by 36.6 minutes at follow-up, it is unlikely that this is purely due to behaviour change; as device wear time also decreased by 27 minutes. Despite the potential changes to sitting time, there did not appear to be any impact on glucose control. However, there were several notable improvements to markers of PF and the intensity profile of habitual daily PA.

Sitting Time and PA

Data from the activPAL device suggested that sitting time at follow-up was approximately 35 minutes lower than at baseline. Although, in the present analysis, device waking wear-time was also lower at follow-up than at baseline. Though not statistically significant, the proportion of waking wear-time spent in different behaviours is promising, with around a 2% decrease in sitting time accompanying a 2% increase in standing and stepping time – which would equate to around an 18-minute reallocation of sitting time to either standing or stepping. This is comparable to SB interventions that have been conducted previously (388) and is close to a previously published MCID of 30 minutes (389). Participants in a behavioural intervention study in Italy were also able to reduce their SB as well as increasing PA over 3 years (390). In the study, average sedentary time for the intervention group was 48 minutes (-0.8 hours [95% CI -1.0, -0.5]) lower than the usual care group after 3 years. However, there are several sitting time interventions that have proved unsuccessful in changing behaviours (261, 391). For example, a recent pilot study investigating the efficacy of a SB intervention in people with chronic kidney disease found that although the intervention was initially successful, the results were not maintained long-term (392). This chronic kidney disease study – implementing the *Sit Less, Interact, Move More* intervention – was similar in structure to the *RESPONSE* study. Participants were provided with access to an education programme, shown graphic displays of accelerometer data and given feedback on when they were most sedentary, and were instructed to break up sitting time at least once per hour. The participants decreased their sitting time by 43 minutes [95% CI 17, 69] at week twenty, but this was largely attenuated by week twenty-four to 18 minutes (10, 46). It may also be important to note the duration of the present intervention – cancer patients receiving a text-based intervention to increase PA and reduce SB over 12 weeks saw increases in MVPA (53 minutes [95% CI 2.9, 103.5] greater

than usual care) at 4 weeks, but no significant change to SB (393). However, at 12 weeks, participants receiving the text-based intervention were engaging in more MVPA (67 minutes [24.0, 110.6] greater than usual care) and less SB (48 minutes [5.6, 89.9] less than usual care). There are a number of potential factors that can influence the success of such interventions. A recent systematic review of interventions designed at reducing SB and increasing PA highlighted several key factors influencing change in behaviours: barriers (e.g. workplace staffing and scheduling); facilitators to intervention delivery (e.g. employer/co-worker/friend and family flexibility); contextual factors (e.g. usual lifestyle and religious events); and individual factors (e.g. pain, tiredness, age, and individual preference) (394). Therefore, future interventions in this population may need to be more holistic, with the inclusion of environmental restructuring.

In addition to the activPAL data, the intensity gradient from the GENEActiv saw a significant increase post-intervention (0.07 [0.02, 0.13]) and became less negative when compared to the healthy control. This is an important development to note as research has recently demonstrated that improving the intensity profile can have substantial improvements to health outcomes, even when volume is not altered (395). Further, average daily acceleration from the GENEActiv increased by 1.38 *m*g. Previous studies have suggested that the MCID for average daily acceleration in inactive adults is 1 *m*g (396); being related to a 2-9% decreased risk of cardiovascular disease morbidity and all-cause mortality rates (178, 240, 397). It should be noted that there is potential for the activities that intervention participants used to break up sedentary time to have an impact on the GENEActiv's measurement of PA time due to the movement patterns involved. For example, exercises like biceps curls and arm circles might increase PA registered by a wrist-worn monitor (GENEActiv), but may not necessarily register a break in sitting time from a thigh-worn monitor (activPAL) if done in a seated position.

Glucose Control

Although not statistically significant, the direction of change in CGM variables indicated an undesirable effect between baseline and follow-up. The unfavourable changes to CGM outcomes may be explained by the distribution of the participants. There were two potential outliers whose data may have skewed the results; however, the decision was taken not to remove them as their results still fell within expected values for this population. This may go some way to explaining the disparity in median values which decreased after intervention compared to GEE analysis which increased – a small number of participants with

higher glucose values at baseline increasing alongside modest changes throughout the rest of the cohort would pull the mean values up while having less of an impact on median values.

Despite eliciting a reduction in sitting time, the intervention in the present study was unable to elicit significant beneficial changes to most glucose markers. The only glucose marker which saw a statistically significant change post-intervention was TAR1 – increasing by 2.17%. This is, of course, not a desirable outcome. However, it is of note that one participant experienced an uncharacteristically large increase in TAR1, and it is likely that this caused the significant increase throughout the cohort. Indeed, when the data were re-analysed excluding this participant, the TAR1 data were not statistically significant (1.28%; 95% CI -0.12, 2.69, p=0.074). With a small sample, such as in the present study, it can be difficult to identify and negate the impact that outlying individuals may have on analysis.

Previously, breaking sedentary time with PA has been found to improve markers of glucose control, including glucose, insulin, and triacylglycerol (258). Outcomes from diabetes prevention programmes have also found that people with lower levels of time spent in SB have lower risk of developing T2D (398). Whilst it is possible that the negative findings for glucose regulation were due to the limited nature of the behaviour change, it is worth noting they are also consistent with a recent analysis of the associations between daily and prolonged sitting and CGM-measured glucose concentrations in people with overweight and obesity which found there to be no association (399). Additionally, there are studies that have determined that the associations between breaks in sedentary time and 2-hour glucose levels may be attenuated after adjustment for BMI (207). This appears to corroborate other previously published studies that have contradicted the proposed link between breaks in SB and markers of IR and lipid variables (223, 400).

Interestingly, there was a higher incidence of hypoglycaemia in people without T2D than in those with. This may be partly due to the FreeStyle Libre Pro being less accurate in the hypoglycaemic range (401). It is also possible that the cut-off used to determine hypoglycaemia (3.9 mmol/L) by the CGM in this study was inappropriate for a healthy population – previous investigations using CGM-determined glucose profiles suggest that a cut-off of 3.0 mmol/L may be more appropriate for healthy, non-diabetic people (402). For example, when comparing TBR 2 (<3.0mmol/l) differences between the groups, we only see 0.31% [-1.12, 0.51] differences at baseline and -0.29% [-1.04, 0.47] difference at follow-up.

Physical Function

Compared to pre-intervention measurements, post-intervention there were a number of notable beneficial changes to markers of PF. These changes appear to be promising – MCID for the STS-60 has been reported as 2 repetitions (345). The changes from baseline to follow-up far exceed this (4 repetitions). Indeed, median STS-60 scores at follow-up bring the T2D cohort in-line with the results from the healthy control group, and differences between the follow-up and healthy control groups are no longer statistically significant. The group also exceeded the MCID for the SPPB cumulative score (1.6 points), which has been cited in other clinical groups as being >1 point (403, 404). Prior to the intervention, there were six participants scoring <10 for the SPPB; which is indicative of impaired PF (95). After the intervention, this number dropped to just one participant. There is a dearth of data investigating the effects of SB interventions on PF in people with T2D – studies have typically focussed on healthy older populations. For example, a study of over 200 older adults found that breaking up sedentary time was associated with beneficial changes to PF (405). Previous meta-analysis investigating chair-based exercise in older adults has found considerable benefits to PF, including HGS (2.10 kg [95% CI 0.76, 3.43]) and STS-30 (2.25 repetitions [0.64, 3.86]) (406). There are also studies that have investigated the replacement of sedentary time with PA time in older adults which have found that replacing 30 minutes of sedentary time with an equal amount of LPA was associated with a 16% decreased risk of frailty (407). Related studies have drawn like conclusions regarding the replacement of sedentary time with MVPA (408). Other similar papers have concluded there to be significant improvements to specific markers of PF with the substitution of SB for PA, such as to the 400m walk test (271). However, the study by Lerma et al. (271) did not identify any significant benefits of substituting sedentary time for PA on SPPB score, as did the present study.

It is worthy of note that the T2D cohort in this study were, on average, 10 years older than the healthy control cohort – a factor which may have influenced PF scores. It may also be worth noting that around 63% of the T2D cohort were receiving treatment with metformin. Whilst, in general, there is a consensus that metformin is likely beneficial for slowing the effects of age on the musculoskeletal system (409, 410), there are studies which have suggested that the drug may in fact induce muscle atrophy through transcriptional regulation of myostatin (411).

Other Measures

The potential changes in sitting time, PF, and PA in the present study appear to have coincided with a reduction in bodyweight (0.93 kg [0.09, 1.78]). WC also appeared to trend downwards, though this was not statistically significant. These factors taken together may be particularly beneficial, as people who maintain weight loss typically report less sitting time than do stable-weight individuals (412). Reductions in weight loss and WC may also go some way to diminishing the risks associated between sitting time with all-cause and CVD mortality (413). More specifically to this cohort, in an assessment of the outcomes from a diabetes prevention programme, each 20-minute reduction in leisure-time SB was associated with a 5% increase in odds of meeting weight-loss goals (414). However, there are studies that have concluded that after accounting for relevant covariates, although the combined association of PA and SB is related to weight loss, the results lack clinical significance (415).

There was not any notable change to results from the SARC-F, mMRC Dyspnoea scale, UKDDQ, NMQ, or MEQ. It is beneficial to note minimal change to usual diet and sleep patterns as these can be highly impactful to glucose control (416-418). Self-reported fatigue scores improved after the intervention – not reaching statistical significance, though within the range of MCID (419). Results from the HADS and EQ-5D-5L appear to be trending in a desirable direction; however, results did not reach statistical significance. Although modest, any improvement in ratings of depression, anxiety, and mood is important within this population, as people with T2D are at considerable risk of depressive disorders, with as many as 1 in 4 people with T2D experiencing depression as a comorbidity (420).

Recruitment, Retention, and Adherence

It is important to understand the benefits and challenges of interventions such as this to inform the design and implementation of future interventions. The study was not able to reach the initial recruitment targets; however, it is possible that the uncertainty surrounding national and local COVID-19 restrictions hindered recruitment to the study (387). Adherence to the intervention was good. Participants who returned process evaluation questionnaires all reported partially or fully completing the online education programme – 8 (72.7% of those who returned questionnaires) reporting have completed the programme in full – a similar percentage to the original *SMART Work and Life* intervention (267). Attendance of weekly coaching calls was good, with a slight decrease in weeks 2 and 3 of the intervention. The use of the *Hama Fit Watch 4900* smartwatch self-monitoring device appeared acceptable to the participants who

ranked it highly; however, there did seem to be a level of obtrusiveness. Participant retention was good – two participants withdrew after baseline measures, but before the start of the intervention. The nineteen participants who completed follow-up represent 90.5% of those who completed baseline measures.

The results of the present study should be used to inform future investigations into the capacity for personalised behavioural interventions to reduce sitting time and elicit beneficial health outcome changes in a range of populations, including T2D. One trial studying the feasibility of the *Frail-LESS* intervention is currently underway investigating a personalised sitting time intervention in frail older adults with an aim to reduce sarcopenia and improve independent living (421). The personalisation in the *Frail-LESS* study differs from the present study in that the researchers are only providing participants with graphical representations and written explanations of their sitting, standing, and stepping behaviours to allow participants to inform their own decisions; whereas, the *RESPONSE* study presented these materials and used them to inform the discussion between the participants and researchers regarding appropriate changes to their sitting behaviours. Further investigation into the effectiveness of these two strategies may be of merit.

4.4.1 Strengths and Limitations

Rate of recruitment to the study based on the number of invitations sent was low; however, was fairly typical for interventions centred around PA (422). Retention to the study, and adherence to the intervention were good and participants reported no adverse effects of taking part. This is particularly of note given that the intervention was set-up and delivered during the highly uncertain and changing restrictions surrounding the COVID-19 pandemic. The study is also strengthened by the use of multiple measures of PF, and by the use of multiple methods of measuring SB and PA. There are several limitations to the study. Due to several COVID-19-related amendments, the study lacked a control arm. As such, it is not possible to determine whether the modest changes to sitting time were a result of the intervention, or natural variation over time. In addition to this, the risk for external factors impacting data is increased – for example, follow-up data collection for several participants coincided with a severe heat wave in the UK (423), which may have acted to reduce PA, increase SB, and increase glucose levels (424). Direct assessments related to cardiometabolic health also had to be removed from the protocol. The use of CGM was therefore a strength in this context, although it does come with some potential limitations. It has been reported that mean daily

glucose, as measured by the FreeStyle Libre, is lower than that derived from point-of-care capillary glucose testing (401). However, other studies have concluded that, in fact, FreeStyle CGM sensors are more accurate than point-of-care capillary glucose testing (425). Though, it is worth noting that these studies have typically been conducted in people with T2D in hospital settings and therefore the results may not apply to people in a community setting. It is possible that improvements to PF could be accredited to a learning effect following the baseline testing battery. However, practice tests were performed in order to minimise this risk. Additionally, the study did not assess whether the behavioural changes or the beneficial changes to PF were maintained after completion of the intervention. Finally, as the study recruited a fairly small number of participants in relation to the number of outcomes, it is important that these data are interpreted based on the overall pattern of the results and not as individual findings.

4.4.2 Conclusion

This study demonstrated that a personalised, remotely delivered, coaching intervention may reduce sitting time and elicit improvements in PF and bodyweight in people with T2D. The COVID-19 pandemic and subsequent restrictions highlighted the need for an overhaul of preconceptions around the delivery of lifestyle interventions. Future research in this area should focus on the development of RCTs to confirm the effects of personalised approaches to reducing sitting time on PF in people with T2D. Future programmes should also look at optimising the individualised aspects of intervention delivery, potentially through automation and user-led personalisation.

5 OVERALL DISCUSSION

5.1 Thesis Summary

This thesis centres around the links step cadence and sitting time can share with PF and cardiometabolic health in people with varying levels of glucose control. It is hoped that by investigating these, future researchers can better understand how to study effective strategies to reduce risk and improve health-related outcomes.

5.1.1 Chapter 2

In Chapter 2 of this thesis, my aim was to investigate the associations between step cadence and PF in healthy older adults and whether these associations were modified when stratifying the data by ethnicity. From this secondary analysis, I was able to determine that compared to older WE people, older SA people take fewer steps/day, brisk steps/day, brisk steps/day in bouts of at least 1-minute, have a lower proportion of overall steps taken at a brisk pace, and average fewer steps/minute for 30- and 60-minute peak step cadence. SAs also scored significantly lower in PF assessment (STS-60). Further to this, in WEs only, brisk steps, proportion of total steps taken at a brisk pace, and 1-, 30-, and 60-minute peak step cadence were all significantly associated with performance in the STS-60. These associations were not observed in the SA participants. The chapter concludes with a number of step guidelines which in older WE people would be associated with improvements in STS-60 scores, and subsequently, PF. This demonstrates the importance of further research into the potential ethnic differences in the responses between step cadence and PF.

5.1.2 Chapter 3

Chapter 3 of this thesis sought to determine the associations between change in a range of step cadence variables and change in markers of cardiometabolic health in people with prediabetes; again, additionally assessing whether these associations would be modified by ethnicity. The chapter concludes that increasing the number of brisk steps/day in this population is associated with modest decreases in WC, BMI, and HbA1c. Increasing brisk steps/day was also associated with a MCID increase in HDL-C. There were also associations between change in slow steps/day and change in BMI; and between 10-minute peak step cadence and change in WC and HDL-C. When stratifying by ethnicity, the results suggest that for SAs only, change in 10-minute peak step cadence is associated with change in BMI and WC. Whereas, in WEs only, change in brisk steps/day and 10-minute peak step cadence is associated with change in HbA1c. Seemingly this was the first study to investigate PA and

cardiometabolic health change data over such a long time period in people with prediabetes and therefore adds to the literature by demonstrating how changing stepping intensity over time could help slow the decline in HbA1c and improve cardiometabolic health in a high-risk population.

5.1.3 Chapter 4

Chapter 4 reports on the design and results of the *RESPONSE* study – a personalised, remote intervention to reduce sitting time in people with T2D or prediabetes aimed at improving glucose control and PF. The chapter concluded that the intervention may reduce overall sitting time, but there was not any improvement in glucose control. It is also important to note that, based on the data available, it is not possible to rule out change in measurement device wear time being a key factor in the apparent change in sitting time. Notwithstanding this, there were several significant improvements to PF and bodyweight after the intervention compared to before. Further, recruitment to the study was good, the intervention was adhered to by participants, with no adverse events, good retention, and promising results for improvements to various health markers, particularly PF. Thus, a larger-scale intervention – ideally an RCT – of this type would garner more generalisable results than previously published, purely lab-based studies looking into reduction and breaks in sitting time (for example (253)).

5.2 Strengths and Limitations

There are considerable strengths to this programme of research. The consistent use of the activPAL device throughout the programme is a strength as it allows for comparisons across different populations. As reported in Chapter 2, the activPAL is a reliable and valid device for measuring step cadence and SB. Consistent use across accelerometer brands is important, as different devices may not produce synchronous data (426, 427). The use of change data in Chapter 3 is also a notable strength of the research. This allowed for the detection of actual change in the step cadence and cardiometabolic health variables over the four years. Whilst still not being causal in nature, it does add another layer of assurance over cross-sectional analysis that the variables were associated with each other over the study period. A further strength of the thesis is the analysis of PF in both older and middle-aged adults. Despite evidence that PF is a clear and present issue within the T2D community, there is a dearth of research investigating groups other than older adults. This research programme also investigated PF across a range of ages and T2D statuses.

However, there are a number of inherent limitations to this programme of research. Due to the emergence of the COVID-19 pandemic within my first year of study, the majority of the programme had to be built around observational research and is therefore limited in concluding association only – not causation. However, this potential limitation is offset by various beneficial factors such as the studies generating novel hypotheses, and being more feasible during times of social restriction compared to RCTs. Additionally, observational studies are typically limited by the span of the data that was collected, meaning there may be potential gaps in the data that cannot be remedied. The COVID-19 pandemic and ongoing restrictions throughout my programme of work severely impacted the originally planned centre piece of my research; a full RCT. The study design and outcomes reported in Chapter 4 had to be adapted to context at the time. In order to minimise participant contact and ensure a programme of work that could be delivered, the planned RCT had to be changed into a simpler before and after study, which required less than half the participants. Unfortunately, this means we cannot rule out other potentially confounding elements from having interfered with the outcomes of the intervention. Additionally, the lack of a control group increases the likelihood of regression to the mean. Further to this, the study did not reach 90% power as planned (86.9% power reached), raising the possibility of type II error and placing a potential question mark over the validity of the results.

5.3 Future Research

Chapters 2 and 3 both highlighted the value of increased stepping intensity as an intervention tool for improving PF and cardiometabolic health markers associated with ageing and cardiometabolic disease. Other research supporting these findings has demonstrated that, in older females (aged 78.9 ± 6.7 years), moderate and vigorous intensity stepping shares a greater association with lower risk of T2D than does light intensity stepping (195). Work in adults aged 60-78 has also demonstrated independent associations between peak step cadence and functional walking capacity (as measured by the 400m walk test) (428). However, it is notable that the strength of the associations in the body of work contained within this thesis, and therefore the effectiveness of any resulting intervention tool may be variable depending on the ethnicity of participants. More work should be conducted to further explore ethnic differences in these associations as this may have implications for PA and SB recommendations that are given to the public. It has already been demonstrated, for example, that different BMI cut-points should be used for determining risk of T2D development in different ethnic groups (429); with particular attention being paid to Black, Hispanic, and Asian groups (430). Perhaps a similar approach is needed for assessing PF risk. It is also possible that different doses, or MCID values, are needed for different health outcomes in different ethnic groups. This theory has already been demonstrated in a recent digital rehabilitation programme for musculoskeletal pain – Hispanic participants in the study reported higher odds of reaching the established MCID for pain; independent of age, BMI, therapy area, education, sex, and employment status compared to non-Hispanic White participants (431). If this concept can be confirmed through further study in diverse populations, this will help with tailoring PA recommendations and prescriptions in the future. The data in this thesis have demonstrated lower PF in SA people compared to WE people, and there are longitudinal data from the US showing that Black and Hispanic people score lower in measures of PF than do White people (432). Per Chapter 2 of this thesis, it would appear that there is an interaction with ethnicity when interrogating the associations between step cadence and PF; therefore, large-scale longitudinal studies are needed that can assess changes in SB and step cadence and their associations with PF and cardiometabolic health in ethnically diverse cohorts. This need is further supported by the results of Chapter 3 of this thesis. The original *PROPELS* intervention was not successful in promoting long-term change to walking behaviour (349). However, there were ethnicity-specific associations between various step cadence variables and markers of cardiometabolic health. There is research that has suggested that specific intervention adaptation is vital for working with ethnic minorities (433). Perhaps future interventions may need to place more

focus on adapting interventions in diverse ethnicities through building trust and community engagement, developing links with existing organisations, assessing risk factors specific to the population, and considering how contextual experiences surrounding ethnicity might influence intervention acceptability and adherence (434). Though the extent to which such an intervention would be beneficial to informing national and international PA guidelines is unclear.

Despite the apparent issues that people with T2D have with impairment to PF, it is frequently seen as an afterthought when assessing the overall health and wellbeing of people with diagnoses and those at high risk of developing T2D. There is a need for researchers and healthcare professionals to recognise functional status as a clinical vital sign – a need that has begun to appear in specific consensus/guideline documents (for example (435)). Current PA recommendations may need to consider the increased risk of impaired PF in people with T2D, and healthcare professionals may need to place more emphasis on the measurement of PF in primary and secondary care and the subsequent introduction of appropriate PA – such as interventions more focussed around breaking up SB with small bouts of PA. It is also important to develop large-scale interventions that bring together more of the vital elements of SB, T2D, and PF – investigating: personalised breaks in SB that work for people with T2D, especially in the context of the emerging mobile health market; and to understand the impact of such an intervention on PF and glucose control. Further, it is important to frame these interventions in the context of NHS and/or NICE guidelines – for example, CGM use has now been approved for T2D by NICE, bolstering the tools available to prompt behaviour change to reduce postprandial glucose spikes (436). A large RCT is currently running in Sweden investigating the effectiveness of a mobile health intervention for reducing SB and increasing PA in people with T2D (437). The programme in Sweden is mainly operated through self-monitoring tools, with little personalisation; however, there are meetings with members of the study team that may guide participants in specific directions based on responses to the intervention. Furthermore, the cost-effectiveness of this intervention is unclear; participants are being given commercial fitness trackers to aid in their self-monitoring – a cost that would likely be unfeasible should such a programme be scaled up to a national level. Additionally, the programme seems to only focus on increasing overall PA through step count targets with no reported targets for different step cadence boundaries.

Work also needs to be done around the methods of delivery of such programmes. Recent analysis has reported that interventions using wearable activity trackers to increase steps per day in people with cardiometabolic conditions are mostly beneficial to older WE males without multimorbidity, reiterating the need to tailor interventions (438). The same study also suggested that face-to-face delivery methods of the tracker by a professional were more effective than interventions self-managed by participants. These are factors that need to be considered when designing future RCTs – in particular, the exploration of how to encourage other demographics, such as females and people from other ethnic backgrounds, to engage with such interventions to a greater degree. Programmes that are investigating very short bouts of PA, such as *Snacktivity*™, to help people meet PA guidelines and reduce SB may yield some promising results in terms of acceptance by the populations in which they are being tested (439). It may be worthwhile to adapt large-scale RCTs, similar to the *PROPELS* study (data reported on in Chapter 3). Although the original intervention (targeted at increasing ambulatory activity) was unsuccessful over the 4-year period (349), there were seemingly health benefits for participants who made changes to markers of step cadence. Perhaps combining the ambitious goals of *PROPELS* with another intervention programme, such as *Snacktivity*™ might encourage more people to increase overall steps and markers of step cadence through short-duration bouts of activity to break up SB. A large-scale intervention such as this would fit well into the NHS Long Term Plan which places particular focus on healthy ageing (376). Further, NICE guidelines (436) and national programmes such as the NHS Diabetes Prevention Programme (6) place emphasis on promoting walking to people with T2D.

5.4 Closing Remarks

It is becoming clearer, as further epidemiological and experimental research is published, that factors like reducing SB and increasing step cadence are important interventional targets for maintaining overall health and wellbeing. These are factors that will likely come to the forefront in coming years (recommendations on limiting SB have already started appearing in PA guidelines (203)). It will also be important to shift towards a focus on 24-hour behaviours centred around how these different behaviours interact with each other.

The programme of research detailed in this thesis has helped to bridge some of the gaps in knowledge surrounding the links between step cadence and SB with PF and cardiometabolic health in a variety of populations including healthy older adults, people with prediabetes, and people with T2D. The research has also helped to bolster the growing trend of research articles that are investigating the potential ethnic differences in these associations.

Given the associations between step cadence and PF in older adults (seen in Chapter 2) and the success that reducing and breaking up time spent sitting can have on PF in people with T2D (detailed in Chapter 4), it is likely that a long-term intervention focussed on SB and step cadence would elicit a beneficial response from PF in these populations. Although the intervention detailed in Chapter 4 did not elicit any changes in glucose control, the associations between change in step cadence and change in cardiometabolic health detailed in Chapter 3 suggest that an intervention which targeted both SB and step cadence may be more beneficial for improving overall cardiometabolic health and PF.

Appendix A1 STATA code for merging all activPAL event files into a single file

```
*************************************************************************
* ActivPal Step
Cadence

                *
* This file merges all event files in a single folder into one file      *
*


                   *
* Predecessor file:
None

             *
* Version number:
2.1

                *
* Author: Danielle
Bodicoat

           *
* Date created:
12/08/2020

             *
*************************************************************************

** WARNING: THE START OF THIS CODE DELETES ANY .DTA FILES YOU HAVE IN THIS
FOLDER **

*** merge all event files into one Stata file ***

* set the folder where the CSV event files are stored >> THIS WILL NEED
EDITING
cd ""

* loop round all CSV files to read in to Stata, add variable with ID
number, then save as .dta file

local datafiles: dir "" files "*.dta"
```

```
foreach datafile of local datafiles {
        rm "`datafile'"
}

local files : dir ""  files "*.csv"

foreach file in `files' {
              insheet using "`file'", comma clear double
              gen id=substr("`file'",1,7)
              save "`file'.dta", replace
}

*combine stata files into one

ssc install fs
fs "*.dta"
append using `r(files)'

*reformat Excel date into stata date format
gen double event_start = round((time+td(30dec1899))*86400)*1000
format event_start %tc
gen date = dofc(event_start)
format date %td

replace id=upper(id)

drop activityscoremeth sum*

rename activitycode0sedentary1standing2 activity

save allevents.dta, replace


*** add in variables from the Summary file from Processing PAL ***

*read in summary data >> THIS WILL NEED EDITING

insheet using "", clear double

sort participantid boutid

rename participantid id
```

```
*create datetime variable

gen date2 = date(date, "DMY")
format date2 %td

drop date invalidreason

*collapse Stepping into one continuous bout

gen activity=0 if activitytype=="Sitting"
replace activity=1 if activitytype=="Standing"
replace activity=2 if activitytype=="Light stepping"|activitytype=="MVPA
stepping"

gen tmp=1 if _n==1
replace tmp=1 if id~=id[_n-1]
replace tmp=1 if id==id[_n-1] & activity~=activity[_n-1]

sort id tmp boutid

by id: gen new_boutid = _n if tmp==1

sort id boutid startdatetime

by id : replace new_boutid = new_boutid[_n-1] if missing(new_boutid) & _n >
1

gen double starttime2=clock(starttime,"hms") if tmp==1
gen double bout_start = date2*24*60*60*1000 + starttime2 if tmp==1
format bout_start %tc

by id : replace bout_start = bout_start[_n-1] if missing(bout_start) & _n >
1

*gen double endtime2=clock(endtime,"hms")
*gen double bout_end = date2*24*60*60*1000 + endtime2

* set bout end as start + interval to make sure every row has an end but
then reset to next start - 1s to make sure bout ends before next one starts
(if just do the latter then last row for each person won't have an end)

drop tmp

gsort id -boutid -enddatetime
```

```
gen tmp=1 if _n==1
replace tmp=1 if id~=id[_n-1]
replace tmp=1 if id==id[_n-1] & activity~=activity[_n-1]

gen double bout_end = bout_start[_n-1] + msofseconds(1) if tmp==1
replace bout_end=bout_start+intervals if _n==1
format bout_end %tc

by id : replace bout_end = bout_end[_n-1] if missing(bout_end) & _n > 1

drop tmp activitytype boutid starttime* endtime* startdatetime enddatetime

rename date2 date

sort id bout_start

collapse (sum) steps (sum) intervals (first) sleep (first) removed (first)
invalid (first) date (first) activity (first) bout_start (first) bout_end,
by(id new_boutid)

save boutdata.dta, replace


***merge the two files together

*rangejoin time startdatetime enddatetime using allevents.dta, by(id)
ssc install rangejoin
ssc install rangestat

rangejoin event_start bout_start bout_end using allevents, by(id activity)

sort id new_boutid cumulativestepcount event_start
drop date_U datacount

rename intervals bout_interval
rename intervals_U event_interval
rename steps bout_steps
rename time event_time

save all.dta, replace

***create step cadence
```

```
gen event_steps=cumulativestepcount-cumulativestepcount[_n-1] if id==id[_n-
1]
replace event_steps=cumulativestepcount if _n==1
replace event_steps=cumulativestepcount if id~=id[_n-1]

gen event_cadence = (event_steps/event_interval)*60*2 if activity==2

**separate out stepping data from sitting/standing
gen group = 1 if activity==0|activity==1
replace group = 2 if activity==2

save all_valid.dta, replace

foreach i of num 1/2 {
  use all_valid if group == `i', clear
  save group`i', replace
}

**create stepping event variable

use group2, clear

sort id new_boutid event_time

egen stepping_event = group(id new_boutid)


**create bout cadence variable
gen bout_cadence = (bout_steps/bout_interval)*60*2

**recreate bout_end based on actual bout_length (i.e. without +1s to force
match)

drop bout_end
gen double bout_end = bout_start + (bout_interval*1000)
format bout_end %tc

save group2, replace

**add sitting/standing back in
append using group1

sort id new_boutid event_time
```

```
drop group

save cadence_all.dta, replace

**set the folder where the output will be stored >> THIS WILL NEED EDITING
**note that this needs to be different to the one with the event files in
otherwise the code to read in the event files will try to pull in this
output csv file as well
outsheet using "", replace comma

** only keep wake and valid data
drop if invalid==1|sleep==1|removed==1
drop sleep invalid removed

save cadence_valid.dta, replace

outsheet using "", replace comma
```

Appendix A2 STATA code for generating peak step cadence metrics

```
* Title: Mx step cadence generator
* Author: Ben Maylor
* Version: 1.0
* Date: 21-09-2020

*Description
*This .do generates Mx values for step cadence per ID and day using valid
AcitvPAL data
**********************************************************

*Where is the csv file?
cd ""

*Import file where cadence_valid.csv is a file within the cd specified
above
*This also works with cadence_all.csv but will potentially/likely include
data for invalid days
import delimited cadence_valid

*Sort data by descending event_cadence per ID and date
gsort id date -event_cadence

*Drop non-step observations
drop if event_steps < 1

*Generate cumulative step var
bysort id date: gen cum_intervals = sum(event_interval)

**This should be repeatable assuming that the largest Mx metric is put
first

*Mx 3600
drop if (cum_intervals > 3600)
*return mean and minimum of event_cadence per ID and date
by id date, sort: egen Day_Mx3600_min = min(event_cadence)
by id date, sort: egen Day_Mx3600_mean = mean(event_cadence)

*Mx 1800
drop if (cum_intervals > 1800)
*return mean and minimum of event_cadence per ID and date
by id date, sort: egen Day_Mx1800_min = min(event_cadence)
by id date, sort: egen Day_Mx1800_mean = mean(event_cadence)
```

```
*Mx 600
drop if (cum_intervals > 600)
*return mean and minimum of event_cadence per ID and date
by id date, sort: egen Day_Mx600_min = min(event_cadence)
by id date, sort: egen Day_Mx600_mean = mean(event_cadence)

*Mx 300
drop if (cum_intervals > 300)
*return mean and minimum of event_cadence per ID and date
by id date, sort: egen Day_Mx300_min = min(event_cadence)
by id date, sort: egen Day_Mx300_mean = mean(event_cadence)

*Mx 60
drop if (cum_intervals > 60)
*return mean and minimum of event_cadence per ID and date
by id date, sort: egen Day_Mx60_min = min(event_cadence)
by id date, sort: egen Day_Mx60_mean = mean(event_cadence)

*Provide day summary - 1 observation per
by id date: drop if _n !=_N

*drop unnecessary vars
drop new_boutid bout_steps bout_interval activity bout_start event_time
event_interval cumulativestepcount event_start event_steps event_cadence
stepping_event bout_cadence bout_end cum_intervals

*generate mean ID values
by id: egen Mx3600_mean = mean(Day_Mx3600_mean)
by id: egen Mx3600_min = mean(Day_Mx3600_min)
by id: egen Mx1800_mean = mean(Day_Mx1800_mean)
by id: egen Mx1800_min = mean(Day_Mx1800_min)
by id: egen Mx600_mean = mean(Day_Mx600_mean)
by id: egen Mx600_min = mean(Day_Mx600_min)
by id: egen Mx300_mean = mean(Day_Mx300_mean)
by id: egen Mx300_min = mean(Day_Mx300_min)
by id: egen Mx60_mean = mean(Day_Mx60_mean)
by id: egen Mx60_min = mean(Day_Mx60_min)


*Reshape data to wide
by id: gen dummy = _n
```

```
reshape wide date Day_Mx3600_min Day_Mx3600_mean Day_Mx1800_min
Day_Mx1800_mean Day_Mx600_min Day_Mx600_mean Day_Mx300_min Day_Mx300_mean
Day_Mx60_min Day_Mx60_mean, i(id) j(dummy)

*save .dta and .csv for ID summary
save cadence_valid_Mx_IDsummaryWide.dta, replace
outsheet using cadence_valid_Mx_IDsummaryWide.csv, replace comma
```

Appendix B Supplementary Tables

Table B1 Characteristics of *PROPELS* study participants stratified by treatment group

	Control (n=282)	***Walking Away (n=256)***	***Walking Away Plus (n=256)***
Fixed variables			
	***n* [%] of participants**		
Ethnicity White European South Asian Other Ethnicities	 198 [70.2%] 70 [24.8%] 14 [5.0%]	 186 [72.7%] 53 [20.7%] 17 [6.6%]	 195 [76.1%] 51 [20.0%] 10 [3.9%]
Sex Male Female	 144 [51.1%] 138 [48.9%]	 131 [51.2%] 125 [48.8%]	 133 [51.8%] 123 [48.2%]
History of Cardiovascular disease	42 [15%]	38 [14.9%]	32 [12.5%]
Employment Full-time Part-time Retired Unemployed or other	 106 [37.7%] 45 [16.1%] 99 [34.9%] 32 [11.3%]	 87 [34.1%] 52 [20.4%] 91 [35.5%] 26 [10.0%]	 95 [37.1%] 48 [18.9%] 86 [33.6%] 27 [10.4%]
	Mean ± SD		
Social Deprivation (IMD decile)	5.5 ± 2.8	5.7 ± 3.0	5.7 ± 2.8
Time varying variables			
	***n* [%] of participants**		
Lipid Lowering Substances	77 [27.3%]	72 [28.2%]	73 [28.3%]
Blood Pressure Medication	100 [35.6%]	90 [35.0%]	92 [36.0%]
Smoking Status Non-smokers Ex-smokers Current smokers	 147 [52.1%] 108 [38.2%] 27 [9.7%]	 141 [55.2%] 93 [36.4%] 22 [8.4%]	 129 [50.4%] 98 [38.2%] 29 [11.4%]
	Mean ± SD		
Alcohol (units per day)	3.5 ± 5.8	3.6 ± 5.0	4.6 ± 6.7
Weight (kg)	81.7 ± 18.1	79.9 ± 16.9	81.2 ± 16.8
BMI (kg/m^2)	29.3 ± 5.8	28.8 ± 5.4	28.9 ± 5.0
Waist Circumference (cm)	99.1 ± 14.3	97.5 ± 13.3	98.3 ± 13.9
HDL (mmol/L)	1.5 ± 0.5	1.4 ± 0.4	1.5 ± 0.4
LDL (mmol/L)	3.0 ± 0.9	3.0 ± 0.9	3.0 ± 1.0
Triglycerides (mmol/L)	1.6 ± 1.5	1.7 ± 1.0	1.5 ± 0.8
HbA1c (%) [mmol/mol]	5.8 ± 0.3 [40.7 ± 3.6]	5.8 ± 0.3 [40.8 ± 3.5]	5.8 ±0.3 [40.6 ± 3.5]

activPAL valid waking wear time (hours/day)	15.8 ± 1.2	16.0 ± 1.2	15.8 ± 1.2
Steps/day	8053 ± 3245	8619 ± 3184	8705 ± 3632
Slow Steps/day	2423 ± 1320	2425 ± 1286	2445 ± 1252
Brisk Steps/day	4459 ± 2701	4938 ± 2765	5021 ± 3108
Peak 10-minute step cadence (steps/minute)	126.8 ± 10.5	128.6 ± 9.6	128.0 ± 10.0

Table B2 Characteristics of *PROPELS* study participants with missing data

	Excluded due to missing data (n = 572)	***Included in analysis (n = 794)***
Fixed variables		
	***n* [%] of participants**	
Ethnicity		
White European	412 [72.1%]	579 [72.9%]
South Asian	137 [23.9%]	174 [21.9%]
Other Ethnicities	23 [4.0%]	41 [5.2%]
Sex		
Male	294 [51.4%]	407 [51.3%]
Female	278 [48.6%]	387 [48.7%]
History of Cardiovascular disease	88 [15.4%]	100 [12.6%]
Employment		
Full-time	211 [36.9%]	288 [36.3%]
Part-time	97 [16.9%]	146 [18.4%]
Retired	197 [34.4%]	275 [34.6%]
Unemployed or other	67 [11.8%]	85 [10.7%]
	Mean ± SD	
Social Deprivation (IMD decile)	5.4 ± 2.9	5.8 ± 3.0
Time varying variables		
	***n* [%] of participants**	
Lipid Lowering Substances	157 [27.4%]	237 [29.9%]
Blood Pressure Medication	204 [35.6%]	295 [37.2%]
Smoking Status		
Non-smokers	265 [46.3%]	443 [55.8%]
Ex-smokers	229 [40.0%]	288 [36.3%]
Current smokers	78 [13.7%]	62 [7.8%]
	Mean ± SD	
Alcohol (units per day)	4.5 ± 7.0	3.7 ± 5.9
Weight (kg)	81.9 ± 18.1	81.0 ± 17.3
BMI (kg/m^2)	29.3 ± 5.9	29.0 ± 5.4

Waist Circumference (cm)	98.8 ± 14.1	98.3 ± 13.9
HDL (mmol/L)	1.4 ± 0.4	1.5 ± 0.4
LDL (mmol/L)	3.1 ± 0.9	3.0 ± 0.9
Triglycerides (mmol/L)	1.6 ± 1.0	1.6 ± 1.1
HbA1c (%) [mmol/mol]	5.8 ± 0.3 [40.5 ± 3.6]	5.8 ± 0.3 [40.7 ± 3.5]

Table B3 Interaction *p* values for associations between change in step cadence and change in cardiometabolic health

	Change in BMI (kg/m^2)	***Change in waist circumference (cm)***	***Change in HDL-C (mmol/L)***	***Change in LDL-C (mmol/L)***	***Change in triglycerides (mmol/L)***	***Change in HbA1c (%) [mmol/mol]***
Group						
Change in Overall steps/day	0.094	0.157	0.235	0.998	**0.035**	0.609 [0.642]
Change in Slow steps/day	0.170	**0.020**	0.090	0.072	**0.014**	0.707 [0.472]
Change in Brisk steps/day	0.343	0.518	0.494	0.629	0.347	0.566 [0.605]
Change in Peak 10-minute Step Cadence	0.323	0.270	0.551	0.485	**0.008**	0.560 [0.559]
Sex						
Change in Overall steps/day	0.583	0.170	0.667	0.064	0.746	0.060 [0.088]
Change in Slow steps/day	0.368	0.681	0.925	0.679	0.632	0.389 [0.585]
Change in Brisk steps/day	0.360	0.205	0.483	**0.029**	0.358	0.088 [0.102]
Change in Peak 10-minute Step Cadence	0.511	0.583	0.852	0.096	0.949	0.052 [0.086]
Ethnicity						
Change in Overall steps/day	0.322	0.913	0.879	0.148	0.332	**0.043** [0.096]

Change in Slow steps/day	0.788	0.318	0.240	0.261	0.548	0.356 [0.509]
Change in Brisk steps/day	0.275	0.691	0.373	0.167	0.563	**0.026** [0.062]
Change in Peak 10-minute Step Cadence	**0.009**	0.058	0.226	0.085	0.151	**0.030** [0.077]

p < 0.05 values in bold
Adjusted for baseline value for both the dependant and exposure variable, change in activPAL waking wear time, group, age, sex, ethnicity (WE, SA, other), deprivation, employment (employed, part-time employed, retired, other), smoking, alcohol (drinks per week), previous CVD (yes/no), blood pressure medication (yes/no), lipid lowering medication (yes/no).

Table B4 Non-standardised associations between change in step cadence and change in cardiometabolic health stratified by ethnicity

	Change in BMI (kg/m^2)	***Change in waist circumference (cm)***	***Change in HDL-C (mmol/L)***	***Change in LDL-C (mmol/L)***	***Change in triglycerides (mmol/L)***	***Change in HbA1c (%)***
Change in Overall steps/day						**WE: -0.010 (-0.018, -0.002) p=0.011** SA: 0.003 (-0.011, 0.016) p=0.707
Change in Slow steps/day						
Change in Brisk steps/day						**WE: -0.013 (-0.023, -0.002) p=0.016** SA: -0.007 (-0.022, 0.009) p=0.421
Change in Peak 10-minute Step Cadence	**WE:** -0.02 (-0.04, 0.01) p=0.226 **SA: -0.08 (-0.11, -0.05) p<0.001**					**WE: -0.003 (-0.006, 0.000) p=0.030** SA: -0.003 (-0.008, 0.001) p=0.157

p < 0.05 values in bold
Adjusted for baseline value for both the outcome and exposure variable, change in activPAL valid waking wear time, group, age, sex, ethnicity (WE, SA, other), deprivation, employment (employed, part-time employed, retired, other), smoking, alcohol (drinks per day), previous CVD (yes/no), blood pressure medication (yes/no), lipid lowering medication (yes/no), plus mutual adjustment for baseline and change in slow steps/day (when brisk steps/day or peak 10-minute step cadence is the exposure variable) or baseline and change in brisk steps/day (when slow steps/day is the exposure variable).
Gaps in the table are where interactions were insignificant.

Table B5 Non-standardised associations between change in step cadence and change in cardiometabolic health stratified by sex

	Change in BMI (kg/m^2)	***Change in waist circumference (cm)***	***Change in HDL-C (mmol/L)***	***Change in LDL-C (mmol/L)***	***Change in triglycerides (mmol/L)***	***Change in HbA1c (%) [mmol/mol]***
Change in Overall steps/day						
Change in Slow steps/day						
Change in Brisk steps/day				**Male: 0.029 (0.002, 0.057) p=0.036** Female: -0.011 (-0.038, 0.016) p=0.435		
Change in Peak 10-minute Step Cadence						

$p < 0.05$ values in bold
Adjusted for baseline value for both the dependant and exposure variable, change in activPAL waking wear time, group, age, sex, ethnicity (WE, SA, other), deprivation, employment (employed, part-time employed, retired, other), smoking, alcohol (drinks per day), previous CVD (yes/no), blood pressure medication (yes/no), lipid lowering medication (yes/no), plus mutual adjustment for baseline and change in slow steps/day (when brisk steps/day or peak 10-minute step cadence is the exposure variable) or baseline and change in brisk steps/day (when slow steps/day is the exposure variable).
Gaps in the table are where interactions were insignificant.

Table B6 Non-standardised associations between change in step cadence and change in cardiometabolic health with multiple imputations for missing data

	Change in BMI (kg/m^2)	***Change in waist circumference (cm)***	***Change in HDL-C (mmol/L)***	***Change in LDL-C (mmol/L)***	***Change in triglycerides (mmol/L)***	***Change in HbA1c (%) [mmol/mol]***
Participants contributing data, *n*	1366					
Change in Overall steps/day	**-0.05 (-0.09, -0.02) p=0.006**	-0.11 (-0.25, 0.02) p=0.089	**0.007 (0.001, 0.013) p=0.021**	0.006 (-0.011, 0.024) p=0.463	-0.019 (-0.045, 0.006) p=0.120	-0.003 (-0.009, 0.004) [-0.043 (-0.103, 0.017)] p=0.157
Change in Slow steps/day	-0.06 (-0.11, 0.02) p=0.058	-0.59 (-0.26, 0.14) p=0.568	0.004 (-0.007, 0.015) p=0.454	-0.003 (-0.036, 0.029) p=0.354	-0.026 (-0.062, 0.010) p=0.115	-0.015 (-0.031, 0.000) [0.101 (-0.033, 0.234)] p=0.053
Change in Brisk steps/day	**-0.07 (-0.11, -0.02) p=0.009**	-0.14 (-0.29, 0.21) p=0.088	**0.008 (0.001, 0.014) p=0.021**	0.009 (-0.009, 0.028) p=0.317	-0.018 (-0.040, -0.003) p=0.094	**-0.006 (-0.014, 0.002) [-0.078 (-0.150, -0.005)] p=0.037**
Change in Peak 10-minute Step Cadence	-0.01 (-0.03, 0.01) p=0.076	**-0.08 (-0.12, -0.04) p<0.001**	**0.002 (0.001, 0.004) p=0.005**	0.002 (-0.003, 0.007) p=0.484	-0.004 (-0.010, 0.003) p=0.223	**-0.003 (-0.005, -0.001) [-0.014 (-0.033, 0.005)] p=0.014**

p < 0.05 values in bold

Adjusted for baseline value for both the dependant and exposure variable, change in activPAL waking wear time, group, age, sex, ethnicity (WE, SA, other), deprivation, employment (employed, part-time employed, retired, other), smoking, alcohol (drinks per day), previous CVD (yes/no), blood pressure medication (yes/no), lipid lowering medication (yes/no), plus mutual adjustment for baseline and change in slow steps/day (when brisk steps/day or 10-minute peak step cadence is the exposure variable) or baseline and change in brisk steps/day (when slow steps/day is the exposure variable.

Appendix C1 Original RESPONSE Study Protocol

Detailed below is the protocol for the original *RESPONSE* study protocol.

Primary Objective

Part 1 – Lab-based

- To ascertain the types of activities used for breaking sitting time which provide the most favourable affective responses.

Part 2 – Intervention

- To investigate whether personalised recommendations for reductions in prolonged sitting time with respect to time and type are more effective than generic advice for improving glucose control over a 4-week intervention.

Secondary Objectives

Part 1 – Lab-based

- To quantify the rate of perceived exertion of different activities used for breaking up prolonged sitting time
- To quantify the energy expenditure of different activities used for breaking up prolonged sitting time
- To quantify degree of muscle activation of different activities used for breaking up prolonged sitting time
- To investigate whether affective responses, perceived exertion, energy expenditure, muscle activation, and the degree of pain observed across different activities used to break up sitting time are associated with baseline measures.

Part 2 – Intervention

- To investigate whether fasting metabolic markers (glucose, insulin, lipid profile) are changed following the intervention.
- To investigate whether variability in blood glucose (weekly average) and time spent in hypo- and hyper-glycaemia change at the end of the intervention as assessed via CGM.
- To investigate whether PF is improved following the intervention.
- To investigate changes to overall SB, sleep, and PA during and at the end of the intervention.

STUDY DESIGN

Summary of Trial Design

The RESPONSE study will consist of two parts: Part 1 – a lab-based study to assess the effects of different activities used to break up prolonged sitting time; and Part 2 – a 4-week randomised trial.

Part 1 – Lab-based will involve participants attending the Leicester Diabetes Centre to participate in a 5.5-hour sitting condition. This will be interrupted every 20-minutes with one of 16 different activities. Affective response, rate of perceived exertion (RPE), muscle activation, and energy expenditure will be recorded for each activity break.

Part 2 – Intervention is a 4-week randomised trial and will involve participants being randomised (1:1) to one of two treatments: 1) an intervention to break up prolonged sitting time that is tailored to individuals sleeping patterns, meal timings, activity break type response, and 24-hour blood glucose profiles; 2) a generic intervention to break up prolonged sitting. The study will include 4 visits to the Leicester Diabetes Centre, Leicester General Hospital.

Visit 1 (week 1): Screening and baseline data collection, including 8-day accelerometer and CGM monitoring.
Visit 2 (week 3): Assessment of individuals responses to activity break regimes prior to randomisation (Part 1 – Lab-based)
Visit 3 (week 7): Follow-up placement of accelerometers and CGM
Visit 4 (week 8): Follow-up clinical data collection after Part 2 – Intervention

Primary and Secondary Endpoints/Outcome Measures

<u>Part 1 – lab-based</u>

The primary outcome of the lab-based study is the quantification affective responses to different activities used to break prolonged sitting time via the feelings scale.

<u>Part 2 – Intervention</u>

The primary outcome measure of this intervention is postprandial glucose excursions assessed via CGM worn in free living conditions.

Secondary Outcomes

Part 1 – Lab-based

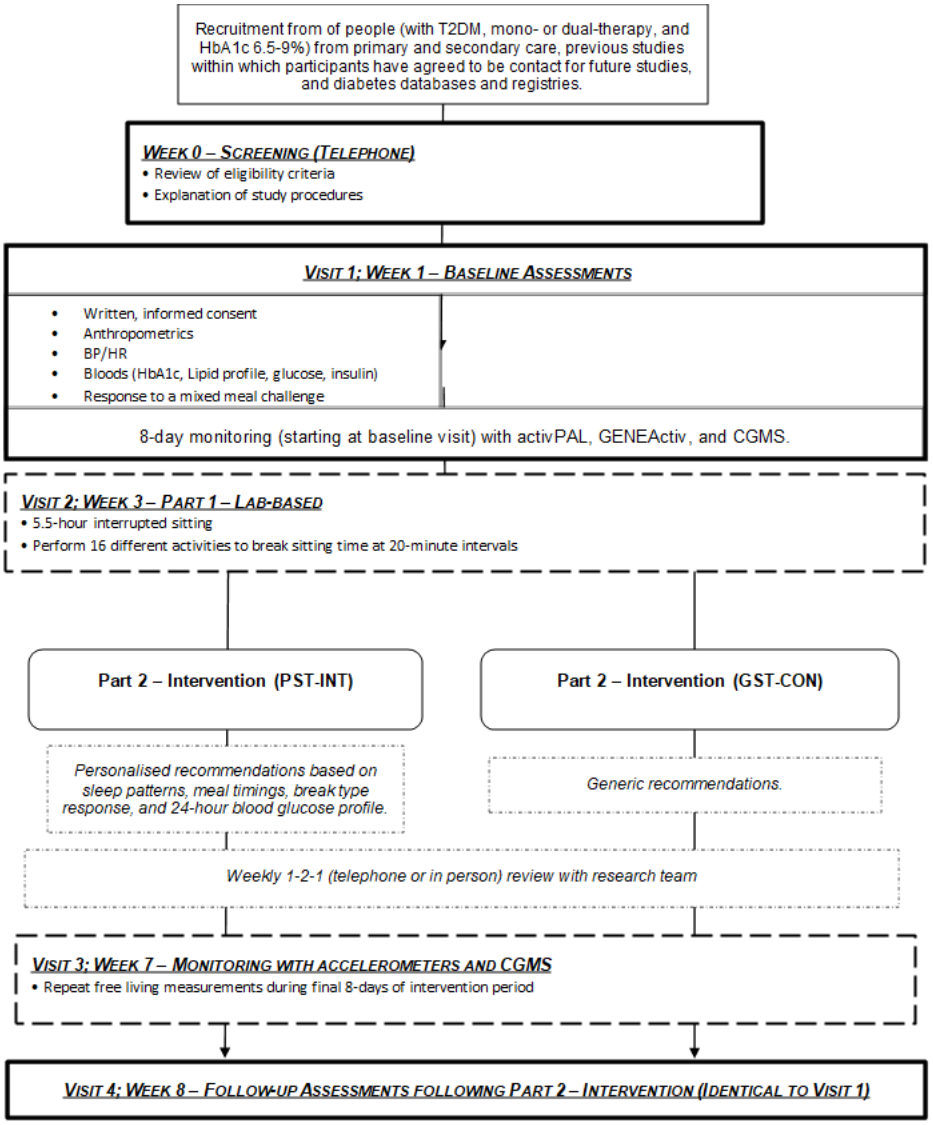
The secondary outcomes for the lab-based study are:

- The RPE of different activities used for breaking up prolonged sitting time
- The energy expenditure of different activities used for breaking up prolonged sitting time
- The degree of muscle activation of different activities used for breaking up prolonged sitting time

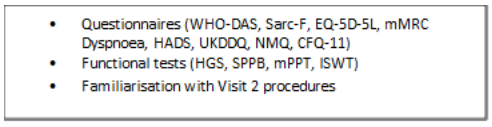
Part 2 – Intervention

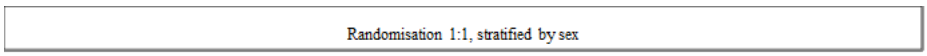
The secondary outcomes in the intervention are:

- Glucose variability (% and standard deviation), average blood glucose, time in range, time above range, time below range, HBGI, LBGI, number of hyperglycaemic episodes, and number of hypoglycaemic episodes derived from CGM
- AUC for postprandial glucose, insulin, triglycerides derived from the mixed meal challenge
- Fasting glucose, insulin, triglycerides, and full lipid profile
- PF
- Adherence to regular light upright movement breaks, sedentary time (total and time spent in prolonged sitting), sleep duration and PA (total, and time spent in LPA, MPA and VPA). All measured objectively via accelerometery



LDC: Leicester Diabetes Centre; HGS: Handgrip strength; CGMS: continuous glucose monitoring system; SPPB: short physical performance battery; HbA1c: glycated haemoglobin; PST-INT: personalised sitting time intervention; GST-CON: generic sitting time control





Trial Schematic

Gantt chart representing predicted timelines for study

Study Phases	**Weeks**							
	1	*2*	*3*	*4*	*5*	*6*	*7*	*8*
Baseline Assessment								
Free-living Assessment								
Part 1 – Lab-based								
Part 2 – Intervention								
Free-living Assessment								
Follow-up Assessment								

Appendix C2 RESPONSE Study REC favourable opinion

Health Research Authority

London - Surrey Research Ethics Committee

Nottingham Centre
The Old Chapel
Royal Standard Place
Nottingham
NG1 6FS

Tel: 0207 104 8372

14 July 2021

Mr Philip McBride
Leicester Diabetes Centre
Leicester General Hospital
LE5 4PW

Dear Mr McBride

Study title:	**Breaking up prolonged sitting in people with type 2 diabetes: Optimising the response**
REC reference:	**20/LO/1102**
Protocol number:	**0791**
Amendment number:	**Substantial Amendment 01**
Amendment date:	**28 April 2021**
IRAS project ID:	**281671**

The above amendment was reviewed by the Sub-Committee in correspondence.

Ethical opinion

The members of the Committee taking part in the review gave a favourable ethical opinion of the amendment on the basis described in the notice of amendment form and supporting documentation.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
Completed Amendment Tool [281671_SA01 28-04-2021_LOCKED]	1	28 April 2021
Letters of invitation to participant [RESPONSE Participant Invitation Letter (Healthy Control), v1.0_28.04.2021_Amendment 1]	1	28 April 2021
Letters of invitation to participant [RESPONSE Participant Invitation Letter, v1.0_28.04.2021_Amendment 1]	1	28 April 2021
Other [RESPONSE Process Evaluation Questionnaire, v1.0_28.04.2021_Amendment 1]	1	28 April 2021
Other [RESPONSE Process Evaluation Self-Monitoring Questionnaire, v1.0_28.04.2021_Amendment 1]	1	28 April 2021
Participant consent form [RESPONSE Consent Form (HC), v2.0_13.07.2021_Amendment 1]	2.0	13 July 2021

Appendix C3 RESPONSE Study Informed Consent form

Participant ID: ☐☐☐☐☐☐

CONSENT FORM

Title of Project: RESPONSE – Breaking up prolonged sitting in people with type 2 diabetes: Optimising the response

Principal Investigator: Prof Melanie Davies Chief Investigator: Prof Tom Yates

Please place your INITIALS in each box as appropriate.

	INITIALS
1. I confirm that I have read and understand the Patient Information Sheet (PIS) version «No.» dated «Date» for the above study and have had the opportunity to ask questions. Any questions I have asked have been answered to my satisfaction.	Initial
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	Initial
3. I understand that my personal details and study data will be stored on secure computers, in secure cabinets or in archiving rooms at the Leicester Diabetes Centre.	Initial
4. I understand that the relevant sections of my medical notes and/or study data may be looked at by responsible individuals from the study team, the Sponsor, NHS Trust, or regulatory authorities, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my relevant records.	Initial
5. I agree to be contacted by the research team over the course of the study.	Initial
6. I understand that I am free to withdraw from the study at any time without giving a reason and it will not affect my standard of care in any way. Should I withdraw from the study, I give my permission for data already collected to be used anonymously for statistical analysis.	Initial
7. I agree that my general practitioner (GP) may be informed of my participation in the study and any results.	Initial
8. I agree to take part in the above study.	Initial
9. I consent to having blood samples taken (as detailed in the PIS)	Initial
10. I give permission for retention of my contact details for contact at a later stage for invitation to participate in relevant studies. (This is optional)	Initial
11. I understand that anonymised study data collected as part of this research may be shared and stored on systems at other academic institutions or commercial organisations with which we have a collaborative agreement (This is optional)	Initial

	YE	NO
	Initial	Initial
	Initial	Initial

An original copy of the

participant information sheet and completed informed consent form will be given to the participant, and an original copy will be filed in the investigator file.

…… …… ……

NAME OF PARTICIPANT (BLOCK LETTERS) SIGNATURE DATE

…… …… ……

NAME OF RESEARCHER (BLOCK LETTERS) SIGNATURE DATE

Appendix C4 RESPONSE Study PIS

Title of study: RESPONSE – Breaking up prolonged sitting in people with type 2 diabetes: Optimising the response

Chief Investigator: Prof Tom Yates

This study will form part of a PhD project being undertaken by Phil McBride (PhD candidate).
PhD Candidate: Phil McBride - pm381@leicester.ac.uk
Principal Supervisor: Prof Tom Yates - ty20@leicester.ac.uk
Secondary Supervisor: Dr Charlotte Edwardson – ce95@leicester.ac.uk

Participant Information Sheet

We would like to invite you to take part in our research study. Before you decide whether you would like to take part, we would like you to understand why the research is being done and what it would involve for you. Please take the time to read the following information carefully and talk to others about the study if you wish.

Part 1 of this information sheet tells you about why we are doing this study.

Part 2 gives you detailed information of what will happen if you decide to take part.

Part 3 gives you information about the funding and support of the study, and potential risks/benefits to you.

Please contact us if there is anything that is not clear. Our contact details can be found at the end of this document.

In this research study we will use information from you. We will only use information that we need for the research study. We will let very few people know your name or contact details, and only if they really need it for this study.

Everyone involved in this study will keep your data safe and secure. We will also follow all privacy rules.

At the end of the study we will save some of the data in case we need to check it **AND/OR** for future research.
We will make sure no-one can work out who you are from the reports we write.

The information pack tells you more about this.

Part 1

1. What is the purpose of the study?

Spending a large amount of time sitting during the day, and particularly in prolonged unbroken bouts is known to have a negative impact on blood sugar levels. The good news is that regularly breaking up sitting time by doing simple activities, such as standing, stretching, etc. for a few minutes can be very effective at improving blood sugar levels as well as many other aspects of health such as the ability to perform daily tasks, heart health, and risk of developing foot ulcers. For example, in people with type 2 diabetes, research has shown that doing simple activities every 30 minutes for 3 minutes over a 6-8-hour period significantly improves glucose control. We want to expand on this research by asking people with type 2 diabetes to take part in a 4-week programme designed to regularly break up sitting time throughout the day with a variety of simple activities. We want to test how well this programme works for improving blood glucose levels and various other indicators of your overall health.

2. What does the study involve?

With your signed consent, we would like to either attend the Leicester Diabetes Centre (Leicester General Hospital) for 2 assessments, OR to schedule 2 video call-based assessments with our research team (e.g., over Skype, Zoom, or another platform that you may be familiar with). We would also like you to take part in a programme designed to regularly break up sitting time over a 4-week period. You do this programme in your daily life. There will also be two 8-day periods wearing activity monitors and a glucose monitor (which measures the amount of sugar in your blood) (one at the start and one at the end of the study). See Part 2 for full study details.

3. Why have I been invited?

You have been invited to take part in this research because you have either a diagnosis of type 2 diabetes or you have a recent HbA1c reading of 6% or more; you are aged 40-75; and have previously taken part in research at the LDC, you have been referred to the study by your health care provider, or you have highlighted your interest based on promotional materials.

4. Do I have to take part?

No. Taking part is entirely voluntary and you can talk to others before deciding whether to take part. If you do decide to take part, or would like further information, we will describe the study and go through this information sheet with you. If you agree to take part, you will be asked to complete and sign a consent form. The consent form must be completed before we can schedule your first appointment. You will be given a copy of the signed consent form and this information sheet to keep. If you prefer not to take part, you do not have to give a reason, and this will not affect the standard of care you receive. If you agree to take part, but later change your mind, you may withdraw at any time, without giving a reason by contacting the research team. This will not affect your care in any way. If you do change your mind and withdraw, we will keep and use the data we have collected up to that point.

Part 2

1. What will I have to do if I take part?

Data Collection Visit to LDC or Video Call 1: 30-60 minutes

The first data collection session may be done with a researcher at the Leicester Diabetes Centre, or via video call (based on your preference) and will be for confirming eligibility and conducting baseline assessments. Depending on the information you have consented to us accessing, you may need to perform a fingerprick blood test (we will send this to you if you choose to have remote assessment). During this visit/call we will explain all the study activities and measurements to you and ask you to perform the activities whilst at the centre/we are on the video call. These activities and measurements are as follows:

<u>Waist Circumference</u>

If you attend the LDC, a member of the research team will measure your waist circumference. Should you opt for remote assessment, we will provide you with the tape measure required to measure your waist circumference. Instructions on how to do this will be given during the video call.

<u>Physical Function</u>

For those who opt for remote data collection, we will ask you to perform some activities whilst we are on the call. We would like you to do the 30-second chair stand test. It includes standing up and sitting down as many times as you can from a sturdy chair (such as a dining chair) in 30-seconds.

We will ask you to watch a series of videos demonstrating different physical movements and indicate how capable you are of completing them.

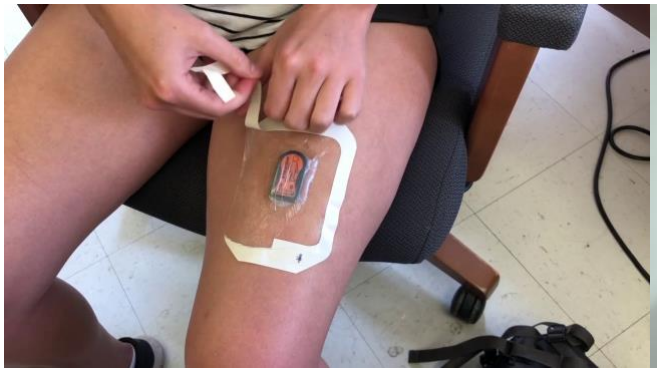
Prior to the video call, we will send you a retractable marker which measures 4-metres. We will ask you to use this to mark out a clear 4-metre space at your home (inside or outside). We will then ask you to walk this 4-metre distance so that we can assess your walking speed.

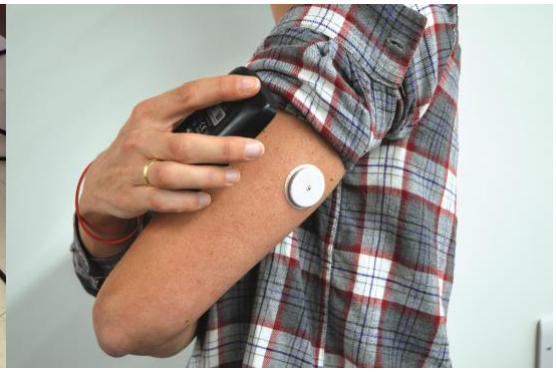
For those who choose to attend the LDC for data collection, you will also complete the assessment detailed above. But we would also like to measure your hand grip strength, standing balance, and some additional assessments to measure your walking pace and ability to stand from a chair.

Physical Activity and Glucose Monitors

For those who choose remote data collection, prior to the video call, we will post you two small activity monitors to wear, one on your wrist and one taped to your leg. These measure how much time you spend sleeping, sitting, and moving. You will also be given a continuous glucose monitor to monitor the changes in your blood sugar throughout the day. They can be worn all day and night and whilst showering/bathing. We will also ask you fill out a wake and sleep log whilst wearing these devices. All these devices will be worn for 8 days, starting on the day you have your video call. During the video call we will talk you through how to wear the devices. At the end of the 8-day monitor wear period, the monitors should be returned to us in a pre-paid envelope (provided).

If you come in to the LDC, you will also wear these devices, but a member of the research team will set them up for you.





Health Questionnaires

We will ask you to complete a small questionnaire booklet. This contains nine questionnaires. They will look at your functional ability, quality of life, breathlessness, anxiety and depression, chronotype (whether you are more of a morning or evening person), chronic pain, fatigue, and dietary intake. This can be completed with us, onsite, or we can post them to you and they can be returned to us in a pre-paid envelope, provided.

Intervention

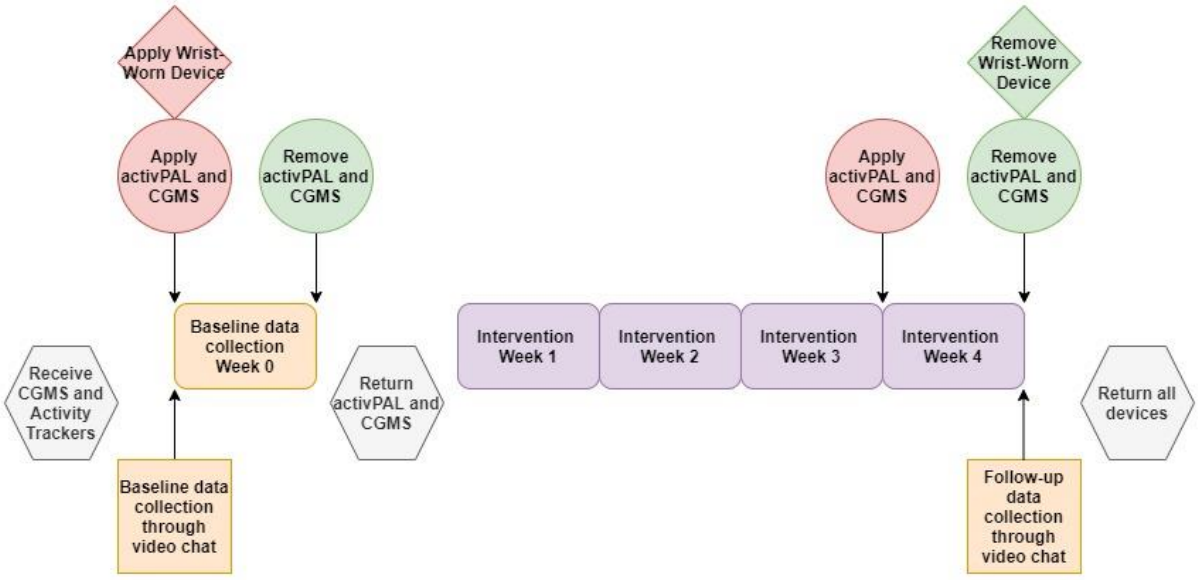
The following phase of the study is the 4-week intervention. You will be given advice on strategies to break up your sitting time throughout the day. You will receive regular (weekly) contact from the study team over the phone or via video chat to monitor your progress. You will also be given a choice from a variety of commercially available tools to help you to monitor your sitting time. These will range from wrist watches (like the Fitbit) to mobile apps or computer programmes which help you to keep track of your sitting time. This may require you to periodically upload data to a system which the research team can monitor. We will be using the information gathered on your usual activity patterns, patterns of changes in your blood sugar, and patterns of sleep to help us to offer you a personalised programme for breaking up your sitting time. Towards the end of the intervention, you will be given another set of activity monitors and a glucose monitor. These should be worn during the final 8-days of the intervention and you should complete a new wake and sleep log. At the end of this 8-

day period, the monitors should be returned to us in a pre-paid envelope (provided) or given to us if you come to the LDC.

Data Collection Visit or Video Call 2

Finally, you will have one further visit or video session which will replicate Visit or Video Call 1.

Flowchart for study procedure



To be returned to the study team at the end of the study:

- ***All activity trackers provided to you by the research team (thigh-worn and wrist-worn)***
- ***All continuous glucose monitoring systems provided to you by the research team***
- ***All self-monitoring activity tracking devices provided to you by the research team***

Part 3

1. What will happen to the information and samples (data from the measurements) I provide?

We will need to use information from you for this research project.

This information will include your ethnicity, age and measures collected as part of the study. People will use this information to do the research or to check your records to make sure that the research is being done properly.

People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

We will keep all information about you safe and secure.

Once we have finished the study, we will keep some of the data so we can check the results. We will write our reports in a way that no-one can work out that you took part in the study.

Only the main research team have access to your personal details and know what your study ID is. The data will be analysed and compiled into a research project for submission as part of a PhD project.

2. What are the possible disadvantages and risks of taking part?

If you choose to participate in the study, then you will be required to dedicate some of your time to the video calls and the intervention itself. You may experience slight irritation from the activity and glucose monitors, although this isn't common.

3. What are the possible benefits of taking part?

While there is no direct monetary benefit to taking part in the study, you will receive data on your health which has been gathered from the study. You will be able to see any information which has been collected from you, including assessments of physical function, and your glucose responses over an extended period. You may also experience benefits to your health by taking part in the intervention and having structured support in reducing the amount of time you spend sitting.

4. Will my taking part in this study cost me anything?

There will be no direct costs to you taking part.

5. Will my taking part in this study be kept confidential?

All the information that is collected about you during the course of the research will be kept strictly confidential. With your permission, we will contact your own doctor (GP) and they will be notified that you have participated in the above study and will be sent details of your results. It is possible that your results could have clinical significance. In this situation, these results will be highlight to you and your GP so that they may follow-up accordingly.

If you consent to taking part in the research study, members of the research team may request data from your medical records to supplement the data gathered during the study. They may also be looked at by the regulatory authorities or a representative of the sponsor (The University of Leicester) or host NHS organisation to check that the study is being carried out correctly. When the results are published, no names will be used, and it will not be possible to identify anyone who has taken part. People who do not need to know who you are will not be able to see your name or contact details. Your data will have a code number instead.

Information collected may be used to support other research in the future and may be shared anonymously with other researchers. If you consent to this, we may share your data in an anonymous format with other organisations for research purposes. Only the main research team have access to your personal details.

6. What will happen to my personal data?

The University of Leicester is the sponsor for this study based in the United Kingdom. We will be using information from you and your medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after your information and using it properly. The University of Leicester will keep identifiable information about you for 5 years after the study has finished.

Your rights to access, change or move your information are limited, as we need to manage your information in specific ways in order for the research to be reliable and accurate. If you withdraw from the study, we will keep the information about you that we have already obtained. To safeguard your rights, we will use the minimum personally identifiable information possible.
You can find out more about how we use your information at www.hra.nhs.uk/information-about-patients/ or https://le.ac.uk/patient-gdpr-guidance or by sending an email to <add your email> or by ringing us on <add your phone number>.

To speak to the University's Data Protection Officer and In-House Commercial Lawyer (Elisabeth Taudi), University of Leicester, University Road, Leicester, LE1 7RH please email ias@le.ac.uk, or ring 0116 229 794.

Should you lose capacity to consent during the course of the study, you would be withdrawn from the study. Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected, or any other research procedures carried out on or in relation to you.

The University of Leicester will collect information about you for this research study from the central NHS database, NHS Digital. This information will include your name/ NHS number/ contact details and health information, which is regarded as a special category of information. We will use this information to track your visits to the GP, visits or admissions to hospital and, in the event of death, the date and cause of death.

What are your choices about how your information is used?

- You can stop being part of the study at any time, without giving a reason, but we will keep information about you that we already have.
- We need to manage your records in specific ways for the research to be reliable. This means that we won't be able to let you see or change the data we hold about you.
- **OPTION if data will be used for future research:** If you agree to take part in this study, you will have the option to take part in future research using your data saved from this study. [**Insert details of any specific bank/ repository**]

7. Will the information obtained in the study be confidential?

All details recorded in the study will be treated in the strictest confidence. The researchers involved in the study will keep your contact details in a secure database so that you can be contacted in the future should the need arise. This data will be held in compliance with the Data Protection Act 2018 and the General Data Protection Regulation (2018).

You can optionally agree to the researcher keeping your contact details to send you invitations to participate in other research projects in the future. You are under no obligation to agree to participate in these.

8. What will happen to the results of the research study?

Once we have analysed the results, we will present the findings in a PhD thesis, at scientific meetings, across Leicester Diabetes Centre networks for educational purposes, and in medical research journals. All these results will be anonymous, and it would not be possible to identify you.

9. Who is organising and funding the research?

The data collected during this study forms part of a PhD project. The study is being run by investigators based at the Leicester Diabetes Centre at the Leicester General Hospital and is Sponsored by the University of Leicester. All student activity is being supervised by senior researchers within Leicester Diabetes Centre. This research is being funded by the Leicester Biomedical Research Centre. The researcher is not being paid for including participants in the study.

10. Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect the safety, rights, wellbeing and dignity of its study participants. This study has been reviewed and given a favourable opinion by the RES Committee – London – Bromley. It has been reviewed by independent medical/research experts and the study sponsor, the University of Leicester.

11. What if I am harmed by the study?

It is very unlikely that you would be harmed by taking part in this type of research study. In the event that something does go wrong and you are harmed during the research and this is due to someone‘s negligence then you may have grounds for a legal action for compensation against University of Leicester but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

12. What if I wish to complain about the way in which this study has been conducted?

If you have a concern about any aspect of the study, please contact the Chief Investigator using contact details given at the bottom of this information sheet. If you remain unhappy and wish to make a formal complaint about any aspect of the study or how you have been treated during the study, the normal hospital complaints procedure is available to you. Please contact the following:

Patient Information & Liaison Service at pils.complaints.compliments@uhl-tr.nhs.uk. The Firs, c/o Glenfield Hospital, Groby Road, Leicester. LE3 9QP

Freephone: 0808 1788337

13. What do I do now?

Now that you have read the information leaflet, if you would like to take part, please complete the reply slip and pre-screening questionnaire and send back to the research team using the pre-paid envelope provided and we will then be in touch with you. If you would like to discuss this information with your family or friends, please do. The researcher's details are given below. If you do not wish to take part, your clinical care will not be affected in any way.

Contact for further information:

If you require any further information you can contact the following:

RESPONSE Study Team — email: responsestudy@le.ac.uk

Phil McBride
Leicester Diabetes Centre (Origin)
Leicester General Hospital
Gwendolen Rd
Leicester
LE5 4PW
email: pm381@le.ac.uk

Professor Tom Yates
Leicester Diabetes Centre (Origin)
Leicester General Hospital
Gwendolen Rd
Leicester
LE5 4PW
Tel: 07941456348
email: ty20@le.ac.uk

Thank you for taking the time to read this information sheet.

You can find out more about how we use your information

- at www.hra.nhs.uk/information-about-patients/
- by asking one of the research team
- by sending an email to queries@hra.nsh.uk

COACHING SESSION CHECKLIST

RESPONSE: breaking up sitting in people with type 2 diabetes: optimising the RESPONSE

Participant ID: Week #:

Coaching Session	Yes/No
Greet participant	
Elicit (from participant) his/her experiences of using self-monitoring device (inc. asking if participant has any particular routine on when they use their device)	
Ask if participant has set themselves any particular goals/targets around reducing their sitting time, clarify these (if they haven't explain why it's helpful to do this and discuss potential goals/targets that they would be happy with) and progress (explain importance of making small changes initially and then gradually increase)	
If necessary, review goal and action plan and amend with participant	
Ask participant about the most useful things that have helped them work towards their goals/targets and why they found them useful (Remind them why it's helpful to track sitting/standing time).	
Ask if participant has experienced any benefits (reinforce the benefits that the participant highlights)	
Ask if participant has experienced any barriers to reducing sitting time and can they see any potential solutions	
Ask participant how important (on a scale of 1-10) it is to them to reduce their sitting time and why/why not (hopefully when they identify why this will reinforce messages around importance of reducing prolonged sitting)	
Ask participants to rate themselves on a scale of 1-10 how confident they are that they can (continue to) reduce their sitting	
Ask if participants have any questions	

NOTES

Appendix C6 RStudio code for defining functions for analysis of CGM data

```
##############################################
# Functions for analysis of CGM data
# Written by Emily Patsko
# Last updated: 02/12/2020

# Added in functionality for flagging the top 10 changes
# in glucose for a participant, both daywise and over the
# entire weartime
##############################################

tidycgmdata <- function(inputdirectory = getwd(), cgmtype="", filetype="")
{

  # VARIABLES #
  #
  # inputdirectory = where the CGM/FGM raw data files are (one file per
participant). Defaults to current working directory
  # cgmtype = what type of monitor has been used. Currently supported:
medtronic ipro, freestyle libre, freestyle libre pro
  # filetype = what type of file the data is stored in. For now, options
are "xlsx", "csv", "txt"

  # Catch errors
  if (!(cgmtype %in% c("ipro", "freestylelibre", "freestylelibrepro"))) {
    stop("Invalid CGM type.")
  }

  if (!(filetype %in% c("xlsx", "csv", "txt"))) {
    stop("Invalid file type.")
  }

  # Identify all the files
  files <- list.files(path = inputdirectory, pattern = paste("*.",
filetype, sep=""), full.names = TRUE)

  # Loop through each file, tidy and append
  for (f in 1:length(files)) {

    # Read in a patient file
    if (filetype == "xlsx") {
      table <- readxl::read_excel(files[f])
```

```
    } else if (filetype == "csv") {

      if (cgmtype == "freestylelibrepro") {
        table <- read.csv(file = files[f], skip = 1, stringsAsFactors =
FALSE, header = TRUE, na.strings = "", skipNul = TRUE)
      } else {
        #table <- read.csv(file = files[f], stringsAsFactors = FALSE,
header = TRUE, na.strings = "", skipNul = TRUE)
        table <- read.delim(file = files[f], stringsAsFactors = FALSE,
header = TRUE, na.strings = "", skipNul = TRUE,
                            sep = ",")
      }
    } else if (filetype == "txt") {
      table <- read.delim(file = files[f], stringsAsFactors = FALSE, header
= TRUE, na.strings = "", skipNul = TRUE)
    }

    if (cgmtype == "ipro") {

      # Tidy it up and just retain necessary info
      colnames(table) <- table[11, ]
      id <- table[2, 2]
      # id <- gsub("[¥¥(¥¥)]", "", regmatches(id, gregexpr("¥¥(.*?¥¥)",
id))[[1]]) # just keep the bit in brackets
      table <- table[-c(1:11), ]
      table$Timestamp <- sub("[.]00", "", table$Timestamp)
      table <- table[, c("Date", "Time", "Timestamp", "Sensor Glucose
(mmol/L)", "Source", "Sensor Event")]
      colnames(table) <- c("date", "time", "timestamp", "sensorglucose",
"source", "sensorevent")

      # Format the dates properly (convert from character to datetime
format)
      if (filetype == "csv" | filetype == "txt") {
        table$timestamp <-
base::as.POSIXlt(lubridate::parse_date_time(table$timestamp, "dmY HM"), tz
= "GMT")
      } else if (filetype == "xlsx") {
        table$timestamp <-
base::as.POSIXlt(lubridate::parse_date_time(table$timestamp, "Ymd HMS"), tz
= "GMT")
      }

      table$date <- base::as.POSIXlt(lubridate::parse_date_time(table$date,
```

```
                                                                    "dmY"), tz
= "GMT")
      table$time <- base::as.POSIXlt(lubridate::parse_date_time(table$time,
                                                                    "HMS"), tz
= "GMT")

      table$sensorglucose <-
base::suppressWarnings(base::as.numeric(table$sensorglucose))
      table$sensorglucose[which(table$sensorglucose==-9999)] <- NA

      # Get rid of rows where the source is "log sheet" or where sensor
event is not blank
      if (NA %in% table$sensorevent) {
        table <- table[-c(which(!is.na(table$sensorevent))),]
      }

      table <- table[-c(which(table$source=="Log sheet")),]

    } else if (cgmtype == "freestylelibre" | cgmtype ==
"freestylelibrepro") {

      # Tidy
      g <- regexpr("¥¥/[^¥¥/]*$", files[f]) # Find the last "/" in the
filename
      id <- substr(files[f],g+1,(nchar(files[f])-(nchar(filetype)+1))) #
take the bit after the "/" and before the file extension
      rm(g)
      table <- table[,2:4]
      colnames(table) <- c("timestamp", "recordtype", "sensorglucose")

      if (sum(table$recordtype!=0)>0) {
        table <- table[-which(table$recordtype!=0),]
      }

      table <- table[,c("timestamp", "sensorglucose")]

      # Format the dates properly (convert from character to datetime
format)

      if (filetype == "csv" | filetype == "txt") {
        table$timestamp <-
base::as.POSIXlt(lubridate::parse_date_time(table$timestamp, "dmY HM"), tz
= "GMT")
      } else if (filetype == "xlsx") {
```

```
        table$timestamp <-
base::as.POSIXlt(lubridate::parse_date_time(table$timestamp, "Ymd HMS"), tz
= "GMT")
      }

      table$date <- format(as.POSIXct(table$timestamp,format='Ymd
%H:%M:%S'),format='%d/%m/%Y')
      table$date <- base::as.POSIXlt(lubridate::parse_date_time(table$date,
                                                                "dmY"), tz
= "GMT")

      table$time <- strftime(table$timestamp, format="%H:%M:%S")
      table$time <- base::as.POSIXlt(lubridate::parse_date_time(table$time,
                                                                "HMS"), tz
= "GMT")

      table$sensorglucose <-
base::suppressWarnings(base::as.numeric(table$sensorglucose))

    }

    # Put columns in this order
    table <- table[,c("date", "time", "timestamp", "sensorglucose")]

    # Get rid rows for which there is no timestamp
    if (NA %in% table$timestamp) {
      table <- table[-c(base::which(is.na(table$timestamp))),]
    }

    # Sort the data into ascending time order
    table <- table[base::order(table$timestamp), ]

    if (f==1) {
      outputtable <- data.frame(cbind(id, table))
    } else {
      outputtable <- rbind.data.frame(outputtable,
data.frame(cbind(id,table)))
    }

  } # end of file loop

  return(outputtable)
}
```

```
processcgmdata <- function(alltable, outputdirectory = getwd(),
outputfilename="", cgmtype = "", trim = TRUE, mindata = 0,
                           ar1 = 10, ar2 = 13.9, br1 = 3.9, br2 = 3.0,
epdur = 15, leeway = 2) {

  # VARIABLES
  # alltable = the tidied data table produced by tidycgmdata function
  # outputdirectory = where you want the final collated dataset to be
saved. Defaults to current working directory
  # outputfilename = what you want to call the final collated dataset
(excluding file extension)
  # cgmtype = "ipro" or "freestylelibre"
  # trim = whether or not to trim off first and last days of wear
  # mindata = minimum percentage time active for a day of wear to be
included (e.g. if 70, any day where the monitor is active less than 70% of
the time
  #           will be dropped)
  # ar1 = threshold for hyperglycaemia
  # ar2 = threshold for severe hyperglycaemia
  # br1 = threshold for hypoglycaemia
  # br2 = threshold for severe hypoglycaemia
  # epdur = user-defined length of an episode of hypo/hyperglycaemia (in
minutes)
  # leeway = amount of discrepancy allowed between consecutive glucose
measurements (in minutes)

  subjects <- unique(alltable$id)

  # Loop through each participant

  for (s in 1:length(subjects)) {

    id <- subjects[s]

    # Portion of the table for participant i
    table <- alltable[which(alltable$id==subjects[s]),]

    # Earliest datetime for which there was a non-missing glucose
measurement
    recordstart <- table$timestamp[min(which(!is.na(table$sensorglucose)))]

    # Latest datetime in the data
    removaltime <- table$timestamp[length(table$timestamp)]
```

```
    # Number of days in the dataset
    numdays <- length(unique(table$date))

    # Get rid of days with no glucose measurement up to first day with non-
zero glucose measurement
    if
(min(which(table$date==table$date[min(which(!is.na(table$sensorglucose)))])
)>1) {
      table <- table[-
c(1:min(which(table$date==table$date[min(which(!is.na(table$sensorglucose))
)]))-1),]
    }

    # Remove days after the final day with any glucose measurement
    if
(max(which(table$date==table$date[max(which(!is.na(table$sensorglucose)))])
)<length(table$date)) {
      table <- table[-
c(max(which(table$date==table$date[max(which(!is.na(table$sensorglucose)))]
))+1:length(table$date)),]
    }

    # If trim is TRUE, remove the first and last days of wear
    if (trim == TRUE) {
      daysbeforetrim <- length(unique(table$date))
      table <- table[-which(table$date==unique(table$date)[1] |
table$date==unique(table$date)[length(unique(table$date))]),]
    } else {
      daysbeforetrim <- NA
    }

    # Number of days worn
    numdaysworn <- length(unique(table$date))

    # Generate variable that is time from current reading to the next one
    for (k in 1:nrow(table)-1) {
      table$timeto[k] <- difftime(table$timestamp[k+1], table$timestamp[k],
units="mins")
    }

    if (numdaysworn>0) {

      daysworn <- as.numeric(unique(table$date))
      dates <- unique(table$date)
```

```
      # Day by day metrics
      pcactive <- vector(mode="numeric", length=numdaysworn)

      # Epoch length in minutes
      if (cgmtype == "ipro") {
        interval <- 5
      } else if (cgmtype == "freestylelibre") {
        interval <- 15
      }

      for (i in 1:numdaysworn) {

        thisday <- which(as.numeric(table$date)==daysworn[i])

        # % of time CGM is active
        pcactive[i] <-
(sum(!is.na(table$sensorglucose[thisday])))/((24*60)/interval)*100
      }


      # CUT OFF INVALID DAYS HERE ###############

      validdays <- which(pcactive>=mindata)
      numvaliddays <- length(validdays)


      ##########################################

      if (numvaliddays>0) {

        if (numdaysworn!=numvaliddays) {
          pcactive <- pcactive[validdays]
          daysworn <- daysworn[validdays]
          dates <- dates[validdays]
          table <- table[-which(!(as.numeric(table$date) %in% daysworn)),]
        }

        # Calculate the change in glucose from the previous time point
        table$row <- c(1:nrow(table)) # variable to keep original order of
data (sorting by timestamp is iffy)
        table$glucosediff <- NA
        for (k in 2:nrow(table)) {
```

```
          if (table$timeto[k-1]<=interval+leeway & table$timeto[k-
1]>=interval-leeway) {
            table$glucosediff[k] <- table$sensorglucose[k]-
table$sensorglucose[k-1]
          }
        }
        table$absdiff <- abs(table$glucosediff) # calculate magnitude of
glucose changes
        table <- table[order(table$absdiff, decreasing=TRUE),] # put these
in decreasing order
        table$flag <- NA
        table$flag[1:10] <- 1 # flag the first 10 absolute glucose changes
as being the 10 largest
        table$flag[11:nrow(table)] <- 0 # others are 0
        table <- table[order(table$row),] # put the data back in original
chronological order

        table$flagday <- NA
        for (day in daysworn) {
          subset <- table[which(as.numeric(table$date)==day),]
          subset$absdiff[1] <- NA # for day to day calculations, at first
index there is no difference from previous measurement
          subset <- subset[order(subset$absdiff, decreasing=TRUE),]
          subset$flagday[1:10] <- 1
          subset$flagday[11:nrow(subset)] <- 0
          subset <- subset[order(subset$row),]
          table[which(as.numeric(table$date)==day),"flagday"] <-
subset$flagday
        }

        table <- table[,-c(7,9)] # delete the row and absdiff variables as
no longer needed

        # write this participant's glucose change values to a separate csv
file
        write.csv(table[,c("date","time","timestamp","sensorglucose",
"glucosediff", "flag", "flagday")],
file=paste(outputdirectory,"/",id,"_glucose_changes.csv", sep=""),
row.names=FALSE)

        meanglucose <- A1c <- glySD <- glyCV <- TAR1 <- TAR2 <- TIR <- TBR1
<- TBR2 <- LBGI <- HBGI <-
          numhypos <- numsevhypos <- numhypers <- numsevhypers <- aucs <-
vector(mode="numeric", length=numvaliddays)
```

```
        # change this loop to go through valid days
        for (i in 1:numvaliddays) {

          thisday <- which(as.numeric(table$date)==daysworn[i])

          # Mean glucose
          meanglucose[i] <- mean(table$sensorglucose[thisday], na.rm=TRUE)

          # Estimated A1c
          A1c[i] <- (2.59+meanglucose[i])/1.59

          # Glycemic variability
          glySD[i] <- sd(table$sensorglucose[thisday], na.rm=TRUE)
          glyCV[i] <- glySD[i]/meanglucose[i]

          # Time in/above/below ranges (as percentages of time active)
          TAR1[i] <- (sum(table$sensorglucose[thisday]>ar2,
na.rm=TRUE)/(sum(!is.na(table$sensorglucose[thisday]))))*100
          TAR2[i] <- (sum(table$sensorglucose[thisday]>ar1,
na.rm=TRUE)/(sum(!is.na(table$sensorglucose[thisday]))))*100
          TIR[i] <- (sum((table$sensorglucose[thisday]>=br1 &
table$sensorglucose[thisday]<=ar1),
na.rm=TRUE)/(sum(!is.na(table$sensorglucose[thisday]))))*100
          TBR1[i] <- (sum(table$sensorglucose[thisday]<br1,
na.rm=TRUE)/(sum(!is.na(table$sensorglucose[thisday]))))*100
          TBR2[i] <- (sum(table$sensorglucose[thisday]<br2,
na.rm=TRUE)/(sum(!is.na(table$sensorglucose[thisday]))))*100

          # LBGI and HBGI
          f_bg <- 1.509*(log(18*table$sensorglucose[thisday])^1.084-5.381)
          r_bg <- 10*f_bg^2

          # Separate blood glucose risk function into left and right
branches corresponding to low "rl" and high "rh"
          rl_bg <- rh_bg <- vector(mode="numeric", length=length(thisday))

          for (j in 1:length(thisday)) {
            if (is.na(f_bg[j])) {
              rl_bg[j] <- rh_bg[j] <- NA
            } else
              if (f_bg[j] < 0) {
                rl_bg[j] <- r_bg[j]
                rh_bg[j] <- 0
```

```
            } else if (f_bg[j] >0) {
              rl_bg[j] <- 0
              rh_bg[j] <- r_bg[j]
            } else {
              rl_bg[j] <- rh_bg[j] <- 0
            }
          }

          LBGI[i] <- mean(rl_bg, na.rm=TRUE)
          HBGI[i] <- mean(rh_bg, na.rm=TRUE)

          # Hypos and hypers
          br <- sbr <- ar <- sar <- vector(mode="numeric",
length=length(thisday))

          # Find epochs where glucose is above or below range
          for (j in 1:length(thisday)) {
            if (is.na(table$sensorglucose[j])) {
              sbr[j] <- br[j] <- sar[j] <- ar[j] <- 0
            } else if (table$sensorglucose[j]<br2) {
              sbr[j] <- 1
            } else if (table$sensorglucose[j]<br1) {
              br[j] <- 1
            } else if (table$sensorglucose[j]>ar2) {
              sar[j] <- 1
            } else if (table$sensorglucose[j]>ar1) {
              ar[j] <- 1
            }
          }

          # See if there are any instances severely below range
          numsevhypos[i] <- counteps(sbr, table$timeto[thisday], interval,
leeway, epdur)

          # See if there are any instances below range
          numhypos[i] <- counteps(br, table$timeto[thisday], interval,
leeway, epdur)

          # See if there are any instances above range
          numhypers[i] <- counteps(ar, table$timeto[thisday], interval,
leeway, epdur)

          # See if there are any instances severely above range
```

```
          numsevhypers[i] <- counteps(sar, table$timeto[thisday], interval,
leeway, epdur) # seems to be bugging

          # AUC
          sensorBG <- base::as.numeric(table$sensorglucose[thisday], length
= 1)
          xaxis <- base::seq(from = 0, length.out = base::length(sensorBG),
                             by = (interval/60))   # interval is epoch
length in seconds
          xaxis[base::which(is.na(sensorBG))] <- NA
          xaxis <- xaxis[!is.na(xaxis)]
          sensorBG <- sensorBG[!is.na(sensorBG)]
          aucs[i] <- pracma::trapz(xaxis, sensorBG)


        } # end looping through days

        # Metrics across whole wear time
################################################################################
#
        pcactive_total <-
(sum(!is.na(table$sensorglucose)))/((24*60*numvaliddays)/interval)*100
        meanglucose_total <- mean(table$sensorglucose, na.rm=TRUE)
        A1c_total <- (2.59+meanglucose_total)/1.59
        glySD_total <- sd(table$sensorglucose, na.rm=TRUE)
        glyCV_total <- glySD_total/meanglucose_total

        TAR1_total <- (sum(table$sensorglucose>ar2,
na.rm=TRUE)/(sum(!is.na(table$sensorglucose))))*100
        TAR2_total <- (sum(table$sensorglucose>ar1,
na.rm=TRUE)/(sum(!is.na(table$sensorglucose))))*100
        TIR_total <- (sum((table$sensorglucose>=br1 &
table$sensorglucose<=ar1),
na.rm=TRUE)/(sum(!is.na(table$sensorglucose))))*100
        TBR1_total <- (sum(table$sensorglucose<br1,
na.rm=TRUE)/(sum(!is.na(table$sensorglucose))))*100
        TBR2_total <- (sum(table$sensorglucose<br2,
na.rm=TRUE)/(sum(!is.na(table$sensorglucose))))*100

        # LBGI and HBGI
        f_bg <- 1.509*(log(18*table$sensorglucose)^1.084-5.381)
        r_bg <- 10*f_bg^2
```

```
        # Separate blood glucose risk function into left and right branches
corresponding to low "rl" and high "rh"
        rl_bg <- rh_bg <- vector(mode="numeric",
length=length(table$sensorglucose))

        for (j in 1:length(table$sensorglucose)) {
          if (is.na(f_bg[j])) {
            rl_bg[j] <- rh_bg[j] <- NA
          } else
            if (f_bg[j] < 0) {
              rl_bg[j] <- r_bg[j]
              rh_bg[j] <- 0
            } else if (f_bg[j] >0) {
              rl_bg[j] <- 0
              rh_bg[j] <- r_bg[j]
            } else {
              rl_bg[j] <- rh_bg[j] <- 0
            }
        }

        LBGI_total <- mean(rl_bg, na.rm=TRUE)
        HBGI_total <- mean(rh_bg, na.rm=TRUE)

        # Hypos and hypers
        numhypos_total <- sum(numhypos)
        numsevhypos_total <- sum(numsevhypos)
        numhypers_total <- sum(numhypers)
        numsevhypers_total <- sum(numsevhypers)

        # AUC
        sensorBG <- base::as.numeric(table$sensorglucose, length = 1)
        xaxis <- base::seq(from = 0, length.out = base::length(sensorBG),
                           by = (interval/60))   # interval is epoch length
in seconds
        xaxis[base::which(is.na(sensorBG))] <- NA
        xaxis <- xaxis[!is.na(xaxis)]
        sensorBG <- sensorBG[!is.na(sensorBG)]
        auc_total <- pracma::trapz(xaxis, sensorBG)


##############################################################################
##################################

        # Bind all data together
```

```
        if (s==1) {
          outputtable <- data.frame(id, day=c(1:numvaliddays), date=dates,
daysbeforetrim, numdaysworn, numvaliddays, pcactive_total,
meanglucose_total, A1c_total, glySD_total, glyCV_total,
                                    TAR1_total, TAR2_total, TIR_total,
TBR1_total, TBR2_total, LBGI_total, HBGI_total,
                                    numhypos_total, numsevhypos_total,
numhypers_total, numsevhypers_total, auc_total,
                                    pcactive, meanglucose, A1c, glySD,
glyCV,
                                    TAR1, TAR2, TIR, TBR1, TBR2, LBGI,
HBGI,
                                    numhypos, numsevhypos, numhypers,
numsevhypers, aucs)

        } else {
          outputtable <- rbind.data.frame(outputtable, data.frame(id,
day=c(1:numvaliddays), date=dates, daysbeforetrim, numdaysworn,
numvaliddays, pcactive_total, meanglucose_total, A1c_total, glySD_total,
glyCV_total,

TAR1_total, TAR2_total, TIR_total, TBR1_total, TBR2_total, LBGI_total,
HBGI_total,

numhypos_total, numsevhypos_total, numhypers_total, numsevhypers_total,
auc_total,
                                                                    pcactive,
meanglucose, A1c, glySD, glyCV,
                                                                    TAR1,
TAR2, TIR, TBR1, TBR2, LBGI, HBGI,
                                                                    numhypos,
numsevhypos, numhypers, numsevhypers, aucs))
        }

      } else if (numvaliddays==0) {

        pcactive <- meanglucose <- A1c <- glySD <- glyCV <- TAR1 <- TAR2 <-
TIR <- TBR1 <- TBR2 <- LBGI <- HBGI <-
          numhypos <- numsevhypos <- numhypers <- numsevhypers <- aucs <-
NA

        pcactive_total <- meanglucose_total <- A1c_total <- glySD_total <-
glyCV_total <- TAR1_total <- TAR2_total <- TIR_total <-
```

```
          TBR1_total <- TBR2_total <- LBGI_total <- HBGI_total <-
numhypos_total <- numsevhypos_total <- numhypers_total <-
numsevhypers_total <-
          auc_total <- NA

        # Bind all data together
        if (s==1) {
          outputtable <- data.frame(id, day=NA, date=NA, daysbeforetrim,
numdaysworn, numvaliddays, pcactive_total, meanglucose_total, A1c_total,
glySD_total, glyCV_total,
                                    TAR1_total, TAR2_total, TIR_total,
TBR1_total, TBR2_total, LBGI_total, HBGI_total,
                                    numhypos_total, numsevhypos_total,
numhypers_total, numsevhypers_total, auc_total,
                                    pcactive, meanglucose, A1c, glySD,
glyCV,
                                    TAR1, TAR2, TIR, TBR1, TBR2, LBGI,
HBGI,
                                    numhypos, numsevhypos, numhypers,
numsevhypers, aucs)
        } else {
          outputtable <- rbind.data.frame(outputtable, data.frame(id,
day=NA, date=NA, daysbeforetrim, numdaysworn, numvaliddays, pcactive_total,
meanglucose_total, A1c_total, glySD_total, glyCV_total,

TAR1_total, TAR2_total, TIR_total, TBR1_total, TBR2_total, LBGI_total,
HBGI_total,

numhypos_total, numsevhypos_total, numhypers_total, numsevhypers_total,
auc_total,
                                                                    pcactive,
meanglucose, A1c, glySD, glyCV,
                                                                    TAR1,
TAR2, TIR, TBR1, TBR2, LBGI, HBGI,
                                                                    numhypos,
numsevhypos, numhypers, numsevhypers, aucs))
        }


      }

    } # end (if numdaysworn>0) loop
```

```
  } # end looping through subjects

  # Export final file
  write.csv(outputtable,
file=paste(outputdirectory,"/",outputfilename,"_long", ".csv", sep=""),
row.names=FALSE)
  test.final <- tidyr::pivot_wider(outputtable, id_cols=c("id",
"daysbeforetrim", "numdaysworn", "numvaliddays", "day", "pcactive_total",
"meanglucose_total", "A1c_total", "glySD_total", "glyCV_total",
                                                    "TAR1_total",
"TAR2_total", "TIR_total", "TBR1_total", "TBR2_total", "LBGI_total",
"HBGI_total",
                                                    "numhypos_total",
"numsevhypos_total", "numhypers_total", "numsevhypers_total", "auc_total"),
                                    names_from=day, names_prefix="day",
values_from=colnames(outputtable[,-c(1:2, 4:23)]))
  #test.final <- test.final[,]
  write.csv(test.final, file=paste(outputdirectory,"/",outputfilename,
".csv", sep=""), row.names=FALSE)

} # end function


counteps <- function(vector, timeto, interval, leeway, epdur) {

  # vector = ar, sar, br, sbr
  # timeto = table$timeto
  # interval = expected interval between CGM readings
  # leeway = amount of deviation allowed from the interval
  # epdur = duration of episode

  numeps <- 0

  # If any 1's in the column
  if (sum(vector==1)>0) {

    # Find first 1
    j <- min(which(vector==1))

    # Won't count as an episode if only a 1 at the very end of the day
    if (j!=length(vector)) {
      count <- 1
      length <- timeto[j]
    }
```

```
    # If it's not the last entry
    while (j<length(vector)) {

      if (vector[j+1]==1 & timeto[j]>=interval-leeway &
timeto[j]<=interval+leeway ) {
        # check if j+1 is 1 and timeto is in interval+/- leeway
        # if so then count <- count+1, j <- j+1
        count <- count+1
        j <- j+1

        if (j!=length) {
          length <- length + timeto[j]
        } else {
          length <- length + interval # if it is the last reading of the
day, assume timeto to be interval length
        }


      } else {

        # Next reading is 1 but timing is off
        if (vector[j+1]==1 & !(timeto[j]>=interval-leeway &
timeto[j]<=interval+leeway) ) {
          ### don't count the current one
          # Just find the next one

          # Or if timing is fine but next reading is zero
        } else if (vector[j+1]!=1 & timeto[j]>=interval-leeway &
timeto[j]<=interval+leeway ) {

          # See if episode is long enough to be counted
          if (length>=epdur) {
            numeps <- numeps+1
          }
        }


        # Find next 1 and repeat
        if (j<length(vector) & sum(vector[(j+1):length(vector)]==1)>0) {
          j <- j+min(which(vector[(j+1):length(vector)]==1)) # check if
there are any, first!
          count <-  1
          length <- timeto[j]
```

```
        } else {
          j <- length(vector)+1 # get out of the loop, no more episodes
left
        }

      }

      # at this point, either the episode has not finished
      # or it has and we've found the next 1
      # but either way we are at the last entry
      if (j==length(vector)) {

        # See if episode is long enough to be counted
        if (!is.na(length) & length>=epdur) {
          numeps <- numeps+1
        }


      }

    } # end of while loop

  } # end of whole process

  return(numeps)
}
```

Appendix C7 RStudio code for processing data using functions defined in Appendix C6 for analysis of CGM data

```
# Processing glucose data using Functions_v10

# Set this to the folder containing the "Functions_v10.R" file
setwd("")
source("Functions_v10.R")

# Tidy up your data:
# inputdirectory = the path to the folder containing your individual
spreadsheets/data files for each participant (and no others!)
# cgmtype = "ipro" or "freestylelibre", depending on which you've used
# filetype = "xlsx", "csv", or "txt". Need to all be the same type
data <- tidycgmdata(inputdirectory = "Raw CGM data",
                    cgmtype = "freestylelibre", filetype = "csv")

# Process the tidied data:
# data = the tidied data produced by tidycgmdata
# outputfilename = what you want the final dataset to be called and saved
as (don't put a file extension! It exports as an excel sheet)
# outputdirectory = where you want the file to be saved (I would strongly
recommend not saving it in the same folder you store the individual's
spreadsheets in)
# cgmtype = "ipro" or "freestylelibre" (freestylelibre should be fine even
if you've used the libre pro)
# mindata = minimum percentage time active for a day of wear to be included
(e.g. if 70, any day where the monitor is active less than 70% of the time
#           will be dropped)
processcgmdata(data,
               outputfilename = "CGM_yourStudyName_processed",
               outputdirectory = "Processed CGM data",
               cgmtype = "freestylelibre",
               mindata = 70)

# Run the code up to this point if you just want to process your raw CGM
data files
# Running the code below will produce plots of each participants
accelerometer and CGM data

source("Plotting functions.R")

plotCGMAccelData(idFormat = "CD[0-9]*", cgmType = "freestylelibre")
```

Appendix C8 RESPONSE Post-follow-up questionnaires

Participant ID: RES☐☐☐☐

INTERVENTION EVALUATION

RESPONSE

Online Education [to be AFTER follow-up only]

1. Did you complete the online education session? Yes all of it ☐ Yes partially ☐ No ☐

If no, please indicate why and then move on to the next section:
……
……
……
……

2. Please tell us your thoughts on the different aspects of the online education session:

		On a scale of 1 to 5, (1 being not at all useful, 5 being extremely useful) how useful did you find this sheet? (please circle)
Did you complete the worksheet to calculate your sitting time?	Yes ☐ No ☐	1 2 3 4 5
Did you complete the goal setting sheet?	Yes ☐ No ☐	1 2 3 4 5
Did you read the top tips to reduce sitting time sheet?	Yes ☐ No ☐	1 2 3 4 5
Did you watch the animations?	Yes ☐ No ☐	1 2 3 4 5
Did you read the case studies from previous participants?	Yes ☐ No ☐	1 2 3 4 5

3. Please tick the box which best matches your overall assessment of the RESPONSE online education session below:

	Strongly disagree	Disagree	Neither disagree or agree	Agree	Strongly Agree

The level of the session was appropriate (i.e., the information provided was easy to understand)					
The length of the session was appropriate					
The session increased **my awareness** of the health consequences of too much sitting					
The health consequences covered in the session **motivated me** to make a change to the time that I spend sitting					
The health benefits of reducing and breaking up sitting **motivated me** to make a change to the time that I spend sitting					
Overall, the session motivated me to make a change to the time that I spend sitting					

What were the key messages that you took away from the online education session:

1……
……
……
……..

2.……
……
……
……..

3.……
……
……
……..

Wrist-worn self-monitoring device Feedback

You were provided with a wrist-worn activity tracker to help you to either track your sitting time or provide prompts to break up sitting.

1. Have you used the wrist-worn device that was provided? Yes ☐ No ☐

   If **YES go to Q3**, if **NO** please use this space to tell us the reasons why you have not used it and **only answer Q2** in this section

   ……
   ……

……
……

2. Do you plan to purchase/use something similar in the coming months? Yes ☐ No ☐

   (Please move on to the next section of questions 'Alternative support')

3. Over the course of the intervention, how often have you used the wrist-worn device:

   Everyday ☐ A few times/week ☐ Once a week ☐ Infrequently ☐

4. In the first week how often did you use the device:

   Everyday ☐ A few times/week ☐ Once a week ☐ Infrequently ☐

5. On a scale of 1 to 5, (1 being not at all useful, 5 being extremely useful) how useful was the device for reminding you to break up your sitting?

1	2	3	4	5
☐	☐	☐	☐	☐

6. The device has actually encouraged me to reduce the time I spend sitting
   a. Strongly agree ☐
   b. Agree ☐
   c. Neither agree or disagree ☐
   d. Disagree ☐
   e. Strongly disagree ☐

7. Do you have any other comments regarding the device? (e.g., usefulness, good points, improvements needed)

   ……
   ……
   ……
   ……
   ……..

Apps/computer software Feedback

The online education session suggested several apps and computer software to help you to either track your sitting time or provide prompts to break up sitting.

4. Have you used any of the apps/software that were suggested? Yes ☐ No ☐
   If **YES go to Q3**, if **NO** please use this space to tell us the reasons why you have not used them and **only answer Q2** in this section
   ……
   ……
   ……
   ……

5. Do you plan to try them in the coming months? Yes ☐ No ☐
   (Please move on to the next section of questions 'Alternative support')

6. Please tick the apps/software that you have used:

	Yes	No
Rise & Recharge App		
MyHealthAvatar App		
Sitting Time App		
Outstanding (Google chrome extension)		
Other (please detail)		

7. Over the course of the intervention, how often have you used any of the apps/software:

   Everyday ☐ A few times/week ☐ Once a week ☐ Infrequently ☐

8. In the first week how often did you use the apps/software:
   Everyday ☐ A few times/week ☐ Once a week ☐ Infrequently ☐

9. On a scale of 1 to 5, (1 being not at all useful, 5 being extremely useful) how useful are the apps/software for reminding you to break up your sitting?

1	2	3	4	5
☐	☐	☐	☐	☐

10. The apps/software have actually encouraged me to reduce the time I spend sitting
    a. Strongly agree ☐
    b. Agree ☐
    c. Neither agree or disagree ☐
    d. Disagree ☐
    e. Strongly disagree ☐

11. Do you have any other comments regarding the apps/software? (e.g., usefulness, good points, improvements needed)

……
……
……
……
……..

Alternative Support

1. Have you used any other devices/tools/methods to encourage you to reduce the time you spend sitting that weren't suggested in the programme? Yes ☐ No ☐

2. If **YES** please use this space to tell us which tools/devices/methods you have used and how they have helped

……
……
……
……
……

Strategies to sit less

Please list all of the strategies you have used to sit less at work and/or at home (e.g., stand during TV adverts) and tick whether you did this at work or at home or tick both

Strategy	Work	Home
1.		
2.		
3.		
4.		
5.		
6.		
7.		

8.		
9.		
10.		

Things that get in the way of sitting less (i.e., barriers)

Please list any barriers that you have or are experiencing when it comes to trying to reduce your sitting time:

1……

……

……2……

……

……

……

3……

……

……

……

4……

……

……5……

……

……

……

Other Lifestyle Changes

1. Since starting the intervention has anything in your life changed that has had an impact on your lifestyle (e.g., moved house, joined a gym, started a diet group, had a major life event)?

   Yes ☐ No ☐

If **YES,** could you please **briefly explain what changes and how** it has impacted your lifestyle below:

……
……
……
……
……
……
……
……

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ordinate the Cochrane Work Group. Sharea Ijaz: None known. Katriina T Kukkonen-Harjula: None known. Veerle Hermans: None known. Zeljko Pedisic: None known.
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