Enhancing Type 1 Diabetes Self-Management: Investigating the Role of Physical Activity and Sedentary Behaviours in Glucose Control

Anwar Mahmoud Ahmad Alobaid

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The candidate confirms that the work submitted is her own, except where work which has formed part of jointly-authored publications has been included. The contribution of the candidate and the other authors to this work has been explicitly indicated below. The candidate confirms that appropriate credit has been given within the thesis where reference has been made to work of others.

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Abstract

Physical activity (PA), sedentary behaviour (SB), and interruptions to prolonged sitting may influence glucose control in adults with type 1 diabetes (T1D). This thesis investigates their impact using experimental studies. One study explored attitudes and barriers to exercise in adults with T1D, stratified by insulin resistance (IR), using estimated glucose disposal rate (eGDR) as a marker. The study found that hypoglycaemia was the main concern for those with IR, whereas non-glycaemic factors were the main barriers for those without IR. A systematic review and meta-analysis showed that adults with T1D are more inactive and sedentary than guidelines recommended (Part A). It also found that acute exercise led to short-term reductions in plasma glucose concentrations, but chronic exercise had no significant impact on glycated haemoglobin (HbA1c) levels or fasting plasma glucose concentrations (Part B). A 14-day observational study using continuous glucose monitoring (CGM) indicated that moderate-intensity PA was associated with higher blood glucose concentrations, while vigorous-intensity PA improved time in range (TIR). Finally, a randomised controlled trial (RCT), demonstrated that interrupting prolonged sitting with short bouts of low-intensity walking improved glucose control, increasing TIR, and reducing hyperglycaemia without raising hypoglycaemia risk in T1D. These findings highlight the importance of reducing sedentary time and incorporating activity breaks to enhance glucose control in T1D, supporting the development of future long-term interventions.

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Abbreviations

AAU	Arbitrary activity units
ACSM	American College of Sports Medicine
ADA	American Diabetes Association
BAPAD-1	Barriers to Physical Activity in Type 1 Diabetes
B-cells	B lymphocytes
BIN file	Binary files
BMI	Body mass index
β-cells	Beta cells
CGM	Continuous glucose monitoring
CI	Confidence interval
CSII	Continuous subcutaneous insulin infusion
CVD	Cardiovascular disease
DCCT	Diabetes Control and Complications Trial
EDIC	Epidemiology of Diabetes Interventions and Complications
eGDR	Estimated glucose disposal rate
GLM	General linear model
GLUT	Glucose transporter
GLUT1	Glucose transporter protein type 1
GLUT2	Glucose transporter protein type 2
GLUT4	Glucose transporter protein type 4
HbA1c	Glycated haemoglobin
HDL	High-density lipoprotein
HLA	Human leukocyte antigens
HOMA-IR	Homeostatic model assessment for insulin resistance
HR_{max}	Maximum heart rate
HR_{peak}	Peak heart rate
HRR	Heart rate reserve
HTN	Hypertension
ICCs	Intraclass correlation coefficients
IDDM	Insulin-dependent diabetes mellitus
IPAQ	International physical activity questionnaire
IPAQ-LF	International physical activity questionnaire – long form
IPAQ-SF	International physical activity questionnaire – short form
IQR	Interquartile range

IR	Insulin resistance
isCGM	Intermittently scanned continuous glucose monitoring
ISRCTN	International Standard Randomised Controlled Trial Number
LTPA	Leisure-time physical activity
LPL	Lipoprotein lipase
MARD	Mean absolute relative difference
MDIs	Multiple daily injections
MET	Metabolic equivalents of task
MeSH	Medical Subject Headings
MVPA	Moderate-to-vigorous physical activity
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NIDDM	Non-insulin dependent diabetes mellitus
NOS	Newcastle-Ottawa Scale
PA	Physical activity
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomised controlled trial
ROB2	Version 2 of the Cochrane Risk-of-Bias
ROBINS-I	Risk of Bias in Non-randomised Studies - of Interventions
rtCGM	Real-time continuous glucose monitoring
SB	Sedentary behaviour
SD	Standard deviation
SEM	Standard error of the mean
SMBG	Self-monitoring of blood glucose
SPSS	Statistical Package for the Social Sciences
TAR	Time above range
TBR	Time below range
T-cells	T lymphocytes
T1D	Type 1 diabetes
T2D	Type 2 diabetes
TDD	Total daily dose
TIR	Time in range
VO_{2max}	Maximal oxygen consumption
VO_{2peak}	Peak oxygen uptake

Chapter 1 – General Introduction & Literature Review

1.1 Diabetes Mellitus

Diabetes mellitus is one of the most prevalent chronic health conditions worldwide, and is characterised by glucose dysregulation, which contributes to diabetes complications such as retinopathy, neuropathy, nephropathy, and cardiovascular disease (CVD) (Huang et al., 2023). The condition is caused by deficiencies in the production and/or sensitivity to endogenous insulin (American Diabetes Association, 2014), a hormone which normally acts to lower blood glucose concentrations by stimulating glucose uptake from the bloodstream into cells (Kahn et al., 2006; Röder et al., 2016). Insulin is a hormone produced by the beta cells (β-cells) of the pancreas, and plays a critical role in glucose utilisation for energy production (Fu et al., 2013). It stimulates glucose uptake in peripheral tissues, such as muscle and adipose tissue, by facilitating the translocation of glucose transporter protein type 4 (GLUT4) from the intracellular stores to the cell membrane, facilitating glucose uptake into muscle and adipose tissue cells and contributing to glucose homeostasis (glucose regulation) (Sanni et al., 2020). In contrast, the liver primarily uses glucose transporter protein type 2 (GLUT2), which is not sensitive to insulin and regulates the release of glucose from liver cells into the circulation via gluconeogenesis to maintain blood glucose concentrations (Simmons, 2017; Chadt and Al-Hasani, 2020; Shen et al., 2024). Therefore, insulin's role in liver is more focused on regulating glucose production rather than directly stimulating glucose uptake.

Symptoms of diabetes mellitus include polyuria (frequent urination), polydipsia (excessive thirst), polyphagia (excessive hunger), weight loss, blurred vision, and fatigue (Razaq et al., 2020). These symptoms reflect the underlying

dysglycaemia, defined as an abnormality in blood glucose regulation (Gerstein, 1998; Monnier et al., 2008). Dysglycaemia includes hyperglycaemia, hypoglycaemia, and glycaemic variability, which contribute to the clinical challenges in managing diabetes and are associated with both short-term complications (i.e., severe hypoglycaemia (< 3.0 mmol/L), which can lead to confusion, seizures, or loss of consciousness (Nakhleh and Shehadeh, 2021), and acute hyperglycaemia (> 13.9 mmol/L), leading to diabetic ketoacidosis) and long-term diabetes complications (Gerstein, 1998; Kahkoska et al., 2019). The global prevalence of diabetes among adults was projected to rise from 536.6 million (10.5% of the global population, one in ten adults) in 2021 to 783.2 million (12.2%) by 2045, affecting approximately one in every eight adults (Sun et al., 2022). This includes type 1 diabetes (T1D), type 2 diabetes (T2D), and gestational diabetes. The overall cost for hospital care for individuals with diabetes in the UK was £5.5 billion per year (Stedman et al., 2020).

The main types of diabetes mellitus include T1D and T2D. Among these, T2D is the most prevalent, accounting for over 90% of all diabetes cases, exceeding the occurrence of T1D, and is also known as non-insulin-dependent diabetes mellitus (NIDDM) (DeFronzo et al., 2015). Where T1D results from autoimmune destruction of pancreatic β-cells, leading to absolute insulin deficiency, individuals with T2D typically do not depend on exogenous insulin for survival, but may require it for effective glycaemic control (Mahan and Escott-Stump, 2008), as there is still a degree of endogenous insulin release and action. In the past, T2D was commonly known as late-onset diabetes, diagnosed in adults aged over 40 years (Herman and Zimmet, 2012), but now children and adolescents are also experiencing its onset (D’adamo and Caprio, 2011), which might be due to an unhealthy lifestyle (e.g., physical inactivity and excess

nutrient/energy intake). This condition is characterised by a progressive decline in sufficient insulin secretion from β-cells, often occurring in the context of insulin resistance (IR) and increased adiposity (Galicia-Garcia et al., 2020), attributed to unhealthy dietary patterns and reduced participation in physical activity (PA) (Herman and Zimmet, 2012). Features of IR and overweight are now observed in some individuals with T1D due to intensive insulin therapy or a sedentary lifestyle; this phenomenon is referred to as double diabetes (Kietsiriroje et al., 2019).

Prolonged insulin deficiency or resistance can lead to hyperglycaemia, causing damage to various organs and posing severe and potentially life-threatening health risks. Once hyperglycaemia occurs, individuals with any type of diabetes face the risk of developing vascular complications, although rates of progression may vary (Marcovecchio, 2017). These complications include CVD, nerve damage (diabetic neuropathy), kidney damage (diabetic nephropathy), and damage to the blood vessels of the retina (diabetic retinopathy), which can ultimately result in visual impairment and blindness (Mouri and Badireddy, 2023). Diabetes complications significantly impact global public health, as individuals with diabetes still present with increased risks of complications even after undergoing intensive glucose control interventions (Ong et al., 2023). Advancements in diabetes management technologies have emerged in response to the secular trends in diabetes prevalence, offering a new avenue for improving glucose control and potentially reducing the risk of complications. Continuous glucose monitoring (CGM) systems provide real-time readings, allowing more frequent and accurate monitoring compared to traditional methods, such as self-monitoring of blood glucose (SMBG) (Janapala et al., 2019). Additionally, closed-loop systems, also known as artificial pancreas, automate insulin delivery based on CGM data, offering the potential for tighter glucose control and increased time

in range (Fuchs and Hovorka, 2020; Boscari et al., 2022). These technologies represent promising tools for optimising diabetes management and reducing the risk of long-term complications (Prahalad et al., 2018; Janapala et al., 2019).

Previous research has examined the effects of PA and exercise in individuals with diabetes has predominantly focused on T2D (Balducci et al., 2022; Zhang, 2022; Qian et al., 2023), and has shown beneficial effects on glycated haemoglobin (HbA1c), fasting plasma glucose and 2-hour postprandial glucose, as well as IR using the homeostatic model assessment (HOMA-IR). Findings from studies on T1D and T2D populations cannot be generalised universally due to their distinct pathophysiology mechanisms, where T1D results from autoimmune destruction of pancreatic β-cells, leading to absolute insulin deficiency, while T2D involves IR and relative insulin deficiency within the context of obesity and metabolic syndrome (Krause and De Vito, 2023). As a result, responses to treatments, disease progression, and associated complications may significantly vary between T1D and T2D populations due to factors such as insulin sensitivity, β-cell function, genetic predisposition, and psychological or environmental influences. Therefore, it is important to be cautions when extrapolating findings from these two conditions in terms of the design of management strategies for both conditions. However, research on T1D, particularly in relation to PA, is lacking. Therefore, this PhD thesis aimed to specifically target adults with T1D to address this important research gap.

1.1.1 Type 1 Diabetes

1.1.1.1 Prevalence of Type 1 Diabetes

An increase in T1D prevalence is being observed worldwide among individuals of all ages, with the majority of cases diagnosed younger than 30 years, and it

constitutes about five to ten percent of all cases of diabetes (Daneman, 2006; Mahan and Escott-Stump, 2008). In 2022, the prevalence of T1D globally was estimated to be 8.75 million, including 530,000 new cases diagnosed at all ages (International Diabetes Federation, 2022). Of the total population with T1D in 2022, 1.52 million were younger than 20 years, and 7.23 million were aged 20 years and older (International Diabetes Federation, 2022). Projections anticipate that by 2040, the number of individuals living with T1D is expected to reach 13.5 to 17.4 million (Ogrotis et al., 2023). The annual hospital care expenditure for individuals with T1D in the UK is £3280 per person (Stedman et al., 2020).

1.1.1.2 Pathophysiology of Type 1 Diabetes

Type 1 diabetes typically results from autoimmune destruction of pancreatic β-cells, which are responsible for producing insulin, leading to lifelong absolute loss of endogenous insulin and hyperglycaemia (DiMeglio et al., 2018; Whitney et al., 2019). It is therefore known as insulin-dependent diabetes mellitus (IDDM), as exogenous insulin administration is required for near-normoglycaemia (3.9 – 10.0 mmol/L). The importance of endogenous insulin loss is evident in the fact that insulin is essential for regulating blood glucose concentrations, and pharmacological replacement of insulin is a hallmark of treating T1D. Insulin secretion loss may manifest quickly or gradually (Lucier and Weinstock, 2023). Findings from the study conducted by Oram and colleagues (Oram et al., 2014) demonstrated that individuals with a longer duration of T1D had lower concentrations of C-peptide (r = –0.46; p < 0.0001), which contributes to increased post-meal blood glucose concentrations. The study also indicated that even in long-standing β-cells survive and produce low concentrations of insulin, with the decline in C-peptide concentrations over time reflecting the cumulative loss of these functional β-cells (Oram et al., 2014).

The primary cause of T1D remains unknown, but there are indications that a genetic predisposition, as well as immunologic and environmental factors trigger an autoimmune reaction (Pociot and Lernmark, 2016; Rewers and Ludvigsson, 2016). In predisposed individuals, early-life environmental factors such as exposure to viruses, diet, toxins, and other environmental polluters can 'activate' self-targeting immune cascades (Raman, 2016; Paschou et al., 2018). In the initial phases, the progressive destruction of β-cells is not associated with changes in blood glucose concentrations, as the pancreatic reserve is sufficient to maintain normoglycaemia (Zaccardi et al., 2016). Subsequently, further destruction of β-cells leads to a reduction in endogenous insulin production and a consequent rise in blood glucose concentrations. As the majority of β-cells are destroyed, overt diabetes develops (Knip et al., 2005; Zaccardi et al., 2016). Once the diagnosis is established, it is crucial to maintain glycaemic control as close to the normal range as possible, not only to reduce the risk of diabetes complications (Diabetes Control Complications Trial/Epidemiology of Diabetes Interventions Complications (DCCT/EDIC) Study Research Group, 2005), but also to preserve any remaining β-cells mass/function (as assessed through the measurement of C-peptide concentrations) (Picardi et al., 2006).

In terms of immunological factors, both humoral immunity (production of antibodies) and cellular immunity (activation and coordination of various types of white blood cells) are involved in T1D pathogenesis, with T lymphocytes (T-cells), which mature in the thymus (a small organ located in the chest that plays an important role in developing T-cells) and play a role in cell-mediated immunity, being predominant (Cano and Lopera, 2013; Zaccardi et al., 2016). T lymphocytes are the main immune cells found in pancreatic islet lesions, accompanied by lower concentrations of other immunological cells, such as

macrophages, B lymphocytes (B-cells) and plasma cells (Cano and Lopera, 2013; Zaccardi et al., 2016). The existing literature suggests that functional defects in the bone marrow, thymus, immune system, and β-cells, induced by genetic and environmental factors, collectively contribute to the pathophysiology of T1D (Atkinson et al., 2014; Skyler et al., 2017; Roep et al., 2021).

The main genes that predispose individuals to T1D are the human leukocyte antigen (HLA) class II genes, located on chromosome 6 (Atkinson et al., 2014), which account for 40 to 50% of the genetic risk of T1D (Noble and Valdes, 2011). T1D is strongly linked to HLA class II genes, particularly those present in the HLA-DR3-DQ2 and HLA-DR4-DQ8 haplotypes, either alone or in combination (Pociot and Lernmark, 2016). HLA genes play an important role in regulating immune responses by encoding cell surface proteins responsible for antigen presentation and maintaining self-tolerance (Zaccardi et al., 2016). Differences in the amino acid sequence of these proteins due to genetic variations can alter the range of peptides presented, potentially resulting in a loss of self-tolerance (Zaccardi et al., 2016).

1.1.1.3 Management of Type 1 Diabetes

Effective management of T1D requires intensive glucose control, regular laboratory measurements of HbA1c, and regular glucose monitoring using the CGM (Diabetes Control Complications Trial Research Group, 1993). Additionally, self-management education and support, which includes training on monitoring glycaemia, administering insulin, engaging in PA and reducing sedentary behaviours (SBs), as well as ways of preventing and managing hypoglycaemia, are essential for achieving favourable health outcomes (American Diabetes Association, 2009; Riddell et al., 2017; Huerta-Uribe et al., 2022).

1.1.1.3.1 Insulin Therapy

Individuals with T1D require insulin replacement therapy, such as multiple daily injections (MDIs), continuous subcutaneous insulin infusion/insulin pump therapy (CSII), or closed-loop/artificial pancreas systems, due to their inability to produce adequate insulin (Wangnoo, 2015). These treatment approaches aim to achieve near-normoglycaemia with target blood glucose concentrations ranging from 3.9 to 10.0 mmol/L (Chiang et al., 2014). Several methods exist for metabolic optimisation through insulin therapy; for MDIs, a long-acting insulin analogue is fundamental therapy, providing basal insulin, also known as background insulin, to supply the body with insulin overnight and for between-meal control (Pettus et al., 2016). In addition to the bolus insulin doses of rapid-acting insulin analogue for expected blood glucose rises from meals or snacks, which are recommended to be injected immediately before or soon after food (Slattery et al., 2018).

The CSII method uses a portable, programmable device powered by batteries to continuously deliver rapid-acting insulin via an insulin pump (Pozzilli et al., 2016). The long-acting insulin analogue and rapid-acting insulin analogues were designed to mimic natural bodily endogenous insulin, and have been associated with a decreased risk of hypoglycaemia and reductions in HbA1c levels in individuals with T1D (American Diabetes Association, 2009). Recently, a new method known as a closed-loop system has been developed, which combines an insulin pump with CGM technology. This system delivers insulin glucose-responsively by adjusting infusion rates based on sensor glucose concentrations to maintain blood glucose concentrations (Boughton and Hovorka, 2019). This system represents an important step towards achieving optimal glucose management.

1.1.1.3.1.1 Impact of Insulin Therapy on Type 1 Diabetes

Insulin is a hormone known for its role in maintaining glucose regulation (Rhoads et al., 2016) and can be essential in preventing fatal complications from hyperglycaemia (Subramanian and Baidal, 2015). Based on the findings from the Diabetes Control and Complication Trial (DCCT) research group, several guidelines suggest using intensive insulin therapies to achieve the HbA1c levels below 6.5% or 7.0%, unless this goal is not feasible due to severe hypoglycaemia (American Diabetes Association, 2020b; Helliwell et al., 2021). Rose and colleagues (Rose et al., 2021) reported that among 131 adults with T1D using either MDIs or CSII in conjunction with the FreeStyle Libre system, a significant reduction in HbA1c levels by 0.75% was observed within three months, with this improvement being sustained over a 12-month period. Additionally, Crabtree and colleagues (Crabtree et al., 2023) observed that in a cohort of 570 adults with T1D using hybrid closed-loop system, there was a significant reduction in HbA1c levels by 1.7% within a median follow-up of approximately five months. This improvement in glycaemic control is associated with an enhanced quality of life, a significant increase in time spent within the target glucose range, and a reduced burden of diabetes-related issues.

Intensive insulin therapy was established as the standard of care based on the results of the DCCT, which conclusively demonstrated the benefits of tight glycaemic control (Control and Complications Trial Research Group, 1994). However, the Epidemiology of Diabetes Interventions and Complications (EDIC) follow-up revealed that the benefits varied with weight gain and the development of metabolic syndrome. Patients with stable insulin maintained long-term glycaemic control, while those with significant weight gain experienced reduced benefits and increased metabolic risk, such as central obesity, dyslipidaemia, and

hypertension (HTN) (Purnell et al., 2013). Subcutaneous insulin administration can lead to peripheral IR both directly (Hother-Nielsen et al., 1987; Donga et al., 2015) and indirectly through weight gain (Purnell et al., 1998). For example, increasing the insulin dosage in individuals with T1D due to IR can lead to further weight gain (Mottalib et al., 2017). This situation poses a difficult challenge, in which escalating insulin doses, greater weight gain, and increased IR contribute to detrimental cycle. The resulting excessive weight gain (body mass index (BMI) > 30 kg/m^2) could lead to adverse vascular effects by developing an inflammatory and thrombotic milieu that is typically associated with states of IR (Helliwell et al., 2021). Excessive weight gain can contribute to chronic inflammation by increasing the secretion of pro-inflammatory cytokines from adipose tissue and promoting immune cell infiltration (Ellulu et al., 2017). This inflammatory environment can lead to adverse vascular effects, including the development of a prothrombotic state, characterised by increased clot formation, thus increasing the risk of thrombotic events such as blood clots and other complications such as atherosclerosis (i.e., accumulation of fatty deposits [plaques] on artery walls) (Purnell et al., 2013; Ellulu et al., 2017). Thus, individuals with T1D who are overweight, have a family history of T2D, and/or show clinical features of IR are considered to have double diabetes (Kietsiriroje et al., 2019).

Insulin resistance has been suggested as a potential contributor to suboptimal glycaemic control in T1D, resulting in increased insulin dose requirements and further weight gain. Therefore, addressing strategies for prevention and/or reduction of IR and weight gain is essential. Reducing sitting time and promoting low-intensity activity breaks, as an easy and applicable strategy to combat SB, holds promise in this regard. This strategy is particularly significant considering that many individuals with T1D encounter challenges in

engaging in regular PA. By incorporating interrupting sitting into daily routines, individuals may effectively reduce IR, thus potentially improving glucose control and reducing the risk of complications associated with T1D.

1.1.1.3.2 Glucose Control

1.1.1.3.2.1 Traditional Glucose Monitoring

Accurate glucose measurements are critical for effectively managing diabetes. Although HbA1c has traditionally been used to assess glycaemic control, it does not capture the intra-day and inter-day glucose fluctuations that can result in acute episodes of hypoglycaemia or postprandial hyperglycaemia. These fluctuations have been associated with microvascular and macrovascular complications (Danne et al., 2017). Moreover, although SMBG has been demonstrated to improve glycaemic control and quality of life in both T1D and T2D individuals when used within a structured testing regimen (Kempf et al., 2012; Kato et al., 2013), it cannot predict impending hypoglycaemia or provide an alert for the onset of hypoglycaemia (Gold et al., 1994; Bolli, 1998). While SMBG provides a snapshot of blood glucose concentrations at a given time and is used to adjust mealtime insulin doses and determine the correction bolus, it does not detect acute fluctuations between individual capillary blood glucose measurements unless testing is done consecutively over short periods, which is not practical in free-living settings (Gabbay et al., 2020). This in part contributes to why individuals with T1D are often unable to maintain blood glucose concentrations within the target range throughout the day (Foster et al., 2018).

1.1.1.3.2.2 Continuous Glucose Monitoring

The development of CGMs addresses several limitations found with both HbA1c testing and SMBG (Danne et al., 2017). Recent advancements in CGM

technologies have led to increased adoption by individuals with insulin-treated diabetes to minimise or avoid severe hypoglycaemia and achieve glycaemic control within target ranges (Haskova et al., 2020). Among T1D Exchange participants, the percentage of individuals using CGM technology increased from 7% in 2010 – 2012 to 30% in 2016 – 2018 (Foster et al., 2018). Reasons behind this increase may be due to the improvements in sensor accuracy (± 10% mean absolute relative difference (MARD)), a reduced need for frequent calibration, and the ability to adjust insulin doses without the need for confirmatory SMBG measurements (Rodbard, 2017). As more individuals with T1D adopt CGM, technological advances such as extended sensor life have further enhanced the cost-effectiveness of these systems (Wan et al., 2018). As the CGM system continuously monitors blood glucose concentrations in the interstitial fluid (Subramanian and Baidal, 2015), it provides users with real-time information about blood glucose concentrations, the direction of blood glucose change, rate of change, and trends in blood glucose data to identify patterns over time (Moser et al., 2010). The increasing use of CGM among individuals with diabetes highlights its potential to improve glycaemic outcomes, enhance overall quality of life, and its importance in diabetes management.

Continuous glucose monitoring is a valuable measure for studying glucose control as it provides continuous and real-time data on blood glucose concentrations every five to fifteen minutes (96 to 288 measurements per day) (Yoo and Kim, 2020). This offers a more comprehensive and dynamic assessment of glycaemic fluctuations compared to traditional SMBG measures, which cannot fully capture these fluctuations. This continuous monitoring allows for a more detailed analysis of blood glucose patterns, trends, and variability, providing valuable insights into the impact of interventions or lifestyle factors on

overall blood glucose control over time. Additionally, the CGM metrics provide standardised and quantifiable parameters for assessing glycaemic outcomes, facilitating more precise comparisons and interpretations of study results. The use of CGM measures as a primary assessment tool is particularly relevant to the studies reported in Chapters 5 and 6 of this PhD thesis.

There are two types of CGM systems currently available for daily diabetes self-management; real-time CGM (rtCGM; e.g., Dexcom and Medtronic) and isCGM also called as flash CGM (e.g., FreeStyle Libre) (Adolfsson et al., 2018). The international consensus on CGM uses the following classifications based on common metrics: time in range (TIR: 3.9 – 10.0 mmol/L), glycaemic variability (< 36%), time above range (TAR), and time below range (TBR). The TAR was differentiated into level 1 (TAR 1: 10.1 – 13.9 mmol/L) and Level 2 (TAR 2 > 13.9 mmol/L). Similarly, TBR was differentiated into level 1 (TBR 1: 3.0 – 3.8 mmol/L) and level 2 (TBR 2: < 3.0 mmol/L) (Danne et al., 2017).

Among CGM metrics, TIR has emerged as a preferred measure for individuals with diabetes due to its impact on daily life (Runge et al., 2018), providing valuable insights into the frequency and duration of hyperglycaemia or hypoglycaemia improvements over time (Lu et al., 2018). TIR is gaining support from major organisations such as the American Diabetes Association (ADA) and the National Institute for Health and Care Excellence (NICE), which recognise its potential to improve glycaemic control and incorporating it into clinical practice guidelines for optimal diabetes management (Wilmot et al., 2021). Tight time in range, with more stringent glucose control targets of 3.9 to 7.8 mmol/L, is also emerging as a valuable metric for reducing complications and enhancing glycaemic control (De Meulemeester et al., 2024; Hamidi and Pettus, 2024). The recommendation for both T1D and T2D includes maintaining a TIR > 70% (16

hours and 48 minutes), with TAR 1 < 25% (6 hours), TAR 2 < 5% (1 hour and 12 minutes), TBR 1 < 4% (1 hour), and TBR 2 < 1% (15 minutes) (Vigersky and McMahon, 2019; Yoo and Kim, 2020). Every 1% change in time equals 14 minutes per day (1 day = 1440 minutes) (Yoo and Kim, 2020). A 70% of TIR approximately corresponds to an HbA1c of 7.0% (Vigersky and McMahon, 2019). A recent international consensus suggested that TIR should be the key metric for determining glycaemic control and predicting the risk of diabetes (Danne et al., 2017). Research on T2D has shown that individuals with CGM-measured lower TIR and higher glycaemic variability are more likely to develop diabetic retinopathy (Lu et al., 2018). Therefore, CGM-derived metrics could serve as a suitable alternative to HbA1c measurement and as an essential tool in diabetes management, helping improve long-term treatment approaches (Vigersky and McMahon, 2019).

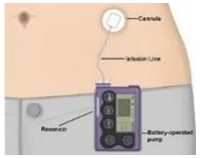
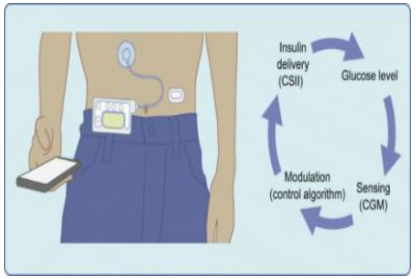
1.1.1.3.2.3 New Technologies for Diabetes Management

New diabetes technologies, such as closed-loop systems, CGMs (rtCGM and isCGM), and ultrarapid-acting insulin (e.g., Fiasp) signify a paradigm shift in T1D care (**Table 1.1**), These advancements promise to contribute to achieving tighter glycaemic control and reducing the burden of diabetes self-management (Sherwood et al., 2020). Innovative tools, such as closed-loop systems, are revolutionising diabetes management (Sherwood et al., 2020; Templer, 2022). The system combines insulin pumps and CGM with a computer algorithm to dynamically adjust insulin delivery, maintaining blood glucose concentrations within the target glucose ranges (Templer, 2022). This reduces the risk of hyperglycaemia and hypoglycaemia (Templer, 2022), consequently decreasing the burden of diabetes, improving quality of life, and reducing anxiety related to managing blood glucose concentrations (Boughton and Hovorka, 2021). Hence,

these advancements represent a significant step forward in improving glycaemic outcomes and enhancing the quality of life for individuals with T1D. Comparison of glucose monitoring and insulin delivery technologies are provided in **Table 1.1**.

Table 1.1 Comparison of Glucose Monitoring and Insulin Delivery Technologies

Measurement Tool	Definition	Measurement Site	Lag time	Accuracy
1. Self-monitoring of blood glucose (SMBG) 	The method by which individuals with diabetes measure their blood glucose concentrations manually and intermittently using a small blood sample from a finger prick (Benjamin, 2002).	Whole blood	N/A	High accuracy (Parkin, 2017).
2. Continuous glucose monitoring (CGM) 	A sensor-based system that continuously provides real-time glucose reading, offering ongoing data on glucose trends day and night (Facchinetti, 2016). There are two types of CGM, real-time CGM (rtCGM) and intermittently scanned CGM (isCGM) (Sherwood et al., 2020). • rtCGM – provides real-time glucose readings with alerts for hypo- and hyperglycaemia. • isCGM – (known as flash glucose monitoring) that stores continuous data in the sensor, accessed by scanning, without real-time alerts.	Interstitial fluid	Yes (5 – 15 minutes)	Moderate accuracy (varies depending on the device; less accurate during rapid glucose changes and after extended use) (Luijf et al., 2013).

3. Continuous subcutaneous insulin infusion (CSII) or insulin pump  Figure adapted from (Gardner, 2024).	Insulin pumps deliver continuous rapid-acting insulin via a subcutaneous cannula, with adjustable hourly basal rates and temporarily modifications, optimising glucose control by adjusting delivery based on real-time glucose reading (UK DTN, 2018).	N/A – links with CGM in closed-loop system; does not measure glucose directly.	N/A	N/A
4. Closed-loop system (known as artificial pancreas)  Figure adapted from (Boughton and Hovorka, 2021).	Insulin delivery system that uses mathematical algorithms to adjust insulin delivery based on CGM data. It is typically includes insulin pump, CGM, and control algorithm (Boughton and Hovorka, 2021). The CGM transmits glucose data wirelessly to a controller (smartphone/tablet-mounted algorithm; black handheld device). The controller uses an algorithm to adjust insulin pump delivery (white device fixed in trouser) based on the CGM data to maintain target blood glucose concentrations. This process is then repeated.	Interstitial fluid (via CGM)	Yes (5 – 10 minutes).	High accuracy (Boughton et al., 2023).

1.1.1.3.3 Physical Activity and Exercise

A multitude of factors influence blood glucose concentrations and insulin sensitivity, causing considerable day-to-day variability in glycaemia and insulin requirements (Ruan et al., 2016). These factors include the composition of meals (Elleri et al., 2013), and the prolonged effect of PA on glucose turnover (Davey et al., 2013), resulting in a high burden of diabetes management. While PA and exercise are often promoted in T1D management (Behrens and Brinkmann, 2023), it is important to recognise that bouts of exercise can sometimes cause fluctuations in blood glucose concentrations (Younk et al., 2011; Colberg et al., 2015), presenting challenges for individuals with diabetes. Regarding the glucose control and PA/exercise, a high proportion of T1D individuals are worried about maintaining their glycaemia, with a fear of hypoglycaemia and loss of control over their diabetes classified as the main barriers to exercise (Brazeau et al., 2008).

The majority of T1D fail to adhere to recommended PA levels (Finn et al., 2022), as only 32% (23 of 72 participants) met the PA recommendations of more than 150 minutes per week (using accelerometry), while 97% self-reported adherence (using International physical activity questionnaire (IPAQ)) (Finn et al., 2022). However, there is a critical need to quantify PA levels among this population, primarily due to the prevalent reliance on self-reported measures in research studies. Furthermore, there exists a notable lack of attention directed towards SB, despite its established status as an independent risk factor, as demonstrated in various populations such as individuals with T2D (Paing et al., 2018; Lin et al., 2022). As such, it is important to define the differences between SB, physical (in)activity, and exercise, and consider some of the methods used to quantify each of these.

1.1.1.3.3.1 Definition of Physical Activity and Exercise

Physical activity involves daily movements and activities using the body's skeletal muscle and requiring energy expenditure (Caspersen et al., 1985; World Health Organisation, 2022). PA includes activities such as household tasks (gardening or vacuuming), occupational activities (lifting or carrying), active transportation (walking or cycling), and leisure activities (camping or skiing). In contrast, exercise is a specific type of PA characterised by planned, structured, and repetitive movements, such as following a structured exercise programme, performed with the goal of improving health and/or fitness, with defined duration, intensity, and frequency (Caspersen et al., 1985; Bird and Hawley, 2017).

1.1.1.3.3.2 Benefits of Physical Activity and Exercise on Health in Individuals with Type 1 Diabetes

Physical activity and structured exercise play fundamental roles in managing T1D by promoting overall health and well-being while specifically targeting key aspects of diabetes management. Previous narrative review papers indicated that regular PA or aerobic exercise improves insulin sensitivity, further reducing the required doses of basal insulin or bolus insulin rate in individuals with T1D (Chimen et al., 2011; Stehno-Bittel, 2012; Moser et al., 2020). Although PA can induce glycaemic fluctuations with an increased risk of hypoglycaemia during and up to several hours following PA (Younk et al., 2011), there are some strategies suggested by the ADA to prevent these side effects, such as consuming additional carbohydrate, reducing peripheral bolus insulin doses, and altering basal insulin (American Diabetes Association, 2020a; American Diabetes Association, 2023). Furthermore, repeated short bouts of activity (i.e., three 15-minute walks and three minutes of low-intensity walking every 30 minutes) during

prolonged sedentary periods provide a valuable strategy for improving postprandial glucose regulation in individuals with T2D (Van Dijk et al., 2013; Dempsey et al., 2016a), potentially improving insulin sensitivity. Incorporating activities of daily living into daily routines can significantly contribute to improving glycaemia, providing a practical and sustainable approach to managing blood glucose concentrations on a day-to-day basis.

Exercise and diabetes management is complex, as various factors can impact an individual's glucose responses, including type, intensity, duration, and frequency of the exercise. Regular exercise on a daily basis, or ensuring no more than two days gap between exercise sessions is recommended to reduce IR, irrespective of the type of diabetes (Tonoli et al., 2012; Jelleyman et al., 2015). For example, aerobic exercise has been shown to decrease IR and improve cardiovascular risk factors (blood pressure and lipid levels) in individuals with T1D (Chimen et al., 2011). Aerobic activities cause changes to the cardiovascular system, such as increased stroke volume, increased capillary density, and reduced peripheral resistance (Powell et al., 2011). These changes can improve the capacity and efficiency of oxygen and glucose delivery to tissues, contributing to improved insulin sensitivity and overall cardiovascular health (Powell et al., 2011). Likewise, a regular aerobic exercise programme over three months led to significant improvements in insulin sensitivity and cardiovascular risk factors, with an increase in self-monitored activity of ~150 minutes per week, without an increase in severe hypoglycaemic episodes in individuals with T1D (Lehmann et al., 1997). This suggests that insulin sensitivity improves in human when they adhere with PA and/or exercise guidelines (Bird and Hawley, 2017). Ultimately, PA and exercise have direct and immediate effects on blood glucose regulation, as they enhance insulin sensitivity and glucose uptake into muscle, thereby

improving blood glucose management and reducing vascular complications.

Physical activity is associated with a wide spectrum of health benefits; therefore, it is recommended for all individuals, including those with T1D, to engage in at least 150 minutes of aerobic moderate-intensity PA, or 75 minutes of aerobic vigorous-intensity PA, or a combination of them per week (Bull et al., 2020). Despite PA and/or exercise being recognised as a critical elements of diabetes care, most individuals in T1D do not meet the guidelines. Indeed, research suggests that fewer than 20% of T1D manage to achieve the guidelines, while ~60% of them remain inactive (Juutilainen et al., 2008). Similarly, another study in T1D finding that 32% of the cohort achieved PA recommendations as measured by an accelerometer (Finn et al., 2022). This may be attributed, in part, to the lack of self-management guidelines tailored for safe participation in PA and exercise (e.g., perceived risk of hypoglycaemia), or tailored recommendations to specifically reduce sedentariness in T1D.

Exercise-specific recommendations of moderate-to-vigorous physical activity (MVPA) translate poorly to general daily PA levels, including daily living and recreational activities, from which most individuals with T1D have most to gain (Campbell et al., 2017c). Within the context of T1D, exercise is often viewed as daunting and unachievable by most and its promotion can often discourage individuals from becoming active (Campbell et al., 2017c). For example, many individuals with T1D report fear of hypoglycaemia and an inability to manage their diabetes as major barrier to regular participation (Brazeau et al., 2008; Bohn et al., 2015). Interestingly, few mention this fear when asked about general day-to-day physical activities (Campbell et al., 2017c). In support of this notion, rather than promoting exercise *per se,* it is important for inactive T1D individuals to begin with achievable routines that increase PA and enhance glucose management.

Practical strategies and tips for incorporating PA and exercise into daily life can significantly benefit individuals managing T1D. By setting realistic goals, individuals can establish achievable targets for PA levels, leading to improvements in insulin sensitivity, blood glucose concentrations, and overall health (Bird and Hawley, 2017; Schubert-Olesen et al., 2022). Overcoming barriers, such as fear of hypoglycaemia, can be achieved by implementing strategies like monitoring blood glucose concentrations before, during, and after activity, and adjusting carbohydrate intake and insulin dose. Additionally integrated movement breaks into sedentary periods helps regulate blood glucose concentrations and enhance insulin sensitivity. A recent cross-sectional study found that in active individuals with T1D, diet adjustment and more frequent glucose monitoring may best improve blood glucose control (Colberg et al., 2021). These strategies may be achievable ways to optimise diabetes management and improve overall health.

Physical activity is critical to managing diabetes, but addressing SB is equally vital for holistic management. Prolonged sitting contributes to IR, cardiovascular risk factors, and subsequently diabetes complications (Cooper et al., 2014; Huerta-Uribe et al., 2023), emphasising the need for movement breaks (interrupted sitting) and reduced sedentary time (Dempsey et al., 2016a; Dempsey et al., 2016b; Dempsey et al., 2017b). By prioritising both PA promotion and SB reduction, individuals with diabetes could achieve comprehensive management strategies for optimal health outcomes.

1.1.1.3.4 Sedentary Behaviours

1.1.1.3.4.1 Definition of Sedentary Behaviours and Physical Inactivity

Sedentary behaviour is defined as any waking behaviour such as lying down, or

sitting during the workplace, leisure time, and domestic environment (Marconcin et al., 2021), with a low energy expenditure of 1.0 to 1.5 metabolic equivalent tasks (METs) (Tremblay et al., 2017). Examples of SBs include watching TV, playing video games, using a computer, or other screen-based activities (Pate et al., 2008). However, physical inactivity is defined as people engage in less than 150 minutes per week of MVPA (Thivel et al., 2018). As a result, SB (i.e., too much sitting) is distinct from physical inactivity (i.e., insufficient PA levels).

1.1.1.3.4.2 Effects of Sedentary Behaviours on Health

Sedentary behaviour is well-established to increase risk of morbidity and mortality (Chau et al., 2013; Biswas et al., 2015). In individuals with diabetes, sitting for a long period of time has been shown to be positively associated with worsening diabetes management, as determined by HbA1c (Cooper et al., 2014; Huerta-Uribe et al., 2022), which may contribute to an increased risk of diabetes complications. Watching TV, often used as a proxy for SB, is associated with obesity and metabolic disturbance in a dose-dependent manner (Patterson et al., 2018; Bailey et al., 2019). In individuals with T1D, watching TV uninterrupted for more than two hours per day is strongly associated with overweight and obesity (Council on Communications Media et al., 2013), a risk factor which has previously been shown to predict macrovascular and microvascular complications independent of glucose control (Helliwell et al., 2021). Sitting for more than four to eight hours per day is significantly associated with a higher risk of mortality (two percent increase per one hour increase in sitting time per day) (Chau et al., 2013). Noteworthy, individuals with T1D have been demonstrated to spend more time on sedentary activities compared to their healthy counterparts (Czenczek-Lewandowska et al., 2019).

The prevalence of SB is increasing worldwide, with 215 children and adolescents with T1D found to spend about 73.34% of their awake time (~10.2 hours per day) in sedentary activities, compared to 115 healthy peers who spent 69.83% of their wake time (~9.7 hours per day) in SBs (Czenczek-Lewandowska et al., 2019). The higher sedentary time in T1D raises concerns due to associated health risks and emphasises the need to accurately quantify and limit sedentary time by incorporating frequent episodes of low-intensity PA (Bull et al., 2020).

Whilst many individuals with T1D do little-to-no exercise, they are often willing to increase participation in lower-intensity PA and are keen to learn how to reduce SBs (Campbell et al., 2017c). Low-intensity PA provides health benefits, such as reducing the prevalence of hyperglycaemia throughout the subsequent 24 hours post-activity in T2D (Manders et al., 2010). When increasing PA toward a desired level, small and well-spaced increments will reduce the incidence of adverse events and improve adherence (Powell et al., 2011). Previous research examining the relationship between PA and health has predominantly emphasised the importance of MVPA above an unspecified and variable baseline (Powell et al., 2011). However, with growing evidence highlighting the health benefits of low-intensity PA and advancements in tools capable of measuring all intensity levels (including sedentary time), it may be appropriate to consider baseline activity (or minimal activity) as the conceptual starting point (Powell et al., 2011). Nonetheless, little information is available to individuals with T1D or the healthcare professionals who support them (Yardley and Campbell, 2020a). Thus, by increasing awareness, education, and research efforts, the quality of care and support for individuals with T1D can be significantly improved across all levels of healthcare and community engagement.

1.1.1.3.5 Interrupting Sitting Effective Strategy for Type 1 Diabetes

Given that individuals with T1D often spend prolonged periods of sedentariness, making a simple, practical change in lifestyle by interrupting prolonged sitting time with short, frequent breaks of low-intensity PA could achieve better glucose control and reduce the risk of diabetes complications. However, there is currently no research on interrupting sitting with low-intensity PA in T1D, and minimal evidence for longer-term effects in other population. Therefore, future research is required to assess the impact of interrupted sitting strategies that feature low-intensity PA on short- and long-term glucose control in individuals with T1D, and whether such interventions yield beneficial effects on complication risk. As sedentary time is associated with premature mortality and cardiovascular risk factors for those with T2D, as well as CVD and some types of cancer (Dempsey et al., 2018), studies examining the effects of interrupted sitting interventions in individuals with T1D are urgently needed. In particular, it would be beneficial to investigate the utility of such an intervention across broad demographics, including individual characteristics such as the presence of IR, which is known to influence glucose control and vascular risk in T1D (Coales et al., 2021; O'Mahoney et al., 2021; Kietsiriroje et al., 2022), and to establish whether this can be translated to a remote, home-based environment. Remarkably, numerous studies conducted in individuals with T2D and those at risk of T2D have demonstrated the beneficial effects of this approach on various health outcomes, including glucose control and cardiovascular risk factors (Loh et al., 2020).

Recently, PA guidelines for individuals with diabetes have evolved to include recommendations specifically targeting prolonged periods of sitting time by 'breaking up' sedentary periods with bouts of standing and/or frequent, short, low-intensity PA intervals, termed 'interrupted sitting' (Dempsey et al., 2016a;

Dempsey et al., 2016b). This simple and acceptable approach may help to enable those inactive individuals to carry out PA across the day and may serve as an effective method for incorporating PA more easily into everyday life and improving health. Interrupting sitting with low-intensity PA could be particularly useful for those who are unable or unwilling to engage in structured exercise, and this approach can be seen as an important 'stepping stone' towards regular participation in PA or exercise (Dempsey et al., 2017a). Despite this, the evidence underpinning these recommendations remains preliminary and focused solely on individuals with or at risk of developing T2D (Dunstan et al., 2012a; Dempsey et al., 2016a; Dempsey et al., 2016b; Dempsey et al., 2016c; Dempsey et al., 2017a; Dempsey et al., 2017b). As such, it is important that focus is given to the potential utility and implications of applying interrupted sitting interventions within the context of adults with T1D.

1.1.1.3.5.1 Interrupting Sitting and Glycaemic Control

Emerging evidence in individuals with T2D suggests that interrupting prolonged periods of time spent sitting with short, frequent activity breaks may be a promising strategy for improving acute glycaemic control. Dempsey and colleagues (Dempsey et al., 2017b) demonstrated that interrupting seven hours prolonged sitting time with brief bouts of low-intensity walking for three minutes every 30 minutes significantly reduced the 22 hours glycaemia in T2D individuals, including nocturnal hyperglycaemia with glycaemic improvements continuing until the next morning. Time spent in nocturnal hyperglycaemia was approximately 60% greater under an uninterrupted sitting condition compared to an interrupted sitting condition (Dempsey et al., 2017b). This suggests that the acute metabolic improvements associated with interrupted sitting carry over into the evening and sleeping periods until the following morning. Further, interrupting prolonged

sitting with frequent three minutes bouts of walking every 15 minutes has also been shown to improve fasting glucose and limit the dawn phenomenon in T2D (Paing et al., 2019a). This is a particularly important consideration should a similar glycaemic pattern be observed within the context of T1D in which the dawn phenomenon is a common issue (Bouchonville et al., 2014), which is when blood glucose concentrations rise due to hormonal changes in the early-morning hours (four am to eight am) (Bolli and Gerich, 1984).

The dawn phenomenon is defined as elevated blood glucose concentrations during early waking hours, and to a large extent persists post-breakfast in T1D individuals (Porcellati et al., 2013). The dawn phenomenon results from increased hormone-stimulated glucose output and impaired glucose utilisation (Campbell et al., 1985a), and represents a key feature of dysglycaemia and increased basal insulin requirements in T1D (Monnier et al., 2012). Results from Campbell and colleagues (Campbell et al., 1985b) indicated that nocturnal surges in growth hormone secretion drive the dawn phenomenon, whereas nocturnal increases in catecholamine concentrations do not appear to be sufficient by themselves to be responsible. Clarke and colleagues (Clarke et al., 1995) demonstrated that a two-to-threefold increase in the amount of insulin can be required to maintain euglycaemia overnight in some T1D individuals. Importantly, Zheng and colleagues (Zheng et al., 2020) noted that moderate-intensity of aerobic exercise prior to breakfast reduced the rate at which of blood glucose concentrations increases in T2D individuals, partially counteracting the dawn phenomenon. Although morning exercise is currently recommended to improve early morning rises in blood glucose concentrations (Bolli and Gerich, 1984), it is unknown whether interrupted sitting may serve as an effective strategy to attenuate the dawn phenomenon, especially in individuals with T1D.

Interrupted sitting interventions can also improve meal-time glucose control. For example, Dempsey and colleagues (Dempsey et al., 2016a) showed that three minutes bouts of low-intensity walking on a treadmill every 30 minutes attenuated postprandial glucose by 39% in T2D. Further, Paing and colleagues (Paing et al., 2019b) demonstrated in 12 individuals with T2D that interrupting sitting time through performing three minutes of low-intensity walking breaks after meals every 15 minutes resulted in a 48% reduction in the post-breakfast glucose (3.5 ± 0.9 mmol/L^{-1}), 62% reduction in cumulative 10.5 hours postprandial glucose (5.6 ± 2.4 mmol/L^{-1}), and 34% reduction in 21 hours glucose (101.5 ± 12.6 mmol/L^{-1}) compared to interrupted sitting every 60 minutes. As such, the frequency of interrupting sitting may be an important factor in achieving better glucose control, but the optimal timing and frequency of these low-intensity bouts remain unknown.

Short activity breaks from sitting have been shown to result in improvements in postprandial glucose responses and daily glycaemic control, albeit with varying efficacy as compared to traditional forms of exercise (Blankenship et al., 2019; Gouldrup and Ma, 2021). For example, Peddie and colleagues (Peddie et al., 2013) reported regular activity breaks to be more effective than continuous PA at decreasing postprandial glycaemia and insulinaemia in normal-weight individuals without diabetes, whereas Blankenship and colleagues (Blankenship et al., 2019) showed continuous walking to be comparable to activity breaks at lowering postprandial glucose in individuals with T2D. Further, Blankenship and colleagues (Blankenship et al., 2019) showed continuous PA was more effective at lowering daily hyperglycaemia as compared to regular activity breaks in T2D, whereas Freire and colleagues (Freire et al., 2019) demonstrated lower daily glucose in response to breaks in sitting time as

compared with low-volume high-intensity interval exercise in overweight adults.

Given that different forms of PA, performed at different times of day induce divergent metabolic responses, it is likely that differences in study methodology, as well as the metabolic health of sampled participants were confounding factors and contribute to mixed study findings. For example, a recent meta-analysis exclusively in individuals without diabetes showed that interrupting sitting time with short, frequent bouts of walking activity was more effective in reducing postprandial glucose than a single continuous session of isoenergetic exercise (Gouldrup and Ma, 2021). A possible explanation for this difference could be that glucose counter-regulatory hormones increase during prolonged exercise, which promotes increased hepatic glucose production at a rate that can exceed glucose uptake and affect, which is further mediated by the fasted versus postprandial state as shown by recent work in T1D (Yardley, 2020b). Although yet untested, the net effect of interrupted sitting within a T1D setting may be an overall increase in blood glucose concentrations (Gouldrup and Ma, 2021). The potential of exercise to induce transient hyperglycaemia in T1D has obvious negative consequences; however, manipulating activity type to diminish the counter-regulatory response may consequently increase risk of hypoglycaemia, particularly late-onset hypoglycaemia (Yardley et al., 2013; Campbell et al., 2015a). As such, it is important that research establishes the impact of frequent, short bouts of activity on risk of hypo- and hyperglycaemia in T1D, and whether and what adjustments to treatment are necessary to maintain glucose control. For example, Campbell and colleagues (Campbell et al., 2014a) demonstrated that reducing pre- and post-exercise rapid-acting insulin is an effective strategy for preventing exercise-induced hypoglycaemia and does not cause adverse hormonal disturbances in individuals with T1D; however, whether insulin dosing

adjustments will be necessary for lower-intensity PA is not currently known.

1.1.1.3.5.2 Interrupting Sitting and Diabetes Complications Risk

Interrupting prolonged sitting has also been shown to improve cardiovascular risk factors in T2D. Three-minute bouts of low-intensity walking every 30 minutes in 24 inactive overweight and obese individuals with T2D have been shown to elicit a reduction in systolic blood pressure by 14 mmHg and diastolic blood pressure by 8 mmHg during the condition (Dempsey et al., 2016c). In one arm, participants replaced about five hours per day sitting with two hours of walking and three hours of standing, which was shown to improve plasma triacyclglycerols (as compared with a sedentary condition (1.46 [0.12] mmol/L versus 1.93 [0.17] mmol/L), which are an energy-dense substance stored primarily in adipose tissue and the liver that serve as a major energy source for the body, and its elevation can lead to cardiovascular risks (Gibbons et al., 2000; Duvivier et al., 2017). Reducing sitting time by engaging in low-intensity activity breaks might be effective in improving features of metabolic syndrome in both T1D and T2D, given similarities in underlying disease pathology. Data from several studies suggest that excessive sitting time is associated with reversible changes in components of the metabolic symptoms (Healy et al., 2008a; Bankoski et al., 2011). Metabolic syndrome is a cluster of conditions that is defined as central obesity plus two additional factors (International Diabetes Federation, 2006), including increased triglyceride levels (> 1.7 mmol/L), blood pressure (≥ 130/85 mmHg) and fasting plasma glucose (> 5.6 mmol/L), and reduced high-density lipoproteins (HDL) cholesterol (< 1.03 mmol/L in males and < 1.29 mmol/L in females) (Kilpatrick et al., 2007). Given the high prevalence of IR and metabolic syndrome in T1D (Kietsiriroje et al., 2019; Helliwell et al., 2021; O'Mahoney et al., 2021; O'Mahoney et al., 2022), interrupting prolonged sitting may be a practical strategy that could

contribute to reducing the risk of vascular complications in this cohort.

1.1.2 Mechanisms and Physiological Responses to Physical Activity and Sedentary Behaviour on Metabolic and Cardiovascular Health

1.1.2.1 Glucose Regulation Responses to Physical Activity

Regulating blood glucose concentration is essential for overall health, requiring a balance between insulin secretion, cellular glucose uptake, and the actions of counter-regulatory hormones to ensure stable energy supply and metabolic health (Wilcox, 2005; Sharabi et al., 2015). In individuals without diabetes, blood glucose concentrations are effectively regulated through a combination of autonomic (e.g., sympathetic and parasympathetic nervous systems) and hormonal (e.g., insulin and glucagon) mechanisms (Zinman et al., 2003; Riddell and Perkins, 2006a). However, in individuals with T1D, there is a lack of hormonal regulation, and an insufficient or excessive amount of exogenous insulin can result in either hyperglycaemia or hypoglycaemia (Riddell and Perkins, 2009).

Exercise has profound effects on the regulation of blood glucose concentrations. During moderate-intensity PA in individuals without diabetes, blood flow to skeletal muscles increases, leading to an increase in glucose uptake from the blood through GLUT4 into cells, resulting in a decrease in blood glucose concentrations (Thorell et al., 1999; Richter et al., 2001). GLUT4, recognised as the main transporter for glucose in the skeletal muscle and adipose tissue (Chadt and Al-Hasani, 2020), is regulated by insulin to facilitate glucose uptake into adipose (fat) and muscle cells (Stockli et al., 2011). Decreased blood glucose concentrations lead to a decrease in insulin secretion and an increase in counter-regulatory hormones secretion. These hormones, such as glucagon, cortisol,

catecholamines, and growth hormone, stimulate the liver to produce glucose through hepatic gluconeogenesis, which generates glucose from non-carbohydrate substrates lactate, glycerol, and amino acids (Snell, 1991). This process compensates for the amount being used by working muscles (Lang and Hussain, 2014), thus maintaining stable blood glucose concentrations. Counter-regulatory hormones are integral to the body's natural mechanisms for evaluating blood glucose concentrations in case of low blood glucose concentrations (hypoglycaemia) (Lang and Hussain, 2014). During activity, glucose production will increase as exercise intensity increases due to hepatic glycogenolysis, which involves the breakdown of glycogen into glucose (Nordlie et al., 1999). The liver plays an important role in regulating glucose concentrations by releasing glucose into the bloodstream, such as during fasting or periods of low blood glucose concentrations (Nordlie et al., 1999; Han et al., 2016).

In individuals with T1D, the regulation of insulin concentrations during exercise is disrupted, and the body's counter-regulatory hormone response may not be adequate. This dysfunction in insulin and counter-regulatory hormone response leads to either no change in insulin concentrations or excessive administration of insulin during exercise, ultimately causing hypoglycaemia (Riddell and Perkins, 2009). The risk of hypoglycaemia is significant, often occurring weekly or even daily due to frequent insulin therapy, which can potentially alter counter-regulatory hormone responses (Cryer et al., 2003). When blood glucose concentrations drop into the hypoglycaemic range (typically between 3.2 to 3.8 mmol/L), it is possible for the function of counter-regulatory hormones to be impaired (Galassetti et al., 2003; Verhulst et al., 2022). In individuals with well-controlled T1D, both at rest and during exercise, glucose production rates increase due to gluconeogenesis. Individuals responses to

exercise vary and can be influenced by multiple factors, resulting in hypoglycaemia, normoglycaemia, and hyperglycaemia (Riddell and Perkins, 2009). Factors that can lead to hypoglycaemia during PA include hyperinsulinemia (high insulin concentrations), a decrease in catecholamine response (Schneider et al., 1991), and the intensity and duration of exercise, which can lead to hypoglycaemia due to depletion of glycogen stores (Mallad et al., 2015; Yardley and Sigal, 2015). Normoglycaemia during exercise can be accomplished through appropriate insulin adjustment and adequate carbohydrate intake (Sane et al., 1988; Scott et al., 2019a). Hyperglycaemia can be caused due to various factors, such as exercise intensity (intense aerobic exercise at over 80% of maximum oxygen consumption (VO_2)) (Mitchell et al., 1988; Sigal et al., 1994), omission of insulin before exercise (Colberg et al., 2016), and excessive carbohydrate intake before or during exercise, along with aggressive reduction in insulin (Campbell et al., 2015b). This indicates that blood glucose concentrations depend on different factors, emphasising the importance of regularly monitoring glucose concentrations before, during, and after activity (Colberg et al., 2016).

1.1.2.2 Insulin Sensitivity and Insulin-Independent Contraction-Mediated Glucose Uptake Pathway Following Physical Activity

Several research findings have established that the improvement in glucose control in response to PA and exercise interventions is likely due to a combination of enhanced insulin sensitivity (Thyfault, 2008) and/or a greater dependence on insulin-independent contraction-mediated glucose uptake pathways (Bergouignan et al., 2016). This improvement is facilitated by the translocation of glucose transporters, such as the GLUT4 transporter, to the surface of skeletal muscle cells directly in response to muscle contraction (Mann et al., 2010).

Glucose uptake remains elevated for up to 120 minutes post-exercise bout due to increased GLUT4, and insulin sensitivity increases for at least 16 hours after a single bout of exercise, a transient effect observed in both healthy and diabetic individuals (Borghouts and Keizer, 2000; Venkatasamy et al., 2013). However, in individuals with T1D, this increase in insulin sensitivity presents a biphasic risk of hypoglycaemia (immediately and several hours post-exercise), particularly during sleep, highlighting the need for careful management strategies to maintain the benefits of exercise while minimising the associated risks (McMahon et al., 2007).

Insulin sensitivity refers to the responsiveness of cells, particularly muscle, liver, and adipose tissue, to the effects of insulin. In T1D, where there is a lack of insulin production, it becomes essential to prioritise the maintenance or enhancement of insulin sensitivity to achieve effective control of blood glucose concentrations (Spellman, 2009). Regular exercise is recognised as an important aspect of maintaining and enhancing various aspects of health, such as insulin sensitivity (Derouich and Boutayeb, 2002; Berman et al., 2012). A study conducted by McMahon and colleagues (McMahon et al., 2007) demonstrated that insulin sensitivity increased for up to 11 hours following 45 minutes of exercise in a supervised, controlled setting among adolescents with T1D.

Breaking sitting with low-intensity PA improved 24 hours blood glucose concentrations and insulin sensitivity (HOMA-IR: 1.89 ± 0.26) compared to structured exercise ($p = 0.02$) and sitting ($p = 0.001$) in adults with T2D (Duvivier et al., 2017). Engaging in real-life PA outside of the laboratory can lead to increased insulin sensitivity for at least 24 hours, thereby increasing the risk of hypoglycaemia during this period (McMahon et al., 2007). Therefore, in individuals with T1D who are not active on a regular basis and only engage in PA randomly (without a regular pattern or with unstructured PA), managing insulin

concentrations can be challenging, especially when experiencing hypoglycaemia after real-life PA. In such individuals, techniques for adjusting insulin to cope with random activity are required. In contrast, regular daily activity allows for more consistent management of blood glucose concentrations and easier management of dietary records, which can lead to better diabetes control (Robertsona et al., 2014). After PA, it is beneficial to consume a high-carbohydrate meal to replenish glycogen stores and lower the risk of hypoglycaemia. During this time, when insulin sensitivity is increased, it is advisable to reduce the insulin dose accordingly (Robertsona et al., 2014).

Acute exercise- or PA-induced insulin sensitivity has clear clinical significance in the prevention and treatment of chronic IR in peripheral tissue, which has direct impacts on glucose control and vascular risk (Thyfault, 2008). This improvement in insulin sensitivity is crucial for enhancing glucose uptake by cells, improving glucose regulation, and reducing the risk of cardiovascular complications associated with IR. For example, skeletal muscle is a major site of glucose uptake in the post-absorpative state (after the absorption of the nutrients from a meal), and thus, an improvement in peripheral insulin sensitivity results in improved glucose tolerance during and after mealtimes (DeFronzo et al., 1981). Indeed, recent investigations demonstrate that skeletal muscle contraction-mediated glucose uptake improves postprandial glucose during one-day interventions employing frequent interruptions in sedentary time (Bergouignan et al., 2016). Exercise-induced glucose uptake through insulin-independent contraction-mediated pathway can help bypass IR and improve glucose uptake in muscle cells, contributing to better glucose control.

Although exercise is a known potent mediator of insulin-independent glucose uptake in T1D, there is no data assessing glucose kinetics in individuals

with T1D in response to lower-intensity PA. Recent research has shown alterations in the mitochondrial ultrastructure and bioenergetics of skeletal muscle in active young adults with T1D (Monaco et al., 2018). For example, mitochondrial oxidised the capacity with significantly lower, and the size and number of autophagic remnants in skeletal muscle higher, in individuals with T1D as compared to control subjects. As such, it may be that lower-intensity PA may be insufficient to prevent skeletal muscle metabolic deficiencies and therefore more vigorous forms of activity are needed to achieve comparable glycaemic improvements. Furthermore, given that muscle mitochondrial impairments are implicated in IR (Hojlund and Beck-Nielsen, 2006), it may be those individuals requiring intervention the most, who may respond the least.

While the mechanisms of improved insulin sensitivity and the insulin-independent contraction-mediated glucose uptake pathway through PA are well established, the exact physiological mechanisms underlying the negative effects of SB on human body remain unknown. Nonetheless, numerous hypotheses have been proposed to understand the overall effect of SB on the human body, which directly impacts on metabolism, vascular health (Park et al., 2020). The physiological effects of SBs on these functions and the biological mechanisms that may mitigate are discussed below.

1.1.2.3 Sedentary Behaviours and Cardiovascular Biomarkers

Sedentary behaviours are associated with metabolic dysfunction, characterised by increased plasma triglycerides, decreased levels of HDL cholesterol, and reduced insulin sensitivity. For example, Yanagibori and colleagues (Yanagibori et al., 1998) examined the effects of 20 days of bed rest on the metabolic health in ten healthy adult who remained in bed except for personal hygiene reasons using a wheelchair controlled by a helper, resulted in a significant decrease in

HDL cholesterol levels and a significant increase in plasma triglyceride ($p < 0.05$). Similar results have been reported by Humburg and colleagues (Hamburg et al., 2007) during five days of bed rest in 22 healthy adults who remained 23.5 hours per day and 30 minutes out of bed for personal hygiene. At the completion of the study, participants experienced a 67% increase in insulin response to glucose loading, suggesting greater IR, along with elevated total levels of cholesterol and triglycerides (Hamburg et al., 2007).

The detrimental effects of SBs on metabolic health seem to be partly influenced by changes in lipoprotein lipase (LPL) activity (Tremblay et al., 2010). The LPL is an enzyme that facilitates the uptake of free fatty acids into skeletal muscle and adipose tissues, and low levels of the enzyme are associated with elevated circulating triglyceride levels, reduced HDL cholesterol, and increased susceptibility to CVDs (Hamilton et al., 2007). Both acute and chronic SBs seem to induce a reduction in LPL activity (Tremblay et al., 2010). Findings have shown that LPL activity reduced in response to SBs in humans. For instance, following 11 days of bed rest in ten healthy Japanese adults, Yanagibori and colleagues (Yanagibori et al., 1998) found a 15.4% decrease in LPL activity (from 0.49 to 0.42 μmol mL^{-1} h^{-1}; $p < 0.05$). SB can lead to reduced activity of LPL in skeletal muscles, obstructing the uptake of free fatty acids and increasing circulating triglyceride levels, which increases the risk of CVDs (Simsolo et al., 1993). Taken together, these findings indicate that prolonged sedentary time significantly increases cardiometabolic risk in humans.

In addition to LPL activity, SB has been shown to affect carbohydrate metabolism through changes in muscle glucose transporter (GLUT) protein content, essential for glucose uptake during resting glucose transporter protein type 1 (GLUT1), insulin- and exercise-induce conditions (GLUT4) (Klip and

Pâquet, 1990; Kawanaka et al., 1997). However, GLUT protein content reportedly increases significantly in response to very low-intensity exercise in individuals who are likely to have a high level of SB, such as those with spinal cord injury (Chilibeck et al., 1999; Phillips et al., 2004). For example, Chilibeck and colleagues (Chilibeck et al., 1999) found that a 52% increase in GLUT1 protein content and a 72% increase in GLUT4 protein content after eight weeks of functional electrical stimulation exercise in human skeletal muscle, as well as improved oxidative capacity and insulin sensitivity. This indicates that even small increases in contractile activity (muscle contractions) can significantly rise muscle GLUT content in individuals with sedentary lifestyle.

1.1.2.4 Sedentary Behaviours and Vascular Health

Sedentary behaviour may also detriment effect of vascular health. Hamburg and colleagues (Hamburg et al., 2007) investigated changes in vascular health after five days of bed rest in 20 health individuals. They observed a decrease in reactive hyperaemia (indicating reduced peripheral vascular function) about ~20% in the legs and 30% in the arms (Hamburg et al., 2007). Additionally, individuals showed a significant increase in blood pressure and a significant decrease in brachial artery diameter ($p < 0.05$) (Hamburg et al., 2007). These results are supported by results from another study, demonstrating that 56 days of head-down bed rest led to decreased endothelium-dependent vasodilation and increased endothelial cell damage (i.e., endothelial dysfunction can indicate impaired blood vessel function, potentially leading to reduced blood flow and increased cardiovascular risk factors such as atherosclerosis (Hadi et al., 2005)) in 16 healthy women (Demiot et al., 2007). Interestingly, Demiot and colleagues (Demiot et al., 2007) observed that exercise during bed rest prevented the adverse effects on vascular health, indicating a beneficial effect vascular health.

Therefore, recent guidelines recommended to limit SB to no more than two hours daily and frequent prolonged sitting (Tremblay et al., 2016; Chaput et al., 2020).

1.2 Chapter Summary

- Type 1 diabetes is a chronic autoimmune condition in which the immune system attacks and destroys the insulin-producing β-cells in the pancreas, resulting in little or no production of insulin responsible for regulating blood glucose concentrations.
- The effective management of T1D requires a comprehensive approach that includes not only insulin therapy and blood glucose monitoring, but also lifestyle modifications such as PA.
- Regular PA and exercise play a key role in improving glucose control and enhancing insulin sensitivity in T1D, but a high proportion of those with T1D do not engage in PA/exercise due to fear or hypoglycaemia.
- Interrupted siting improves glucose control in T2D by reducing overall blood glucose concentrations, enhancing fasting glucose, and attenuating postprandial increases, but there is a lack of research in T1D.
- Therefore, interrupted sitting approach may benefit T1D care, improving health outcomes and quality of life.

1.3 Researcher Experience and Positionality

I am a Kuwaiti female nutritionist with a BSc in Nutrition from Kuwait University and clinical experience in government hospitals in Kuwait from 2013 to 2017. During this time, I worked in medical, surgical, and gynaecology wards, as well as in polyclinics, which gave me practical experience with Kuwait's healthcare system and its nutritional challenges.

Building in this foundation, I pursued an MSc and now a PhD at the University of Leeds, UK, where I have gained experience in Western research methodologies and public health approaches. My academic and professional background across both Middle Eastern and Western settings informs my research and enables me to integrate diverse perspectives.

I recognise that my education, work experience, and cultural background shape how I approach my research. To ensure objectivity and cultural awareness, I regularly reflect on my views and consider different perspectives.

1.4 Thesis Aims and Objectives

This thesis aims to examine the effects of PA and SBs on glucose control in individuals with T1D, and in particular, the effects of interrupting prolonged sedentary time with frequent activity breaks on glucose control. As highlighted in the literature above, research regarding the influence of interrupting prolonged sedentary time on glucose control in T1D is extremely limited. While evidence suggests beneficial effects of interrupting sitting interventions in individuals with T2D, it is important to note that T1D and T2D have distinct disease aetiologies. Examining whether interrupting sitting strategies that employ frequent low-intensity PA can improve glucose management in individuals with T1D is important because it can enhance insulin sensitivity, reduce blood glucose

concentrations, and potentially mitigate the adverse effects of prolonged sitting.

1.4.1 Overall Thesis Research Questions

In chapters three to six the specific aims of each study are provided. This thesis addresses the following research questions:

- What are the attitudes and barriers toward exercise among adults with T1D, with and without IR? How do attitudes and barriers toward exercise impact the quality of life in those populations? (Chapter 3).

- What is the amount of PA and sedentary time undertaken by adults with T1D? Do adults with T1D meet current UK recommendations for PA of at least 150 minutes per week of MVPA? What moderators effect levels of PA and sedentary time? (Chapter 4; Part A).

- Are PA and sedentary time associated with glycaemia? (Chapter 4; Part B).

- How do glycaemic patterns vary across different activities of daily living in adults with T1D?
    - **Null hypothesis:** Daily living activities, including PA and SBs, do not significantly impact glucose control in free-living adults with T1D (Chapter 5).
- Does breaking up prolonged sitting with frequent activity breaks improve 48-hour glucose control in adults with T1D?
    - **Null hypothesis:** Frequent activity breaks from sitting do not significantly improve 48-hour glucose control in adults with T1D (Chapter 6).

Chapter 2 – General Methods

2.1 Ethical Consideration

Ethical approval was obtained by the Health Research Authority (National Health Service (NHS) – London - Hampstead Research Ethics Committee) for the study reported in Chapter 5 (REC reference: 23/PR/0500) and for the study in Chapter 6 (NHS – London-Surrey Research Ethics Committee, REC reference: 20/LO/0650). Prior to taking part in the study, the main objective and procedures of the research project were explained to the interested participants, and they were given the opportunity to ask questions. Written informed consent was obtained for all participants before taking part in testing. In both experimental studies, participants received an Amazon voucher upon completing the study (state value) and were re-embused travel expenses. However, the systematic review and meta-analysis in Chapter 4 did not require ethical approval, as it is used publicly available data from previously published studies.

2.1 Participants Recruitment and Screening

For Chapters 5 and 6, participants were recruited through various channels at the University of Leeds, including university mailing lists, website, and local notice boards on campus. Additionally, recruitment efforts targeted local NHS general practitioners and dental clinics, gyms, and local and national diabetes charities via poster advertisements and mailing lists. A participant information sheet with all details regarding the study aim and procedures was provided to interested participants, and they were invited to complete an online screening questionnaire to assess eligibility, which included information about medical history, insulin regimens, mobility issues, as well as food allergies or intolerances. In addition to an unawareness hypoglycaemia questionnaire assessed through a combination

of the Clarke and Gold methods (Gold et al., 1994; Clarke et al., 1995) for participants safety and to tailor interventions effectively. Specific inclusion/ exclusion criteria for the experimental studies included in this thesis are presented in Chapters 5 and 6.

2.2 Measurements

2.2.1 Anthropometry

Body mass (kg) and height (cm) were measured using an electronic body mass and height scale (Seca 764, GmbH & Co. KG, Hamburg, Germany; **Figure 2.1**), with light clothing, removed shoes, and emptied pockets. BMI was calculated using the following formula:

$$BMI\ (kg/m^2) = \frac{Body\ mass\ (kg)}{Height\ (\mathrm{m}^2)}$$

Figure 2.1 Electronic Body Mass and Height Scale

2.2.2 Blood Pressure

Blood pressure was measured using automated blood pressure device (Omron HBP – 1300, Omron Corporation, Japan; **Figure 2.2**) with an adjustable cuff placed on the participant's upper arm.

Figure 2.2 Automated Blood Pressure Device

2.2.3 Continuous Glucose Monitoring

In Chapters 5 and 6, participants wore the FreeStyle Libre Pro iQ (Abbott Diabetes Care) to measure the blood glucose concentrations in interstitial fluid surrounding cells below the skin. FreeStyle Libre Pro system comprises of a handheld reader and a sensor (Abbott Diabetes Care, 2024). The reader comes with a USB cable and power adapter, while the sensor kit includes a sensor applicator and sensor pack, **Figure 2.3**. The sensor is small, discreet, and water-resistant, with a very thin filament (0.4 millimetre), painlessly, flexible, sterile fibre that is inserted five millimetres beneath the skin surface on the upper arm. The sensor remains attached to the back of the upper arm, where it is least vulnerable to impacts from knocks or bending/folding the skin, for a maximum duration of 14 days. This location has been established as more accurate than the back and chest (Hall et al., 2022).

1. Applicator: use to apply the sensor. 	**2.** Sensor: apply on the back of the upper arm. 	**3.** Reader: scan and activate the sensor. 

Figure 2.3 FreeStyle Libre Pro System

The fibre draws interstitial fluid from the muscle, measuring blood glucose concentrations automatically every minute and storing data at 15-minute intervals (National Institute for Health and Care Excellence, 2017). The dermal interstitial fluid is an optimal site for glucose monitoring because it rapidly and accurately reflects changes in blood glucose concentrations (Ribet et al., 2018). The sensor is calibrated at the factory, making it more convenient to use and eliminating the risk of sensor inaccuracies due to calibration error (such as capillary meter inaccuracy or not washing hands) seen with other devices (Hoss and Budiman,

2017). The accuracy of the FreeStyle Libre has been demonstrated, with 96.5% of the readings considered clinically accurate and 98.9% deemed clinically acceptable (National Institute for Health and Care Excellence, 2017). Furthermore, the MARD of 11.4% further confirms its high levels of accuracy (National Institute for Health and Care Excellence, 2017).

As the FreeStyle Libre Pro is a blinded CGM, the glucose data was masked from participants (Longo and Sperling, 2019). As such, participants in Chapters 5 and 6 did not adjust their treatment regimen based on blood glucose readings while wearing the sensor. The single-use sensor holds data for 14 days before being returned to the researcher. The data is then downloaded using the FreeStyle LibreView software and analysed. The procedures to fit the CGM are presented in **Figure 2.4** (Abbott Diabetes Care, 2023).

The metrics assessed include the percentage of blood glucose readings per day within the target range (TIR: 3.9 – 10.0 mmol/L), time below the target range (TBR 1: 3.0 – 3.8 mmol/L and TBR 2: < 3.0 mmol/L), time above the target range (TAR 1: 10.1 – 13.9 mmol/L and TAR 2: > 13.9 mmol/L), mean glucose (average blood glucose concentrations over a specific period), and glycaemic variability (defined as fluctuations in blood glucose concentrations over a specific time period (Cañas et al., 2023)).

1. Press the home button to turn on the reader and touch “Get Sensor Data”. 	**2.** Hold the reader within 1 cm to 4 cm (1.5 inches) of the sensor. 	**3.** Touch “View” to view the daily glucose graph. 

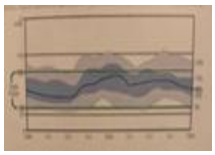
4. Go to FreeStyle Libre website to create the report and follow the onscreen instructions. 	**5.** Connect the reader to a computer with the USB cable provided in the reader kit. 	**6.** View daily glucose patterns with the ambulatory glucose profile. 

Figure 2.4 Continuous Glucose Monitoring Procedures

2.2.4 Physical Activity

2.2.4.1 GENEActiv Accelerometer

In Chapter 5, participants wore the GENEActiv accelerometer version 1.2 (Activinsights Ltd, Cambridge, UK) to measure habitual PA. The GENEActiv is a small-sized (43 x 40 x 13 mm), lightweight (16 g without strap), and waterproof device that objectively measures PA levels and sedentary time (Activinsights, 2022a). The GENEActiv system (including the wrist-worn accelerometer, charger/download cradle, and USB cable) is shown in **Figure 2.5**.

Figure 2.5 GENEActiv System

Participants were instructed to wear the wrist-worn triaxial accelerometer continuously on their non-dominant wrist, 24 hours a day, during the study period. Research has demonstrated that the GENEActiv worn on the non-dominant wrist is more accurate in detecting PA compared to the dominant wrist (Fraysse et al., 2021). GENEActiv monitors various metrics, including different levels of PA

intensity and sedentary time, and has been shown to be reliable and valid in their measurement (Pavey et al., 2016). A study by Antczak and colleagues (Antczak et al., 2021) confirms the reliability of GENEActiv for measuring PA, showing that three to four days are needed for acceptable reliability (intraclass correlation coefficients [ICCs], which measure the consistency or reliability of repeated measurements, = 0.7, indicating moderate reliability) and five to six days for higher reliability (ICC = 0.8). For validity, GENEActiv showed strong agreement with ActivPAL for measuring sedentary time (ICCs = 0.80; Pearson's *r* = 0.81) (Pavey et al., 2016).

GENEActiv was configured using the GENEActiv software (version 2.2). This configuration required accessing the "config setup" tab to input recording parameters and trial-specific data, covering operator ID, measurement frequency and period, recording start mode (immediately or scheduled), and subject information (i.e., subject ID, date of birth, and BMI). A measurement frequency of 50 Hz was chosen to ensure a substantial number of data points were collected over a 24-hour period during the entire 14 days, starting from the preliminary visit (Activinsights, 2022b).

Data from GENEActiv was extracted using the 'Data Extractor' option in the software, saved as raw binary files (BIN file) containing acceleration data for the x, y, and z axes after the completion of the study period, and subsequently imported into R software (Pavey et al., 2016). Proprietary algorithms classify PA levels by processing raw three-axis acceleration data into Sum of Vector Magnitudes and mean values over epochs, where Sum of Vector Magnitudes quantifies the intensity of movement by combining acceleration data from three axes and adjusting for gravity, enabling classification into sedentary, low-, moderate-, and vigorous activity levels (Activinsights, 2022b). A six-day

monitoring period, including Saturday and Sunday, has been shown to capture habitual PA using the GENEActiv, with results valid if wear time exceeds ten hours on those days (Dillon et al., 2016; Ricardo et al., 2020).

2.2.4.2 Physical Activity Questionnaire

The long form of the International Physical Activity Questionnaire (IPAQ-LF) (Craig et al., 2003) was completed in the preliminary visit prior to study commencement, as shown in **Appendix B (Table B.4)**, to assess habitual PA levels for study participants in Chapters 5 and 6. The IPAQ is a self-reported, semi-structured questionnaire in which participants reported PA duration (hours or minutes per day), frequency (times per day), and intensity (walking, moderate, and vigorous) over the previous seven days within four different domains related to work, transportation, domestic tasks, and leisure-time activities (Wanner et al., 2016). In addition to time spend in SBs during waking hours (at work, at home, while doing coursework, and during leisure time) on a usual weekday and weekend day (Ruescas-Nicolau et al., 2021).

The total scores in the IPAQ-LF are calculated by adding the duration in minutes and frequency in days for all types of activities across all domains. Activities are assigned as MET based on the intensity levels (walking = 3.3 METs, moderate = 4.0 METs, and vigorous = 8.0 METs), and the total PA score is classified as low (< 600), moderate (600 – 3000), and vigorous (> 3000 MET-minutes per week) (International Physical activity questionnaire, 2005; Ahn et al., 2015). Additionally, the time spent in sitting is reported in hours and minutes per day. PA scores have been analysed using an Excel-generated form, following the scoring protocol (International Physical activity questionnaire, 2005). The calculated IPAQ score has demonstrated reliability and validity, with higher scores indicating greater levels of activity (Craig et al., 2003). However, the IPAQ

relies on self-reporting, which may overestimate PA and underestimate SBs (Klesges et al., 1990; Segura-Jimenez et al., 2013).

2.2.4.3 Barriers to Physical Activity in Type 1 Diabetes Scale

The Barrier to Physical Activity in Type 1 Diabetes (BAPAD-1) scale, which is a validated and widely used questionnaire (Brazeau et al., 2012a), was completed during the preliminary visit prior to study commencement, as shown in **Appendix B (Table B.5)**, to assess salient barriers to PA for study participants in Chapters 5 and 6. The BAPAD-1 is a self-reported scale consisting of 11 equally weighted diabetes-specific items, with answers coded on a seven-point rating scale ranging from one (extremely unlikely) to seven (extremely likely) to represent the likelihood of individuals participating in regular PA during the next six months (Dube et al., 2006; Brazeau et al., 2012a).

This scale is a valid and reliable measure for assessing perceived barriers to PA in T1D, with high reliability scores and strong psychometric properties (i.e., attributes measuring consistency and accuracy) (Dube et al., 2006; Koehn and Amirabdollahian, 2021). The BAPAD-1 evaluates perceived PA barriers with an 11-item scale: loss of control over diabetes, risk of hypoglycaemia and hyperglycaemia, fear of being tired, fear of hurting yourself, fear of suffering a heart attack, low fitness levels, physical health status excluding diabetes, presence of diabetes, weather conditions, and location of a gym (Dube et al., 2006).

2.2.5 Sedentary Behaviours

2.2.5.1 ActivPAL Accelerometer

In Chapter 5, participants wore the ActivPAL4 accelerometer to measure SBs (Version 8.12.6.118, PAL Technologies Ltd, Glasgow, Scotland; **Figure 2.6**). The

ActivPAL is a triaxial accelerometer, small-sized (43 x 23.5 x 5 mm), lightweight (9.5 g), and waterproof, used to quantify free-living daily activities (Alkalih et al., 2022; PAL Technologies Ltd, 2024). The accelerometer was sealed with a nitrile finger cot and a transparent film (3M Tegaderm™ Roll), then attached to the skin with another transparent film to provide a waterproof barrier. The device was attached at the midpoint of the right thigh, midway between the hip and knee joint, as recommended by the manufacturers (Steeves et al., 2015; Edwardson et al., 2017). ActivPAL equipment (e.g., ActivPAL4 accelerometer, USB portal and cable, nitrile finger cot, and transparent film) is shown in **Figure 2.6**.

Figure 2.6 ActivPAL Equipment

Participants were provided with the ActivPAL4 and instructed to wear it for 24 hours a day during the study duration. Prior to use, each accelerometer was set up by the researcher using ActivPAL software. In preparation for data collection, the researcher inserted the ActivPAL into a designated cradle and set up recording parameters, such as starting condition (immediate or scheduled), recording duration, and assigning a unique identifier ID to each participant. Upon confirming these settings, data recording began. ActivPAL software uses an algorithm to determine the time spent in different body positions. This determination is based on a combination of static acceleration (due to gravity) and the angle of the thigh, which is used to classify posture as either lying/sitting

or standing. Data from the ActivPAL were exported in both events format and 15-second epochs format, with each minute constituted by summing every four epochs (Carpenter et al., 2021). These data are saved in raw format as a comma-separated values file through PAL Batch for analysis (Edwardson et al., 2022).

The validity and reliability of the ActivPAL have been demonstrated as a measure of SB in individuals with T2D (Alothman et al., 2020). In accordance with prescribed accelerometer methodologies, wear days were considered valid if participants wore the ActivPAL continuously for a period of at least ten hours during waking hours (Pavey et al., 2016; Edwardson et al., 2017; Carpenter et al., 2021), with a minimum of five days of data collection required, including at least one weekend for greater precision in estimates (Aguilar-Farias et al., 2019).

2.3 Statistical Analyses

Data were analysed using the Statistical Package for the SPSS (IBM Corp, Armonk, New York, US; version 28.0). The data are presented as mean ± standard deviation (SD), with figures reporting mean ± standard error of the mean (SEM). Data were visually inspected for normality prior to statistical analysis using the Kolmogorov-Smirnov test. For all analyses, statistical significance was established at $p < 0.05$. All statistical procedures are described in detail in the methods section for each experimental chapter in this thesis.

Chapter 3 – Barrier to Exercise in Adults with Type 1 Diabetes and Insulin Resistance

What do we know? Chapter 1 discussed the importance of PA and exercise as fundamental strategies in managing glucose control in individuals with T1D. However, many of them do not achieve the recommendations due to barrier to exercise in terms of glucose control. Thus, in Chapter 3, barrier to exercise in T1D, with and without IR, were highlighted.

Key issues: Previous studies have not investigated whether attitudes and barriers toward exercise in individuals with T1D are influenced by IR, and how this relationship affects their quality of life.

Chapter aims: To examine the attitudes and barriers toward exercise, and their impact on the quality of life, among adults with T1D with and without IR.

Chapter implications: Identifying attitudes and barriers to exercise in adults with T1D, and whether these are influenced by IR, may help inform targeted interventions to improve PA/exercise participation and quality of life. This insight also helped guide the study design and direction of Chapters 4, 5, and 6, emphasising the need for personalised strategies to enhance glucose control through PA and manage SBs.

3.1 Introduction

Regular participation in PA reduces the risk of developing IR, metabolic syndrome, and progression to overt T2D. In individuals with T1D, regular PA also improves features of metabolic syndrome, including IR (Riddell et al., 2017), and lowers the risk of long-term health complications (Bohn et al., 2015). A recent large, cross-sectional survey of 18,028 adults with T1D demonstrated that ~60%

of individuals with T1D did not achieve the recommended PA levels of at least 150 minutes of MVPA per week (based on self-reported PA) (Bohn et al., 2015), a finding that supports some (Waden et al., 2008; Matson et al., 2018), but not all (Brazeau et al., 2012a) studies. Previously, fear of hypoglycaemia and a lack of knowledge about managing diabetes around exercise have been reported as salient barriers to exercise in those with T1D (Brazeau et al., 2008; Lascar et al., 2014; McCarthy et al., 2022a), but it has yet to be established whether these perceived barriers differ between individuals with and without IR. Furthermore, T1D has consistently been shown to be associated with reduced quality of life (Cho and Kim, 2021; Bekele et al., 2022), and exercise (Domínguez-Domínguez et al., 2021) and IR have been identified as factors that mediate the relationship between T1D and quality of life.

Insulin resistance is highly prevalent within the T1D population and represents a strong independent risk factor for diabetes complications (Cefalu, 2001; Schauer et al., 2011; Krochik et al., 2015). Although individuals with T1D are more prone to IR than those without diabetes (Nadeau et al., 2010), participating in PA improves insulin sensitivity (Ykijarvinen et al., 1984; Landt et al., 1985). Given the health benefits associated with PA, individuals with T1D with IR are likely to benefit greatly from regular participation in PA. However, little is known about the attitudes to exercise or quality of life in individuals with T1D and associated IR. Existing research has focussed principally on T1D as a single clinical entity when considering attitudes and barriers to exercise, and quality of life (Brazeau et al., 2008; Lascar et al., 2014; Kennedy et al., 2018; Brennan et al., 2021). In the general population, obesity is associated with lower PA levels and poorer quality of life (McIntosh et al., 2016), suggesting that some barriers to exercise and quality of life outcomes are weight-specific. Furthermore, IR is

generally associated with increased insulin dose requirements and poorer glycaemic management in T1D (Priya and Kalra, 2017), both of which increase the burden of disease (Joensen et al., 2016). As such, it is possible that individuals with T1D and IR have greater barriers to PA than those with T1D without IR. To the best of our knowledge, however, no research has explored whether attitudes toward PA in individuals with T1D are mediated by IR, and how it affects quality of life. This information is important for the future design of individualised and person-centred PA interventions that target those with T1D at high risk of complications. Therefore, the aim of this study was to examine the attitudes and barriers toward exercise in individuals with T1D with and without IR, and their impact on quality of life.

3.2 Methods

In this chapter data was pooled and analysed from two previously conducted randomised controlled trials (RCTs; Clinical Trial Registration numbers ISRCTN40811115 and NCT05231642), each of which received approval from local NHS Research Ethics Committees (REC references 17/NE/0244 and 21/WA/0381). Briefly, ISRCTN40811115 was an RCT investigating the impact of omega-3 supplementation on glycaemic management in T1D, and NCT05231642 was an RCT exploring interpersonal postprandial glucose responses in T1D. In both RCTs, participants were recruited from the Yorkshire, Humber, and northeast regions of the UK, in-clinic and through university-led advertisements, and written informed consent was obtained from all participants. Only baseline pre-treatment data from the two RCTs was used in the present chapter, with 85 participants included who met the inclusion criteria for these studies. As described elsewhere (Campbell et al., 2017b; O'Mahoney et al., 2020), the inclusion/exclusion criteria required a clinical diagnosis of T1D with a

classical presentation, an age between 18 and 50 years, a diabetes duration of five years or more, and treatment on a stable (> 12 months) basal-bolus insulin regimen delivered through MDIs or CSII. None of the study participants had clinically established diabetes-related complications.

3.2.1 Data Collection and Study Procedures

The cross-sectional analyses were performed using baseline pre-treatment data across each RCT. Clinical information obtained included age, sex, BMI, HbA1c, HTN status, insulin regimen, estimated glucose disposal rate (eGDR), and self-reported exercise levels, where participants first indicated if they exercised (0 = no exercise, 1 = exercise) and were then classified as engaging in moderate exercise (if they engaged in three days or more of vigorous activity for at least 20 minutes per day, five days or more of moderate activity or walking at least 30 minutes per day, or five days or more of any combination of (walking, moderate, or vigorous activities) totalling ≥ 600 MET-minutes per week)) or vigorous exercise (if they engage in vigorous activity on at least three days and accumulating at least 1500 MET-minutes per week or seven or more days of any combination of low, moderate or vigorous activities accumulating at least 3000 MET-minutes per week), as determined by the International Physical Activity Questionnaire – Short form (IPAQ-SF) criteria (International Physical activity questionnaire, 2005). Participants were defined as hypertensive if blood pressure was ≥ 140/90 mmHg (Whelton and Carey, 2017), if they had a pre-existing diagnosis of HTN, or if they were prescribed antihypertensive drugs. Participants were classified by IR status using the eGDR – a validated and reliable surrogate marker of IR in T1D (Epstein et al., 2013; Zhang et al., 2024) – calculated using BMI, HbA1c, and HTN status as follows: $eGDR = 19.02 - (0.22 \times BMI\ [kg/m^2]) - (3.26 \times HTN) - (0.61 \times HbA1c\ [\%])$, where HTN = 1 if yes and HTN = 0 if no

(Kietsiriroje et al., 2019). A lower eGDR is associated with a higher risk of CVDs, diabetic kidney disease, and all-cause mortality in individuals with T1D (Orchard et al., 2002; Kilpatrick et al., 2007; Nyström et al., 2018).

Self-reported attitudes to exercise were assessed using the BAPAD-1 scale to assess the various barriers to PA in individuals with T1D. A detailed description of the BAPAD-1, including its structure, item descriptions, seven-point rating scale, and its validity and reliability in T1D, is in **Appendix B, Table B.5**.

Quality of life was determined using the SF-36 questionnaire, a comprehensive and reliable tool (Ware Jr and Sherbourne, 1992) that has been previously validated in individuals with diabetes (Speight et al., 2009). It was chosen over the EQ-5D questionnaire due to its greater sensitivity in detecting small changes and its ability to assess multiple dimensions of physical and mental health. The SF-36 has strong reliability, with high internal consistency ($\alpha \geq 0.70$) and good test-retest reliability, ensuring consistent and accurate measurement of quality of life over time (Ware Jr and Sherbourne, 1992). Additionally, the SF-36 assesses both physical and mental domains in eight multiple-item scores: physical functioning, limitations due to physical problems, social functioning, bodily pain, general mental health (psychological distress and well-being), limitations due to emotional problems, vitality (energy and fatigue), and general health perceptions. All domains contribute differently to the scoring for both measures (Lins and Carvalho, 2016). Scores from different domains were converted and combined to indicate a range from low to high quality of life.

3.2.2 Statistical Analysis

Descriptive information for each variable was calculated and assessed for normality using the Kolmogorov-Smirnov test. Normally distributed variables are

reported as mean ± SD, non-normally distributed variables are reported as median (interquartile range (IQR)), and categorical variables are reported as frequency (%). Beta coefficients with confidence intervals (CIs) were presented whenever appropriate. The cohort was stratified according to eGDR into IR status, with a cut-off point of < 6 mg/kg/mL for the determination of IR, as reported elsewhere (Kietsiriroje et al., 2019). Continuous variables were examined using independent t-tests for normally distributed variables and Mann–Whitney U tests for non-normally distributed variables, and categorical variables were examined with Fisher exact tests. Linear regression was used to investigate the association between eGDR and barriers to exercise (BAPAD-1) and quality of life (SF-36) questionnaires, respectively, with sequential adjustment for confounders (age, sex, diabetes duration, and exercise participation levels) using the subscores for each domain. Data analysis was performed using SPSS version 28 (IBM Corp, Armonk, New York, US), with $p < 0.05$ considered statistically significant.

3.3 Results

The clinical characteristics of the cohort stratified by IR status are presented in **Table 3.1.** A total of 85 individuals (39 with IR and 46 without IR) were included in the analysis. Individuals with IR were significantly more likely to be older, have a longer duration of diabetes, a higher total daily dose (TDD) of insulin, an increased prevalence of HTN, and lower levels of exercise participation ($p < 0.05$; **Table 3.1**).

Table 3.1 Characteristics of the Study Population Stratified by Insulin Resistance Status

	IR status			
	All data	**IR**	**non-IR**	***P*-value**
n	85	39 (46%)	46 (54%)	-
Age (years)	28.60 ± 5.44	30.66 ± 4.99	26.86 ± 5.23	**< 0.001[a]**
Sex Male (%)	43 (51%)	22 (56%)	21 (46%)	0.22[c]
BMI (kg/m^2)	26.52 ± 3.36	28.21 ± 3.21	25.09 ± 2.79	**< 0.001[a]**
HbA1c (mmol/mol)	60.96 [13.30]	67.15 [22.16]	56.43 [9.10]	**< 0.001[b]**
HbA1c (%)	7.73 [1.22]	8.29 [2.03]	7.32 [0.83]	**< 0.001[b]**
Length of diagnosis (years)	16.27 [2.90]	19.17 [12.94]	14.58 [11.38]	**0.003[b]**
Hypertensive (%)	44 (51.80%)	39 (100%)	5 (10.90%)	**< 0.001[c]**
Bolus insulin aspart (%)	54 (63.50%)	23 (59.00%)	31 (67.40%)	0.28[c]
TDD (IU)	45 [8]	46 [9]	42 [7]	**< 0.001[b]**
No exercise (%)	38 (45%)	28 (72%)	10 (22%)	**0.004[c]**
Moderate exercise (%)	32 (38%)	13 (33%)	19 (41%)	0.30[c]
Vigorous exercise (%)	15 (18%)	9 (23%)	6 (13%)	0.18[c]

Normally distributed variables are reported as mean ± SD; non-normally distributed variables are reported as median [IQR]; categorical variables are reported as frequency (%). [a] = Independent t-test; [b] = Mann-Whitney U test; [c] = Fisher's exact test.

P < 0.05 indicates statistical significance. **BMI**, body mass index; **HbA1c**, glycated haemoglobin; **TDD**: total daily dose.

The mean BAPAD-1 total score was higher for individuals with IR (IR 3.87 ± 0.61; non-IR 2.83 ± 0.55; $p < 0.001$; **Table 3.2**). The highest exercise barrier scores for IR were risk of hypoglycaemia (IR: 5.67 ± 1.26), risk of hyperglycaemia (IR: 5.23 ± 1.20), presence of diabetes (IR: 4.46 ± 1.27), and loss of diabetes management (IR: 4.33 ± 1.83). The highest exercise barrier scores for non-IR were not diabetes-related, with low level of fitness (3.91 ± 1.26) and physical health status excluding diabetes (3.67 ± 1.48) listed as the most salient barriers in non-IR (**Table 3.2**).

Table 3.3 presents the unadjusted and adjusted associations between IR status and BAPAD-1 subscales. Significant associations were observed between eGDR and BAPAD-1 subscales (i.e. loss of control over your diabetes, risk of hypoglycaemia, fear of hurting yourself, fear of suffering a heart attack, presence of diabetes, and risk of hyperglycaemia ($p < 0.05$; **Table 3.3**). The strongest association was for risk of hypoglycaemia in both unadjusted and adjusted models (Model 1: $\beta = -0.82$; Model 2: $\beta = -0.73$; Model 3: $\beta = -0.71$; $p < 0.001$; **Table 3.3**). These associations remained robust after adjustment for age, sex, diabetes duration, and exercise participation, except for fear of being tired and a low level of fitness in Model 2 and 3, and weather conditions in Model 2 ($p > 0.05$; **Table 3.3**). Furthermore, significant associations were observed between fear of being tired, a low level of fitness, and weather conditions with eGDR. The subscale for location of a gym was not significantly associated with eGDR ($p > 0.05$; **Table 3.3**).

Table 3.2 Barriers to Physical Activity in Individuals with Type 1 Diabetes, Stratified by Estimated Glucose Disposal Rate (Insulin Resistance status)

	IR status			
	All data (n = 85)	**IR (n = 39)**	**non-IR (n = 46)**	***P*-value**
1. Loss of control over your diabetes	3.49 ± 1.71	4.33 ± 1.83	2.78 ± 1.24	**0.004[a]**
2. Risk of hypoglycaemia	4.24 ± 1.78	5.67 ± 1.26	3.02 ± 1.15	**< 0.001[c]**
3. Fear of being tired	1.81 ± 0.93	1.97 ± 1.06	1.67 ± 0.79	0.14[c]
4. Fear of hurting yourself	1.92 ± 0.97	2.08 ± 1.96	1.78 ± 0.96	0.34[c]
5. Fear of suffering a heart attack	2.61 ± 1.57	3.49 ± 1.72	1.87 ± 0.93	**< 0.001[c]**
6. A low level of fitness	4.08 ± 1.31	4.28 ± 1.36	3.91 ± 1.26	0.85[c]
7. Presence of diabetes	3.80 ± 1.40	4.46 ± 1.27	3.24 ± 1.27	**0.01[c]**
8. Risk of hyperglycaemia	4.14 ± 1.63	5.23 ± 1.20	3.22 ± 1.35	**< 0.001[c]**
9. Physical health status excluding diabetes	3.51 ± 1.41	3.31 ± 1.34	3.67 ± 1.48	0.66[c]
10. Weather conditions	3.49 ± 2.38	3.87 ± 1.15	3.17 ± 3.04	**0.01[c]**
11. Location of a gym	2.76 ± 1.14	2.87 ± 1.08	2.67 ± 1.19	0.73[c]
Standardised total score	3.31 ± 0.77	3.87 ± 0.61	2.83 ± 0.55	**< 0.001[b]**

Normally distributed variables are reported as mean ± SD; non-normally distributed variables are reported as median and IQR; categorical variables are reported as frequency (%). [a] = Independent t-test; [b] = Mann-Whitney U test; [c] = Fisher's exact test.

P < 0.05 indicates statistical significance.

Table 3.3 Association between Estimated Glucose Disposal Rate and Barriers to Physical Activity in Type 1 Diabetes Subscales in 85 Individuals

	Model 1		Model 2		Model 3	
	β (95% CI)	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
eGDR						
1. Loss of control over your diabetes	−0.63 (−1.13 to −0.65)	**< 0.001**	−0.52 (−0.96 to −0.52)	**< 0.001**	−0.50 (−0.92 to −0.49)	**< 0.001**
2. Risk of hypoglycaemia	−0.82 (−1.29 to −0.95)	**< 0.001**	−0.73 (−1.19 to −0.81)	**< 0.001**	−0.71 (−1.16 to −0.78)	**< 0.001**
3. Fear of being tired	−0.22 (−1.13 to −0.02)	**0.04**	−0.17 (−0.91 to −0.05)	0.07	−0.13 (−0.82 to −0.16)	0.18
4. Fear of hurting yourself	−0.29 (−1.26 to −0.21)	**0.01**	−0.28 (−1.15 to −0.25)	**0.003**	−0.27 (−1.12 to −0.24)	**0.003**
5. Fear of suffering a heart attack	−0.57 (−1.16 to −0.61)	**< 0.001**	−0.47 (−0.99 to −0.48)	**< 0.001**	−0.45 (−1.96 to −0.43)	**< 0.001**
6. A low level of fitness	−0.28 (−0.91 to −0.13)	**0.01**	−0.12 (−0.58 to 0.15)	0.25	−0.17 (−0.69 to 0.04)	0.08
7. Presence of diabetes	−0.46 (−1.14 to −0.46)	**< 0.001**	−0.34 (−0.90 to −0.28)	**< 0.001**	−0.34 (−0.89 to −0.27)	**< 0.001**
8. Risk of hyperglycaemia	−0.71 (−1.29 to −0.83)	**< 0.001**	−0.60 (−1.11 to −0.69)	**< 0.001**	−0.58 (−1.08 to −0.66)	**< 0.001**
9. Physical health status excluding diabetes	0.15 (−0.12 to 0.63)	0.18	0.22 (0.07 to 0.69)	**0.02**	0.26 (0.15 to 0.76)	**0.004**
10. Weather conditions	−0.24 (−0.46 to −0.03)	**0.03**	−0.18 (−0.37 to −0.01)	0.06	−0.19 (−0.38 to −0.01)	**0.04**
11. Location of a gym	−0.09 (−0.67 to −0.26)	0.39	−0.11 (−0.63 to 0.16)	0.24	−0.08 (−0.57 to 0.22)	0.37

Model 1 unadjusted; Model 2 adjusted for age, sex, length of diagnosis; Model 3 adjusted for age, sex, duration of diabetes, and exercise participation. $P < 0.05$ indicates statistical significance.

Table 3.4 Quality of Life Scores for 85 Individuals with Type 1 Diabetes Stratified by Estimated Glucose Disposal Rate (Insulin Resistance Status)

	IR status			
	All data (n = 85)	**IR (n = 39)**	**non-IR (n = 46)**	***P*-value**
1. PF-NBS	48.00 (20.00)	52.00 (20.00)	43.00 (20.25)	0.73[b]
2. RP-NBS	44.00 (27.00)	48.00 (25.00)	39.00 (29.00)	0.42[b]
3. BP-NBS	42.00 (22.00)	42.00 (21.00)	38.00 (22.00)	0.92[b]
4. GH-NHS	41.02 ± 11.64	41.45 ± 12.36	40.65 ± 11.13	0.75[a]
5. VT-NBS	43.75 ± 12.20	44.08 ± 12.95	40.48 ± 11.67	0.82[a]
6. SF-NBS	42.00 (30.00)	42.00 (30.00)	39.50 (25.00)	0.52[b]
7. RE-NBS	46.00 (31.00)	49.00 (28.00)	37.00 (28.75)	0.05[b]
8. MH-NBS	46.00 (23.00)	46.00 (21.00)	43.00 (23.00)	0.53[b]
9. PCS	43.81 ± 11.63	43.67 ± 11.69	43.93 ± 11.69	0.92[a]
10. MCS	40.82 ± 14.74	42.85 ± 15.77	39.11 ± 13.75	0.25[a]

Normally distributed variables are reported as mean ± SD; non-normally distributed variables are reported as median and IQR; and categorical variables are reported frequency. [a] = Independent t-test; [b] = Mann-Whitney U test; [c] = Fisher's exact test. $P < 0.05$ indicates statistical significance.

PF, physical functioning; **RP**, role limitation due to physical health; **BP,** Bodily pain; **GH**, general health; **VT**, vitality; **SF**, social functioning; **RE**, role limitations due to emotional problems; **MH**, mental health; **PCS,** physical component summary; **MCS,** mental component summary.

Table 3.5 Association between Estimated Glucose Disposal Rate and Quality of Life in 85 Individuals with Type 1 Diabetes

		Model 1		Model 2		Model 3	
		β (95% CI)	***P*-value**	**β (95% CI)**	***P*-value**	**β (95% CI)**	***P*-value**
				eGDR			
1.	PF-NBS	0.003 (−0.04 to 0.05)	0.89	−0.001 (−0.03 to 0.04)	0.96	−0.002 (−0.04 to 0.04)	0.92
2.	RP-NBS	−0.01 (−0.05 to 0.03)	0.76	−0.01 (−0.04 to 0.03)	0.69	−0.01 (−0.04 to 0.03)	0.58
3.	BP-NBS	0.003 (−0.04 to 0.04)	0.88	−0.01 (−0.04 to 0.03)	0.77	−0.01 (−0.05 to 0.03)	0.62
4.	GH-NBS	−0.01 (−0.05 to 0.04)	0.83	−0.02 (−0.06 to 0.02)	0.40	−0.02 (−0.06 to 0.02)	0.24
5.	VT-NBS	0.01 (−0.04 to 0.05)	0.70	0.001 (−0.04 to 0.04)	0.95	−0.004 (−0.05 to 0.04)	0.83
6.	SF-NBS	0.000 (−0.04 to 0.04)	0.99	−0.01 (−0.05 to 0.02)	0.38	−0.02 (−0.06 to 0.01)	0.20
7.	RE-NBS	−0.02 (−0.06 to 0.01)	0.15	−0.03 (−0.06 to −0.001)	**0.04**	−0.03 (−0.06 to −0.003	**0.03**
8.	MH-NBS	−0.003 (−0.04 to 0.04)	0.86	−0.02 (−0.05 to 0.02)	0.29	−0.02 (−0.06 to 0.01)	0.22
9.	PCS	0.01 (−0.04 to 0.06)	0.69	0.01 (−0.03 to 0.05)	0.72	0.004 (−0.04 to 0.05)	0.85
10.	MCS	−0.01 (−0.05 to 0.02)	0.50	−0.03 (−0.06 to 0.001)	0.11	−0.03 (−0.06 to 0.002)	0.06

Model 1 unadjusted; Model 2 adjusted for age, sex, length of diagnosis; Model 3 adjusted for age, sex, length of diagnosis, and exercise participation. $P < 0.05$ indicates statistical significance.

The mean SF-36 subscale scores are presented in **Table 3.4**. No differences were observed across any physical or mental components of the SF-36 when assessing the cohort stratified by IR status. **Table 3.5** presents the unadjusted and adjusted associations between eGDR and SF-36 subscales. No significant associations were observed in SF-36 subscales and eGDR after unadjusted and adjusted models for age, sex, length of diagnosis, and exercise participation, with the exception of emotional problems, which was significantly associated with eGDR after sequential adjustment**, Table 3.5**.

3.4 Discussion

To our knowledge, this is the first study to explore attitudes toward exercise and quality of life in individuals with T1D with and without IR. Our study found that individuals with T1D with IR reported lower exercise participation levels and greater barriers to exercise than their counterparts without IR. Additionally, it was noted that the main barriers to exercise differ between individuals with T1D with and without IR; in our cohort, diabetes-specific factors, specifically fear of hypoglycaemia, were the most salient barriers to exercise in individuals with T1D with IR, whereas fitness and non-diabetes-specific physical health were the greatest barriers to exercise in individuals with T1D without IR. These findings remained robust after adjusting for age, sex, and diabetes duration. However, other potential barriers, such as time constraints, were not included due to the use of the BAPAD-1 scale.

The fear of hypoglycaemia had the strongest association with eGDR in the present findings. Findings from other studies, including those employing the BAPAD-1, demonstrated that fear of hypoglycaemia is a salient barrier to exercise in individuals with T1D (Brazeau et al., 2008; Lascar et al., 2014).

Hypoglycaemia is a common occurrence in response to exercise in individuals with T1D, and it can be difficult to predict, avoid, and manage (Martyn-Nemeth et al., 2019; Faradji et al., 2023). Studies have shown that the frequency of hypoglycaemia outside the context of exercise ranges from 42 to 91 events per person-year in adults with T1D, with ~12% of individuals having at least one episode of severe hypoglycaemia per year (Cengiz et al., 2013; Weinstock et al., 2013). Data regarding the prevalence of exercise-induced hypoglycaemia in T1D are limited largely to laboratory-based studies, which have varied depending on the nature of exercise and treatment strategies employed (Cockcroft et al., 2020), although no single exercise modality or treatment strategy is fully protective. The finding that individuals with IR reported glycaemic factors, specifically hypoglycaemia, as more salient barriers to exercise than individuals without IR could be related to the greater exposure to exercise-induced dysglycaemia, given that exercise participation levels were, on average, lower in those with IR. However, the association between glycaemia-related barriers to exercise and eGDR remained robust after adjustment for exercise participation levels. Importantly, the association between eGDR and subscales of the BAPAD-1 scale suggests that this measure captures general aspects related to T1D, and it is therefore possible that individuals able to navigate exercise barriers are also better equipped to manage weight, diabetes control, and blood pressure. Although individuals without IR outlined non-glycaemic factors, specifically fitness and physical health status excluding diabetes, as salient barriers to exercise compared with those with IR, this could be related to the stabilisation of their blood glucose concentrations. Notably, moderate exercise participation levels were, on average, higher in individuals without IR.

In this study, we did not observe differences in quality of life between those

with T1D stratified by IR status. It has been consistently shown that quality of life is lower in individuals with T1D compared to those without T1D, and that the presence of IR also lowers quality of life in the general population (Rubin and Peyrot, 1999; Cho and Kim, 2021; Nijole et al., 2021; Bekele et al., 2022). As such, it was unexpected that IR in T1D was not associated with further decrements in quality of life. This may be due to the relatively small sample size as well as the exclusion of individuals with established diabetes complications, who often experience a lower quality of life. Importantly, when comparing the quality of life data normalised to a general population with the present T1D data, the overall physical health domain and mental health domain values for SF-36 were lower than those reported for the general population (Garratt and Stavem, 2017; Salem et al., 2019). Furthermore, our data show that individuals with T1D with IR had lower quality of life scores in each domain, when compared with individuals with IR in another study (Nijole et al., 2021). The association between the emotional problems subscale and eGDR became significant after sequential adjustment, which warrants further study, particularly as this is at odds with the other subscales.

3.4.1 Study Strengths and Limitations

In addition to being the first investigation on the effects of IR on barriers to exercise in T1D, this study has a number of notable strengths. Firstly, validated questionnaires were used to assess attitudes toward exercise and quality of life. Secondly, sampling came from a broad and representative population of individuals with T1D, although the study population excluded individuals with established diabetes complications. Thirdly, eGDR was used – a robust and validated surrogate measure of IR that has previously been shown to be a strong predictor of both diabetes complications and mortality (Kietsiriroje et al., 2019) –

while also examining the sample separately for those with and without IR.

Given the cross-sectional design of the study, it is not possible to infer causation from the findings. Although it is possible that the lower exercise participation level may be a contributing factor to the development of IR, it is also likely that the presence of IR impacted exercise participation. The participants' understanding of IR was not assessed; however, their informal experiences and personal observations suggest that IR is generally poorly understood within the context of T1D and is rarely discussed in routine diabetes practice. The study participants were not informed of their IR status before completion of the questionnaire. As such, it is speculated that it is unlikely that awareness of IR influenced the questionnaire responses. Furthermore, it was not possible to objectively measure exercise participation levels, and the findings were based on self-report data. Lastly, pooled data from two previous RCTs were used, and thus there is potential for selection bias due to variations in study populations and methodologies; therefore, real-world studies using larger cohorts and involving different ethnic groups are needed to ensure the generalisability of these findings.

3.5 Conclusion

In conclusion, individuals with T1D and IR exercise less frequently and have greater perceived barriers to exercise than individuals with T1D without IR. Risk of hypoglycaemia was the greatest barrier to exercise in individuals with T1D with IR, yet non-diabetes-related barriers to exercise were found to be more salient in individuals with T1D without IR. Nevertheless, no effect was seen on the SF-36 quality of life domains between IR groups. As such, individually centred PA interventions should be designed that consider and account for differences in exercise attitudes in specific subpopulations of individuals with T1D.

3.6 Chapter Summary

- The presence of IR was associated with lower PA levels and greater barriers to exercise in individuals with T1D.
- Glycaemic factors, such as the risk of hypoglycaemia, risk of hyperglycaemia, presence of diabetes, and loss of diabetes management were the main barriers to exercise. Among individuals with T1D and IR, the risk of hypoglycaemia was the most salient barrier to exercise.
- Non-diabetes factors, such as low levels of fitness and physical health status excluding diabetes, were the most salient barriers to exercise in T1D individuals without IR.
- Quality of life did not differ significantly between individuals with T1D with and without IR.

Chapter 4 – Quantifying Physical Activity and Sedentary Time in Individuals with Type 1 Diabetes (Part A) and their Effects on Glucose Control (Part B): A Systematic Review and Meta-Analysis

In this chapter two separate research questions are addressed using the same systematic review methodology, but these two questions are presented as separate part for clarity. Part A (systematic review) quantifies the levels of PA and SBs in adults with T1D and explores factors that moderate these behaviours. Part B (meta-analysis) assesses the effects of acute aerobic exercise on acute glycaemia and examines the impact of long-term aerobic exercise training on chronic glycaemia. Separating these parts allows for clearer and more focused analysis and discussion of each research question.

What do we know? The literature in Chapter 1 shows that adults with T1D struggle to achieve the PA guidelines of at least 150 minutes of MVPA per week; however, the amount of PA reported is inconsistent between studies, which use a variety of measurement tools, and few report sedentary time.

Key issues: There is a need to quantify PA and sedentary time in those with T1D, particularly in studies using objective rather than self-reported measures of PA and sedentary time (e.g., accelerometry). Furthermore, there is a need to examine the factors that moderate PA and sedentary time in those with T1D to better understand why some fail to meet the current PA guidelines.

Chapter aims: Part A of this chapter aims to quantify PA and sedentary time in adults with T1D based on studies that used objective and self-report measures, and to examine the factors that influence the PA levels.

Chapter implications: Quantifying the levels of PA and time spend in SBs in individuals with T1D provides a comprehensive understanding of their lifestyle patterns. Thus, the findings bring together existing evidence and identify gaps, which help inform the development of targeted interventions and study design in subsequent chapters.

4.A Systematic Review

4.A.1 Introduction

Physical Activity recommendations for adults with T1D are the same as for those without diabetes, aiming to achieve at least 150 minutes of moderate-intensity PA, 75 minutes of vigorous-intensity PA, or a combination of both per week with no more than two consecutive days without PA (Colberg et al., 2016; National Health Service, 2021). Despite these recommendations, previous studies have

found conflicting results in whether individuals with T1D meet the guidelines and if they are less active than those without diabetes using self-reported measures. For example, one study found that 63% (11,357 of 18,028) of adults with T1D did not meet the general PA guidelines (Bohn et al., 2015), while another study reported that only ~50% (1164 of 2313) of T1D met these guidelines (Soulimane et al., 2022). Overall, difference in findings could be due to differences in the demographics of the sample (age, diabetes duration, and sex) or inconsistencies in how PA was assessed (i.e., self-reported versus objective measures, and use of different cut-off points to define PA intensities and SB).

Current PA and health guidelines now make recommendations to limit the time spent in prolonged sitting due to its adverse effects on health (World Health Organisation, 2020). However, there is little information on how much time individuals with T1D spend sedentary, and whether this differs from those without diabetes. Gathering accurate data on SB is vital to determine prevalence and effectiveness of interventions to reduce time spent in SB (Urda et al., 2017), and to examine the impact this has on glycaemic control in individuals with T1D. Indeed, PA and SB are not mutually exclusive (Biswas et al., 2015), as individuals can achieve the recommended levels of PA while still spending a large proportion of their day in sedentary activities, both of which have independent effects on health (Craft et al., 2012). Thus, measuring individual PA and SBs using objective measures provides a comprehensive picture of individuals overall activity throughout the day, and how this pattern influences important health outcomes like glycaemic control in individuals with T1D.

Previous systematic reviews have reported PA levels and SBs using objective and/or self-reported measures in youths and adolescents with T1D (Liese et al., 2013; MacMillan et al., 2014a; Huerta-Uribe et al., 2023), but these

have not yet been quantified in adults with T1D. Therefore, this systematic review synthesises data from both objective and self-reported measures of PA and sedentary time to provide a comprehensive assessment of PA and SBs in adults with T1D. Furthermore, this systematic review aims to examine the factors that moderate PA and sedentary time in T1D to help inform future intervention studies designed to promote PA and reduce sedentary time.

4.A.2 Methods

The systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (Page et al., 2021), and the review protocol was prospectively registered in the PROSPERO database (registration ID: CRD42021286201).

4.A.2.1 Study Eligibility

The PICOs principles for systematic review were used to inform the design of this review (McKenzie et al., 2019).

- **Population:** adults aged 18 years or older with T1D, free of other diseases or infections.
- **Intervention:** -
- **Comparator(s)/control:** no advice, free-living, standard of care, or lower levels of PA or sedentary time.
- **Outcome**: PA levels and/or SBs.
- **Study designs:** experimental and observational.

All studies included measures of PA and/or SBs using (1) self-reported tools, such as questionnaires or diaries (i.e., a written record of time spent in different activities), or (2) objective measures (device-based), such as accelerometry (e.g., ActiGraph or SenseWear armband) or activity trackers/pedometers (e.g., step

counters). Only peer-reviewed studies in English were included, with no restrictions on year of publication. Terms and phrases related to children, adolescents, animals, or nonhumans were excluded from the search.

4.A.2.2 Search Strategy and Data Sources

Studies were identified through a systematic search of Medline (Ovid), Embase (Ovid), Web of Science, and the Cochrane Library. The search strategy, consisting of a combination of three key concepts (e.g., PA, SB, and T1D) was reviewed by the research team and an experienced subject librarian. Relevant keyword variations, including the controlled vocabularies of the different databases, were used for the three concepts. For example, PA terms (physical activity, sport, fitness, aerobic exercise, accelerometry, actimetry, pedometer, activity tracker); SB terms (sedentary, sitting, stationary, desk sitting, computer time or screen time, watching television, seated, video game); and T1D terms (insulin-dependent-diabetes mellitus, IDDM, type 1 diabetes mellitus, T1DM, type 1 diabetes, or T1D). These keywords were informed by previous reviews in the area (Liese et al., 2013; Biswas et al., 2015; Loh et al., 2020). A combination of Medical Subject Headings (MeSH) and key search terms was used. Reference lists of key studies were searched for eligible studies. The original search was conducted in January 2021. Writing of the systematic review began in June 2022, and a follow-up search was conducted from July 2022 to May 2024 to capture additional relevant studies published during this interim period.

4.A.2.3 Data Extraction

Study titles and abstracts were screened independently by three researchers (AA 100%, MH 50%, MZ 50%) following the review protocol. Full studies were reviewed independently by the researchers, and disagreements were resolved

by discussion. All selected studies were imported into DistillerSR software (Evidence Partners Incorporated; Ottawa, Canada (Hamel et al., 2020)) to obtain the final number of studies and remove duplicates.

Data extraction was performed by one researcher (AA), including information on publication details; participants characteristics (e.g., age, sex, and diabetes duration); study sample size; country of study; study design; movement behaviour (PA and/or SB); activity assessment measures (e.g., self-reported measure and/or objective measure) for PA or SBs; units of measures (e.g., time per week, minutes per day, minutes per week, or steps per day); study outcomes levels of PA and/or SBs; and the moderators that affect the levels of activities individuals might undertake include factors such as age, sex, diabetes duration, and other factors. Studies with unclear data or unavailable full texts were excluded if authors did not provide additional information upon request.

To ensure consistency across studies reporting PA and to enhance clarity and ease of interpretation, PA data were converted from hours (per day or week) to minutes (per day or week).

4.A.2.4 Quality Assessment for Included Studies

Quality assessment for included studies was individually conducted by one researcher (AA) using different tools. For the randomised studies (RCTs and crossover designs), Version 2 of the Cochrane Collaboration's risk of bias tool (ROB 2) was used to assess the risk of bias in individual studies (Sterne et al., 2019). This tool categorises bias into three categories: low risk (low risk of bias for all key domains), some concerns (low risk or some concerns for key domains), and high risk (high risk of bias for one or more key domains) across five domains: randomisation process and timing of identification or recruitment of participants

(for RCTs), or bias arising from period and carryover effects (for crossover designs) (selection bias); deviations from the intended interventions (performance bias); missing outcome data (attrition bias); measurement of the outcome (detection bias); and selection of the reported result (reporting bias) (**Appendix A, Table A.1**) (Higgins et al., 2011). The RoB 2 tool uses an algorithm based on specific probing questions to evaluate risk of bias in individual domains, providing an overall assessment of risk of bias (Higgins et al., 2019).

For non-randomised experimental studies, the Risk of Bias in Non-randomised Studies – of Interventions (ROBINS-I) tool was used to appraise the quality of the included studies (Sterne et al., 2016). This tool categorises risk into five levels (low risk, moderate risk, serious risk, critical risk, and no information) across seven domains (Sterne et al., 2016), which are as follows: pre-intervention (confounding bias and selection of participants into the study bias); at intervention (classification of intervention bias); and post-intervention (deviations from intended interventions bias, missing outcome data bias, and measurement of outcomes bias) (**Appendix A, Table A.2**) (Moore et al., 2023). The ROBINS-I tool uses a set of signalling questions to assess the risk of bias for each domain, helping to determine the level of bias in each individual study (Moore et al., 2023).

The Newcastle-Ottawa Scale (NOS) was used to assess the quality of the observational studies due to its validity and ease of use in assessing methodological quality. It consists of three domains: selection of the study groups, comparability of the groups, and assessment of either the outcome (for cohort and cross-sectional studies) or the exposure (for case-control studies) (**Appendix A, Table A.3**) (Wells et al., 2021). Studies are scored one point for all items except for comparability, which has a potential score of two points, with the maximum possible score being nine for the NOS (for case-control, retrospective,

and prospective cohort studies) (Wells et al., 2021) and ten score for a modified NOS version for cross-sectional studies (Modesti et al., 2016). Studies with NOS scores of 0 – 3, 4 – 6, and 7 – 10 stars were classified as low, moderate, and high quality, respectively (Koshy et al., 2021).

4.A.3 Results

4.A.3.1 Study Selection

A total of 1923 studies were identified through database searches and other sources. After de-duplication, 1700 were assessed for title and abstract screening. Of these, 225 records progressed to full-text screening, of which 130 were excluded for not meeting the inclusion criteria, resulting in 95 records for further analysis. Additionally, after updating the search strategy to ensure the inclusion of recent literature and refine search terms, eight additional studies met the inclusion criteria and were included in the final analysis. The PRISMA flow diagram of studies through the review process is presented in **Figure 4.1**.

4.A.3.2 Study Characteristics of Included Studies

A total of 53 studies were included, all examining adults with T1D free of other diseases or infections. Of these, 52 reported both PA and/or SBs, with five focusing specifically on SBs and three reporting no PA levels (0 PA), while the remaining 44 reported PA. One additional study, making the total 53, reported only sitting time per day. Among the 53 studies, seven studies measured PA levels objectively using different devices (e.g., accelerometry or pedometers/ activity trackers), 44 studies measured PA and/or SBs subjectively using self-reported measures (e.g., questionnaires or activity logs/diaries), and two studies measured PA using both objective and self-reported measures. The included studies were published between 1992 to 2024. The total number of adults with

T1D in the included studies was 96,568, with data on PA/SB obtained from 63,600 respondents, ages ranging from 18 to 57 years, and diabetes duration ranging from recently diagnosed to 62 years. The characteristics of the included studies measuring PA and SBs using both measures are presented in **Tables 4.1** and **4.2**.

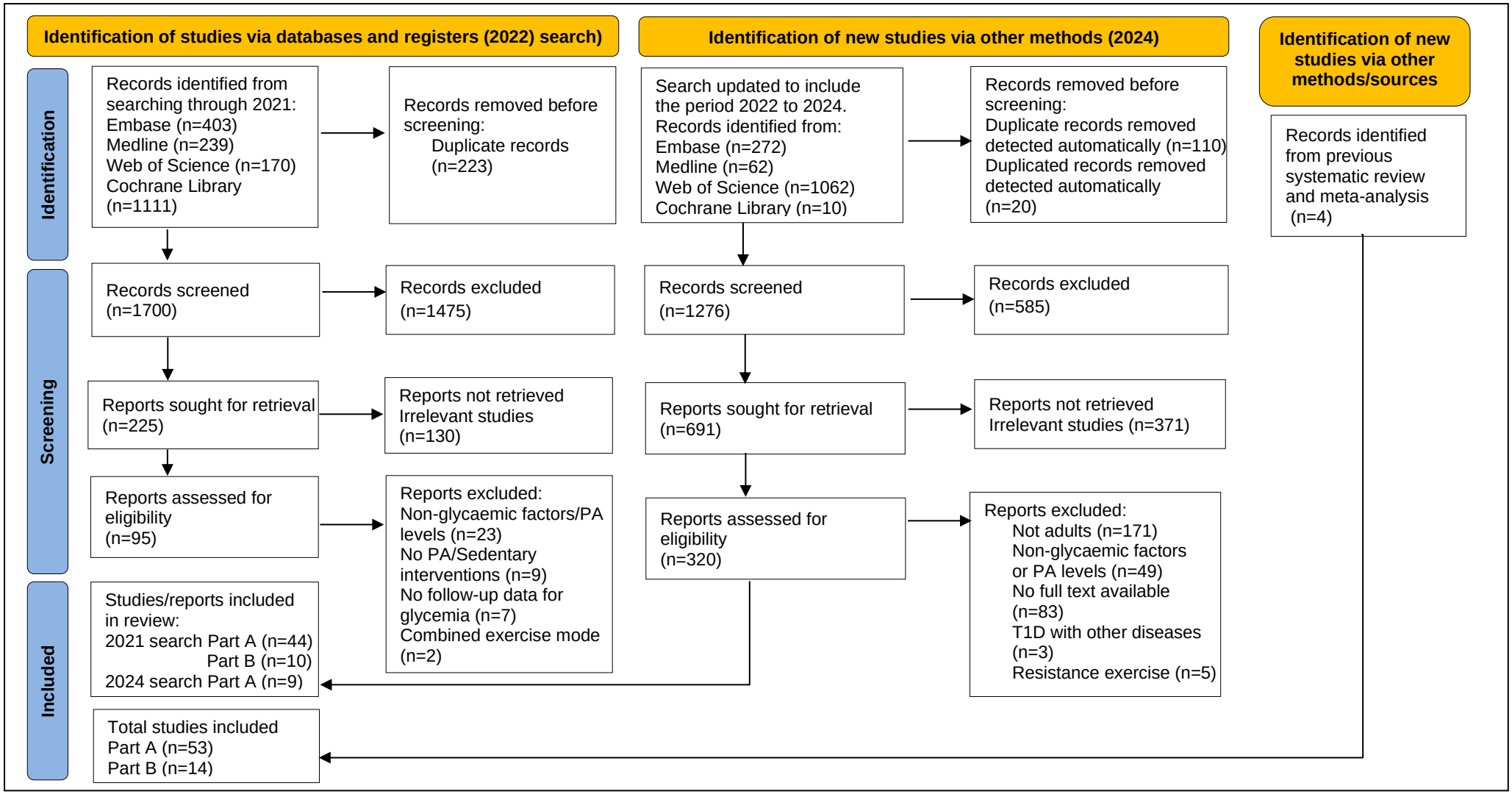


Figure 4.1 Flow Diagram of Study Selection

4.A.3.3 Quantifying Physical Activity and Sedentary Behaviours

4.A.3.3.1 Studies using Objective Measures of Physical Activity and Sedentary Behaviour

Table 4.1 presents the studies that reported the amount of PA performed and time spent in SB among adults with T1D using objective measures. These studies used various wearable devices, including activity trackers/pedometers, accelerometers, multi-sensors, and motion meters, over durations ranging from seven days to four weeks. Of the studies included in this review, four studies measured step counts, three studies measured total PA and SBs in minutes per week or minutes per day, and two studies measured total PA using other metrics.

4.A.3.3.1.1 Step-based Counts of Physical Activity (Steps per day)

Four studies reported steps as their measure of PA (Brazeau et al., 2012b; Brazeau et al., 2014; Assaloni et al., 2020; Turner et al., 2024). A study by Turner and colleagues (Turner et al., 2024) reported that in 464 who wore a wrist-worn activity tracker (Verily Study Watch) for four weeks, 36.21% (n = 168) performed less than 7000 steps, 33.84% (n = 157) performed between 7000 to 10,000 steps, and 29.96% (n = 139) performed more than 10,000 steps. During the pre-COVID-19 quarantine period, data from 100 participants indicated mean steps counts per day of 12,606 ± 5026 steps, but this decreased significantly to 4760 ± 3145 steps during the COVID-19 quarantine period ($p < 0.001$) (Assaloni et al., 2020). In this study the activity tracker was unspecified, and only a three-day pre-quarantine period (February 11,12, and 15, 2020) and a five-day quarantine period (March 17 to 21, 2020) were assessed (Assaloni et al., 2020). Brazeau and colleagues (Brazeau et al., 2014) reported that 23 individuals averaged 9971 [95% CI 8556 – 11,386] steps per day at baseline (SenseWear armband), which subsequently

increased to 10,641 [95% CI 9080 – 12,201] steps per day (n = 22) following a three month PA intervention. However, this declined to 9124 (95% CI 7725 – 10,524) steps per day at the 12 months follow-up period (n = 22) (Brazeau et al., 2014). Brazeau and colleagues (Brazeau et al., 2012b) reported that participants leading an active lifestyle (PA levels ≥ 1.7) recorded a higher step counts, with men (n = 22) averaging 11,866 (SD 3541) steps per day and women (n = 15) averaging 11,683 (SD 2931) steps per day compared to those with a sedentary lifestyle (PA levels < 1.7), with men (n = 18) averaging 7856 (SD 1864) steps per day and women (n = 20) averaging 7559 (SD 2087) steps per day, as measured using a motion sensor (SenseWear Pro three armband) for seven days.

Individuals with T1D were varied in their activity levels, with some engaging in low daily steps (e.g., during quarantine and in the sedentary lifestyle group), while others maintained moderate to high activity levels, particularly those exceeding 10,000 steps per day. Overall, a high proportion of adults with T1D appear to fail to meet the recommended target of 10,000 steps per day, with approximately 72.46% (n = 463) failing to meet this target.

4.A.3.3.1.2 Studies Quantifying Physical Activity and Time Spent in Different Activity Domains using Accelerometry

Three studies using ActiGraph devices reported total PA levels in minutes per day or minutes per week (Tagougui et al., 2015; Keshawarz et al., 2018; Matson et al., 2018). Keshawarz and colleagues (Keshawarz et al., 2018), used an ActiGraph (wGT3X-BT) that was worn on the hip to assess the PA levels, with the time spent in MVPA per week averaging 209 ± 180 minutes in 44 participants over a 14-day period. An ActiGraph (GT1M) was also used to measure the mean daily total PA over seven consecutive days in two groups of participants with T1D – those with adequate glycaemic control (T1D-A: HbA1c < 7.0%) and those with

inadequate glycaemic control (T1D-I: HbA1c > 8.0%). Mean daily PA levels in the T1D-A group (n = 8) was 72.9 ± 23.1 minutes, while in the T1D-I group (n = 10) it was 76.5 ± 19.6 minutes (Tagougui et al., 2015). Furthermore, mean daily PA levels in 50 participants, measured over seven days using ActiGraph devices (GT1M or GT3X), averaged 37.4 (SD 9.1) minutes of MVPA (Matson et al., 2018).

All 112 adults with T1D across the three studies, on average, met the recommended PA guidelines of at least 150 minutes per week.

4.A.3.3.1.3 Studies Reported Physical Activity and Sedentary Behaviours using Alternative Measurement Devices

Two studies using different metrics to measure total PA levels and SB (Chantelau and Wirth, 1992; Valletta et al., 2014). Valletta and colleagues (Valletta et al., 2014) included 23 participants who wore a multi-sensory PA armband (SenseWear Pro2/3 armband) for at least 12 days found that 69.8 ± 9.3% of their total daily time spent in SB (< 2 METs), while 17.5 ± 6.3% of their time spent in low-intensity PA (2 – 3 METs), 11.8 ± 4.9% in moderate-intensity PA (3 – 6 METs) and 0.2 ± 1.4% in vigorous-intensity PA (> 6 METs). Additionally, Chantelau and colleagues (Chantelau and Wirth, 1992) measured habitual PA for 34 participants using a portable motion meter (Kenz calorie counter) for seven consecutive days. The findings revealed that T1D individuals on MDIs (n = 14) engaged in an average of 42.4 ± 12.0 activity arbitrary units (AUU) per week, while those on CSII (n = 20) engaged in an average of 36.4 ± 11.1 AUU per week.

Findings from one study indicate that 23 adults with T1D spend a significant amount of their total daily time in SB (69.8%) with limited time in PA across all intensities. Another study used AAU measurement to show that both T1D groups engaged in habitual PA, as indicated by the AAU values.

Table 4.1 Characteristics of Included Studies on Physical Activity and Sedentary Behaviours in Adults with Type 1 Diabetes using Objective Measures

Author, Year	Study Design	Country & participants characteristics	Type of self-reported measures	Amount of physical activity & Sedentary time
(Assaloni et al., 2020)	Observational (Cross-sectional study)	Italy; (n = 154) Age (44.8 ± 12.5 years).	Activity tracker (three days pre-quarantine (February 2020) and five days during quarantine (March 2020). (Model not stated).	Daily step counts (n = 100) Pre-COVID-19 quarantine 12,606 ± 5026 steps. During COVID-19 quarantine 4760 ± 3145 steps.
(Brazeau et al., 2012b)	Observational (Cross-sectional study)	Canada; (n = 75) Age (41.8 ± 11.8 years); T1D duration (23.4 ± 12.0 years).	Motion sensor worn on the arm for seven days. (Model: SenseWear Pro 3 Armband, Body media, Pittsburgh, US).	Daily step counts Active lifestyle (PA levels ≥ 1.7) Men data (n = 22) 11,866 (SD 3541) steps. Women data (n = 15) 11,683 (SD 2931) steps. Sedentary lifestyle (PA levels < 1.7) Men data (n = 18) 7856 (SD 1864) steps. Women data (n = 20) 7559 (SD 2087) steps.
(Brazeau et al., 2014)	Experimental (RCT)	Canada; (n = 23) Age 45.1 (SD 14.5) years; T1D duration 20.3 (SD 12.9) years.	Motion sensor worn over seven days. (Model: SenseWear armband; Body media, Pittsburgh, US).	Daily step counts Means [95% CI] Inclusion (n = 23) 9971 [8556 – 11,386] steps. 3 months [post-PA] (n = 22) 10,641 [9080 – 12,201] steps. 12 months [follow-up] (n = 22) 9124 [7725 – 10,524] steps.

(Chantelau and Wirth, 1992)	Observational (Case-control study)	Germany; (n = 34) MDI group (n = 14) Age (28 ± 5 years). CSII group (n = 20) Age (32 ± 11 years).	Portable motion meters worn at the waist for seven consecutive days. (Model: Kenz Calorie Counter, Suzuken, Japan).	Total PA levels MDIs group (n = 14) 42.4 ± 12.0 AAU/week. CSII group (n = 20) 36.4 ± 11.1 AAU/week.
(Keshawarz et al., 2018)	Observational (Prospective cohort study)	US; (n = 44) Age (49 ± 9 years); T1D duration (36 ± 8 years).	ActiGraph on the hip over 14 days. (Model: wGT3X-BT triaxial accelerometer).	Total PA levels (n = 44) MVPA: 209 ± 180 minutes/week. Threshold of PA levels Average weekly MVPA time, including non-bout periods and bouts; weekly MVPA bouts.
(Matson et al., 2018)	Observational (Cross-sectional study)	UK; (n = 50) Age 33 (SD 10) years; T1D duration 62 (SD 23) years.	Actigraph worn on the waist during waking hours for seven days. (Model: GT1M or GT3X).	Total PA levels (n = 50) 37.4 (SD 9.1) minutes/day.
(Tagougui et al., 2015)	Observational (Cross-sectional study)	France; (n = 18) T1D-A (n = 8) Age (30.1 ± 6.8 years); T1D duration (4.3 ± 3.5 years). T1D-I (n = 10) Age (26.1 ± 7.8 years); T1D duration (10.7 ± 3.7 years).	ActiGraph worn for seven consecutive days. (Model: GT1M).	Total PA levels T1D-A (n = 8): 72.9 ± 23.1 minutes.day^{-1}. T1D-I (n = 10): 76.5 ± 19.6 minutes.day^{-1}.

(Turner et al., 2024)	Observational (Prospective cohort study)	Canada; (n = 464) Age (37 ± 14 years); T1D duration (18 ± 13 years).	Activity tracker on the wrist for four weeks. (Model: Verily Study Watch, US).	Daily step counts (n = 464) < 7000 steps: 168 participants (36.21%). 7000 – 10,000 steps: 157 participants (33.84%). > 10,000 steps: 139 participants (29.96%).
(Valletta et al., 2014)	Experimental (Cross-sectional study)	UK; (n = 23) Age (37 ± 11 years); T1D duration (17 ± 11 years).	Multi-sensory PA armband worn for at least 12 days. (Model: SenseWear Pro2/3 armband, Body media, Pittsburgh, US).	Total activity levels (n = 23) Sedentary: 69.8 ± 9.3% Low: 17.5 ± 6.3% Moderate: 11.8 ± 4.9% Vigorous: 0.2 ± 1.4% Threshold of PA levels Sedentary < 2 METs; low (2 – 3 METs); Moderate (3 – 6 METs); vigorous (> 6 METs).

T1D-A: type 1 diabetes individuals with adequate glycaemic control; **T1D-I:** type 1 diabetes individuals with inadequate glycaemic control; **MDIs:** multiple daily injections; **CSII:** continuous subcutaneous insulin infusion; **AAU:** arbitrary activity units; **SD:** standard deviation; **CI:** confidence Interval.

4.A.3.3.2 Studies using Self-reported Measures of Physical Activity and Sedentary Behaviour

Table 4.2 presents the studies that reported the levels of PA and SBs among adults with T1D using the self-reported measures. A total of 46 studies included in this review measured levels of PA and/or SBs using self-reported measures such as questionnaires or activity logs. Among the studies analysed, the IPAQ questionnaire emerged as the most frequently employed assessment measure, with 14 studies using the IPAQ-SF and two studies using the IPAQ-LF. Additionally, activities during leisure-time were assessed in 13 studies using different self-reported measures. Furthermore, PA and SBs were measured using researcher-developed questionnaires, activity logs as well as unspecified self-reported measures in 17 studies.

4.A.3.3.2.1 Self-reported Measures of Total Physical Activity Levels

4.A.3.3.2.1.1 Total Physical Activity Assessed by the International Physical Activity Questionnaire (MET-minutes per week)

The total PA score was computed as the sum of walking, moderate, and vigorous MET-minutes per week scores (International Physical activity questionnaire, 2005). Eight studies reported that the total PA score from the IPAQ-SF varied markedly between studies and one study from the IPAQ-LF (Moser et al., 2017; Duda-Sobczak et al., 2018; Nystrom et al., 2022; Tan et al., 2022; Brugnara et al., 2023; Çelik et al., 2023; Turčinović et al., 2023; Kowal et al., 2024; Murillo et al., 2024). Murillo and colleagues (Murillo et al., 2024) involved 232 participants and reported an average of 2202 ± 1839 MET-minutes per week, while two studies found that 25 men had an average of 1668.50 ± 1228.45 MET-minutes per week and 18 women had an average of 1181.94 ± 1056.66 MET-minutes per

week (Kowal et al., 2024), and 32 participant reported an average of 1610.1 ± 1907.9 MET-minutes per week (Tan et al., 2022). However, a study by Celik and colleagues (Çelik et al., 2023) recorded weekly median levels of PA of 1194 [IQR 466, 1194] MET-minutes in 44 participants. According to the IPAQ classification, these adults with T1D were classified as moderately active (600 – 3000 MET-minutes per week) (International Physical activity questionnaire, 2005).

While a study by Duda-Sobczak and colleagues (Duda-Sobczak et al., 2018) recorded weekly levels of PA of 1782 [IQR 975, 4290] MET-minutes in 119 participants, and another study by Brugnara and colleagues (Brugnara et al., 2023) recorded 2772 [IQR 1485, 4679] MET-minutes in 135 participants, these adults with T1D were classified as failing within the 'moderately active' range (600 – 3000 MET-minutes per week) and 'physically active' range (> 3000 MET-minutes per week) (International Physical activity questionnaire, 2005). Interestingly, in three studies, it was consistently found that in total 269 adults with T1D were classified as physically active, exceeding 3000 MET-minutes per week (International Physical activity questionnaire, 2005), with an average of 3086 ± 2736 MET-minutes per week (n = 64) (Moser et al., 2017), 3628 (SD 4524) MET-minutes per week for those using CGM then SMBG (n = 61) and 3158 (SD 3389) MET-minutes per week for those using SMBG then CGM (n = 73) (Nystrom et al., 2022). A study by Turčinović and colleagues (Turčinović et al., 2023) using the IPAQ-LF with 71 adults with T1D found that average weekly PA was 5746.8 ± 3634.3 MET-minutes per week.

The mean total PA score across the nine studies was 2657.52 ± 1294.34 MET-minutes per week, classifying most participants as moderately active based on the IPAQ thresholds. Specifically, 351 adults with T1D were moderately active, 254 were moderately to physically active, and 269 were active.

4.A.3.3.2.1.2 Total Physical Activity Levels Assessed using Alternative Self-reported Questionnaires (minutes per week or minutes per day)

Seven studies reported weekly PA levels in minutes using different self-reported measures (Lehmann et al., 1997; Rooijackers et al., 2017; Adelborg et al., 2020; Lee et al., 2020b; Notkin et al., 2021; Jabbour et al., 2022; Soulimane et al., 2022), and one study reported daily PA levels in minutes (Reddy et al., 2019). Jabbour and colleagues (Jabbour et al., 2022) reported that among 102 participants, the average weekly time spent in low-intensity PA was 46.1 ± 3.1 minutes, MVPA 50.5 ± 10.3 minutes, and vigorous-intensity PA 30.5 ± 5.3 minutes using the IPAQ-SF. Similarly, Soulimane and colleagues (Soulimane et al., 2022) involved 2313 participants and reported an average of 330 ± 624 minutes per week of moderate-intensity PA and average of 138 ± 402 minutes per week of vigorous-intensity PA, with the threshold for moderate activities defined as one to two times per week and for vigorous activities as one or three times per month, which were then converted to minutes per week for both activities. Among 12 participants, the average weekly moderate-intensity PA was 29 ± 36 minutes (Lee et al., 2020b). Additionally, 20 participants in a study that examined the total weekly PA in two groups of T1D (group A with normal awareness of hypoglycaemia (n = 10) and group B with impaired awareness of hypoglycaemia (n = 10)) revealed averages of 250 ± 174 minutes for group A and 294 ± 222 minutes for group B (Rooijackers et al., 2017).

Of these eight studies, three studies recorded weekly PA levels in minutes using logbooks or diaries (Lehmann et al., 1997; Adelborg et al., 2020; Notkin et al., 2021). Lehmann and colleagues (Lehmann et al., 1997) recorded MVPA (50 – 70% of the VO_{2max}) for ten participants at two different time points at baseline

195 ± 176 minutes per week and after three months 356 ± 164 minutes per week, while Notkin and colleagues (Notkin et al., 2021) included 12 participants and reported moderate-intensity PA at a single time point, averaging 167.0 ± 82.5 minutes per week. Likewise, Adelborg and colleagues (Adelborg et al., 2020) reported weekly PA at a single time point in 3284 participants with a median of 210 [IQR 96, 420] minutes. Whereas Reddy and colleagues (Reddy et al., 2019) reported the total daily PA levels of ten participants and found that an average of 66 ± 42 minutes per day of moderate-intensity PA.

Across the eight studies, three involving 2345 adults with T1D met or exceeded the recommended weekly PA guidelines, with moderate-intensity PA ranging from 167 to 330 minutes, MVPA ranging from 195 to 356 minutes, and vigorous-intensity PA averaging of 138 ± 402 minutes. Additionally, one study reported daily moderate activity of 66 ± 42 minutes, which met or exceeded the guidelines. While two studies with 114 individuals fell below the recommendations of moderate activity, ranging from 29 to 50 minutes per week. However, in two studies the intensity of PA was not reported, making it unclear whether the individuals met the guidelines.

4.A.3.3.2.1.3 Quantifying Leisure Time Activities

Eight studies specifically reported leisure-time activities using a variety of self-reported tools (Tikkanen-Dolenc et al., 2017; Keshawarz et al., 2018; Sadarangani et al., 2019; Stotl et al., 2019; Yardley et al., 2019; Assaloni et al., 2020; Golka et al., 2021; Richardson et al., 2023). Of these, two studies used the Godin Leisure-Time Exercise Questionnaire to evaluate the frequency of strenuous, moderate, and mild exercise activities during a typical seven days of leisure-time (Yardley et al., 2019; Assaloni et al., 2020). The questionnaire categorised respondents as either insufficiently active (≤ 23 score) or active (≥ 24

score) (Amireault and Godin, 2015). Assaloni and colleagues (Assaloni et al., 2020) involving 154 participants found that the average total leisure-time activity score decreased from 38.6 ± 1.7 points pre-COVID-19 quarantine to an average of 25.0 ± 1.7 points during the COVID-19 quarantine. Furthermore, with 12 participants, the average total leisure-time activity score was 48.2 ± 41.5 points (Yardley et al., 2019). These studies suggest that adults with T1D were classified as active, although one showed a decline in activity levels during the COVID-19 period compared to the pre-COVID-19 period.

Five studies examined the total weekly time spent in PA, with some assessed during leisure and occupation, while others focused on leisure and transportation or travel or work, or leisure and household activities using different questionnaires. Of these, two studies used the Global Physical Activity Questionnaire to assess the frequency and duration of PA across three different domains: leisure-time, occupational, and travel. A study of 101 participants measured total leisure-time activity, using a threshold of greater than 4 METs (as MVPA), with participants averaging 180.7 (SD 390.0) minutes per week (Sadarangani et al., 2019). A study by Stotl and colleagues (Stotl et al., 2019) involving 109 participants found that the average total weekly moderate-intensity PA (i.e., sum of moderate activities in the three domains (e.g., at work, during travel and leisure activities)) was 688.20 (SD 711.13) minutes, while the average total weekly vigorous-intensity PA (i.e., sum of vigorous activities at work and leisure activities) was 418.16 (SD 649.45) minutes. Furthermore, two studies used a PA questionnaire developed, it assesses historical, past year, and past-week leisure and occupational PA related to T1D population (Keshawarz et al., 2018; Richardson et al., 2023). A study of 44 participants reported an average weekly duration of moderate to vigorous leisure time activity of 274 ± 188 minutes

(Keshawarz et al., 2018). Furthermore, a study of 563 participants reported median weekly moderate-intensity PA 180 [IQR 90, 300] minutes (64 – 76% maximum heart rate (HR_{max}) threshold) and median vigorous-intensity PA at 150 [IQR 60, 305] minutes (77 – 93% HR_{max} threshold) in leisure and occupational activities (Richardson et al., 2023). The median weekly MVPA was 333 [IQR 125, 630] minutes in 563 participants, calculated by multiplying in vigorous-intensity PA by two, and no change in moderate-intensity PA (Richardson et al., 2023). Additionally, a study by Golka and colleagues (Golka et al., 2021) included 117 participants and provided data on PA for 35 participants, revealing an average of 180 ± 180 minutes per week spent in traveling on foot or bike during leisure and at work using a researcher-developed questionnaire. While a study by Tikkanen and colleagues (Tikkanen-Dolenc et al., 2017) reported that the median total score for leisure-time activities was 1032 [IQR 402, 2028] MET-minutes per week among 2099 participants, which were classified as moderately active (600 – 2400 MET-minutes per week).

Leisure time activities across eight studies varied, with weekly averages ranging from 180.0 to 688.2 minute of moderate-intensity PA (n = 707), 150.00 to 418.16 minutes of vigorous-intensity PA (n = 672), and 180.7 to 333.0 minutes of MVPA (n = 708). The findings indicate that adults with T1D met or exceeded the PA guidelines.

4.A.3.3.2.2 Proportion of Participants Classified as Active or Inactive

4.A.3.3.2.2.1 Classification Based on Physical Activity Levels using International Physical Activity Questionnaire

Five studies have reported the proportion of individuals participating in different categories of PA intensity: low-intensity PA (3.3 METs), moderate-intensity PA (4

METs), and vigorous-intensity PA (8 METs) (four studies using the IPAQ-SF, and one using the IPAQ-LF) (Zielińska et al., 2018; Koca et al., 2019; Riddell et al., 2021; De Ridder et al., 2022; Zaccaria et al., 2023), which assesses PA over the past seven days (International Physical activity questionnaire, 2005). A study by De Ridder and colleagues (De Ridder et al., 2022) involving 21 participants showed that 9.52% (n = 2) were engaged in low-intensity PA, 52.38% (n = 11) were involved in moderate-intensity PA, and 38.10% (n = 8) in vigorous-intensity PA. Similarly, a study involved 150 participants, showing that 31.33% (n = 47) were engaged in low-intensity PA, 36.00% (n = 54) in moderate-intensity PA, and 32.67% (n = 49) in vigorous-intensity PA (Koca et al., 2019). Furthermore, a study used a validated IPAQ-LF to measure PA, assessing a wide range of activities including leisure-time, domestic and gardening activities, work-related and transport-related activities (Craig et al., 2003). The IPAQ-LF findings in 90 participants showed that 21.11% (n = 19) participated in low-intensity PA, while 41.11% (n = 37) were involved in moderate-intensity PA, and 37.78% (n = 34) in vigorous-intensity PA (Zaccaria et al., 2023). Across the three studies, the majority of adults with T1D were engaged in moderate-intensity PA, followed by vigorous-intensity PA, with the fewest participants reporting low-intensity PA.

Riddell and colleagues (Riddell et al., 2021) reported that among 39 participants, 10.26% (n = 4) engaged in low-intensity PA, 33.33% (n = 13) in moderate-intensity PA, and 56.41% (n = 22) in vigorous-intensity PA. A study included 209 participants found that 7.18% (n = 15) engaged in low-intensity PA, 22.97% (n = 48) in moderate-intensity PA, and 69.86% (n = 146) in vigorous-intensity PA (Zielińska et al., 2018). The two studies indicated that the majority of participants participated in vigorous-intensity activities, followed by moderate-intensity activities and then low-intensity activities.

Findings from five studies suggest that a high proportion of adults with T1D were involved in vigorous-intensity PA (50.88%; n = 259), followed by moderate-intensity PA (32.02%; n = 163), and then low-intensity PA (17.09%; n = 87) using the IPAQ measure.

4.A.3.3.2.2.2 Physical Activity Levels Measured using Alternative Self-reported Tools

Ten studies reported the proportion of participants engaged in different PA levels (Melin et al., 2013; Martínez-Ramonde et al., 2014; Melin et al., 2014; Farabi et al., 2015; Jayawardene et al., 2017; Van Mark et al., 2019; Lee et al., 2020a; Ajčević et al., 2021; Melin et al., 2021; Flotynska et al., 2022). Melin and colleagues (Melin et al., 2021) investigated at least 30 minutes of moderate-intensity PA in 292 participants, of whom 275 reported that 11.27% (n = 31) were inactive (< 1 time per week), 21.45% (n = 59) were moderately inactive (1 – 2 times per week), 31.27% (n = 86) were moderately active (3 – 5 times per week), and 36.00% (n = 99) were active (daily). Martínez-Ramonde and colleagues (Martínez-Ramonde et al., 2014) found that out of 19 participants, 8 (42.11%) participated in regular PA, defined as five or more hours per week, both before and after being diagnosed with diabetes, as measured through self-reported data on exercise type, duration, frequency, and intensity, documented in clinical records. Similarly, a study involved 99 participants and examined PA frequency and type before and after diabetes diagnosis, revealing that 48.48% (n = 48) were less active (< 2.5 times per week), while 51.52% (n = 51) were more active (≥ 2.5 times per week) (Flotynska et al., 2022). A study by Farabi and colleagues (Farabi et al., 2015) included 12 participants who were assessed for moderate and

vigorous activity and the number of days per week they engaged in activities for at least 60 minutes. The findings revealed that 80.00% (n = 8) participants reported engaging in moderate-intensity PA, 20.00% (n = 2) in vigorous-intensity PA, with an average of 4.70 ± 1.42 days per week dedicated to engage for at least 60 minutes (Farabi et al., 2015). Ajcevic and colleagues (Ajčević et al., 2021) reported that the 26 participants were categorised based on their self-reported PA habits into two groups: active, which included 19 participants (73.08%) who exercised regularly for at least 30 minutes on three or more days per week, and those who exercised only occasionally, consisting of seven participants (26.92%). This indicates that the proportion of active adults with T1D was significantly higher than that of inactive adults who exercised occasionally.

Of the ten studies that reported the proportion of adults with T1D engaging in PA, two studies involving 12 participants each, the number of participants engaged in daily PA was reported. Jayawardene and colleagues (Jayawardene et al., 2017) reported that 58.33% (n = 7) were engaged in less than 30 minutes PA and 41.67% (n = 5) were engaged in 30 to 60 minutes PA. Similarly, Lee and colleagues (Lee et al., 2020a) recorded that 25.00% (n = 3) participated in less than 30 minutes PA, 58.33% (n = 7) in 30 to 60 minutes PA, and 16.67% (n = 2) in more than 60 minutes PA. According to the findings from two studies, most adults with T1D performed PA for 30 to 60 minutes a day.

Furthermore, three studies, findings revealed that varying rates of physical inactivity, defined as engaging in less than 30 minutes of moderate-intensity PA once a week. Van Mark and colleagues (Van Mark et al., 2019) reported that out of 56,250 participants, 23,310 (41.43%) were physically inactive; Melin and colleagues (Melin et al., 2014) found that 19 out of 196 participants (9.69%) were inactive; and Melin and colleagues (Melin et al., 2013) observed that 36 out of

292 participants (12.33%) were physically inactive.

Out of the 57,191 adults with T1D in the included studies that measuring PA levels using different self-reported measures, only 23,807 individuals had their PA levels reported. There were grouped into three categories inactive, moderately active, and active to make the data easier to understand and to help draw clear conclusions about their PA levels.

- Inactive (< 1 time per week of at least 30 minutes of PA; exercise occasionally): 23,403 (98.30%) individuals.
- Moderately active (1 – 5 times per week): 266 (1.12%) individuals.
- Active (≥ 4 hour per week, daily, or at least 60 minutes per week): 138 (0.58%) individuals.

4.A.3.3.2.2.3 The Proportion of Participants Engaged in Leisure-time Activities

Five studies reported the proportion of participants engaged in leisure-time activities (Waden et al., 2007; Bohn et al., 2015; McCarthy et al., 2016; Cigrovski Berkovic et al., 2017; Tikkanen-Dolenc et al., 2020). Of these three studies categorised the total amount of leisure-time activities, expressed as MET-minutes per week (Wadén et al., 2005; Tikkanen-Dolenc et al., 2020), consistently classifying participants as physically inactive (< 600 MET-minutes per week), moderately active (600 – 2400 MET-minutes per week), and physically active (> 2400 MET-minutes per week) (Tikkanen-Dolenc et al., 2020). A study involved 1612 participants, with 29.90% (n = 482) participants were classified as physically inactive, 51.67% (n = 833) as moderately active, and 18.42% (n = 297) physically active (Tikkanen-Dolenc et al., 2020). Additionally, 1028 participants participated in leisure-time activities, with 24.71% (n = 254) classified as physically inactive,

57.20% (n = 588) as moderately active, and 18.09% (n = 186) as active (Waden et al., 2007). A study included 55 participants, found that 63.64% (n = 35) were physically inactive, while 36.36% (n = 20) engaged in MVPA at least three times per week between 600 – 2400 MET-minutes (Cigrovski Berkovic et al., 2017).

However, McCarthy and colleagues (McCarthy et al., 2016) out of 7135 participants, 54.91% (n = 3928) engaging in 30 minutes of PA (1 – 4 days per week) and 33.23% (n = 2377) engaging in PA (≥ 5 days per week), based on a researcher-developed question including various PA, often during leisure time. Additionally, Bohn and colleagues (Bohn et al., 2015) reported that out of 18,028 participants, 19.19% (n = 3459) engaged in at least 45 minutes of PA (1 – 2 times per week), and 17.81% (n = 3212) engaged in PA (> 2 times per week), based on researcher-developed question designed to assess recreational activities.

Of the five studies, three revealed that a significant proportion of adults with T1D were moderately active (52.71%, n = 1421), while 28.61% (n = 771) were inactive, 17.92% (n = 483) were active, and 0.74% (n = 20) participated in MVPA. Additionally, findings from the two remaining studies varied, with an average of 29.34% (n = 7387) of participants being moderately active (1 – 4 days per week or 1 – 2 times per week) and 22.20% (n = 5589) being active (> 4 times per week or > 2 times per week). A total of 48.47% (n = 12,205) of participants were classified as sedentary (not engaged in any PA), with detailed reported in next **section 4.A.3.3.2.3**.

4.A.3.3.2.3 Quantifying Sedentary Behaviours in Individuals with Type 1 Diabetes

Five studies included reported SB using various self-reported measures, four studies reported daily time spent in SBs (Honda et al., 2020; Golka et al., 2021;

Jabbour et al., 2022; Brugnara et al., 2023), and one study recorded weekly time (Turčinović et al., 2023). Additionally, three studies used the IPAQ self-reported measures to report the daily time spent in SBs; Jabbour and colleagues (Jabbour et al., 2022) indicated that an average screen time (e.g., TV, video games, computer) of 408.0 ± 159.60 minutes per day (n = 102), while s study by Honda and colleagues (Honda et al., 2020) documented a median of 360 [IQR 276, 480] minutes per day (n = 360) and Brugnara and colleagues (Brugnara et al., 2023) reported a median of 300 [IQR 180, 420] minutes per day (n = 135).

Golka and colleagues (Golka et al., 2021) provided details of daily SB in 27 adults with T1D during the weekday and weekend separately, including daily time spent in each SBs as computer use, watching TV, reading, using the car, and other SBs. For the weekday, participants spent an average of 48 ± 36 minutes on computer use, 108 ± 60 minutes watching TV, 30 ± 36 minutes reading, 18 ± 30 minutes sitting in the car, and 18 ± 42 minutes on other SBs, while during the weekend, the average daily time spent on these activities increased to 78 ± 84 minutes for computer use, 144 ± 108 minutes for watching TV, 60 ± 54 minutes for reading, 24 ± 42 minutes in the car, and 24 ± 90 minutes for other SBs (Golka et al., 2021). While Turčinović and colleagues (Turčinović et al., 2023) reported an average weekly sitting time of 270.00 ± 153.96 minutes per week in 71 participants. Additionally, across three studies, a significant proportion of adults with T1D did not engage in any PA, with 62.99% (11,357 of 18,028) (Bohn et al., 2015), 11.86% (848 of 7153) (McCarthy et al., 2016), and 57.89% (11 of 19) (Martínez-Ramonde et al., 2014).

There was limited research examining SBs, with only eight studies reporting time spent in these activities. Across four studies that measured daily SB, participants spent an average of ~351 minutes per day (~6 hours) in sedentary activities, with a total of 597 participants using self-reported tools. While in the study reporting weekly SBs, participants spent an average of 270 minutes, equivalent to ~38 minutes per day among 71 participants. Three studies showed that a significant proportion of adults with T1D did not participate in any activity 48.48% (12,216 of 25,200) individuals.

Table 4.2 Characteristics of Included Studies on Physical Activity and Sedentary Behaviours in Adults with Type 1 Diabetes using Self-reported Measures

Author, Year	Study Design	Country & participants characteristics	Type of measures	Amont of PA and/or SB
(Ajčević et al., 2021)	Experimental (Randomised crossover design)	Italy; (n = 26) Age (42.3 ± 13.3 years); T1D duration (17.2 ± 13.7 years).	Self-reported (Researcher developed questionnaire).	PA levels (n = 26) Inactive: 7 participants (26.92%). Active: 19 participants (73.08%). Threshold of PA levels Inactive: exercised occasionally; Active: ≥ 30 minutes (3 days/week).
(Adelborg et al., 2020)	Observational (Prospective cohort study)	Denmark; (n = 3691) Age 42 [IQR 27, 55] years; T1D duration 11 [IQR 3, 24] years.	Self-reported (Reported weekly PA in diary).	Total PA levels (n = 3284) 210 [IQR 96, 420] minutes/week.
(Assaloni et al., 2020)	Observational (Cross-sectional study)	Italy; (n = 154) Age (44.8 ± 12.5 years).	Self-reported (Godin LTPA).	Total PA score (n = 154) Pre-COVID-19 quarantine 25.0 ± 1.7 points. During COVID-19 quarantine 38.6 ± 1.7 points. Threshold of Godin LTPA Active (score > 23 units).

(Bohn et al., 2015)	Observational (Cross-sectional study)	Germany and Austria; (n = 18,028) Age 33.86 [IQR 20.18, 52.09] years; T1D duration 11.85 [IQR 5.90, 21.13] years.	Self-reported (Researcher developed questionnaire). Question "How often and how long is your weekly recreationally?	Total PA levels (n = 18,028) PA 0: 11,357 participants (63.00%). PA 1: 3459 participants (19.19%). PA 2: 3212 participants (17.82%). Threshold of PA levels At least 45 minutes; PA 0: (no PA); PA 1: (1 or 2 time/week); PA 2: (≥ 2 times/week).
(Brugnara et al., 2023)	Observational (Cross-sectional study)	Spain; (n = 135) Age 40 [IQR 25, 52] years; T1D duration 20 [IQR 10, 30] years.	Self-reported (IPAQ-SF).	Total PA levels (n = 135) 2772 [IQR 1485, 4679] MET-minutes/ week. Daily sedentary time (n = 135) 300 [IQR 180, 420] minutes.
(Çelik et al., 2023)	Observational (Cross-sectional study)	Turkey; (n = 44) Age (27.50 ± 7.12 years)	Self-reported (IPAQ-SF).	Total PA levels (n = 44) 1194 [IQR 446, 1194] MET-minutes/week.
(Cigrovski Berkovic et al., 2017)	Observational (Cross-sectional study)	Croatia; (n = 55) Age 37 [IQR 26, 44] years; T1D duration 11 [IQR 5, 19] years.	Self-reported (LTPA).	Total PA levels (n = 55) Inactive: 35 participants (63.64%). MVPA: 20 participants (36.36%).
(De Ridder et al., 2022)	Observational (Prospective multicentre pilot study)	Belgium, France, Italy; (n = 21) Age 29.0 [IQR 27.5, 37.5] years; T1D	Self-reported (IPAQ-SF).	Total PA levels (n = 21) Low: 2 participants (9.52%).

		duration 18.0 [IQR 10.50, 27.0] years.		Moderate: 11 participants (52.38%). Vigorous: 8 participants (38.10%).
(Duda-Sobczak et al., 2018)	Observational (Cross-sectional study)	Poland; (n = 119) Age 34 [IQR 26, 41] years; T1D duration 17 [IQR 12, 25] years.	Self-reported (IPAQ-SF).	Total PA levels (n = 119) 1782 [IQR 975, 4290] MET-minutes/week.
(Farabi et al., 2015)	Observational (Prospective cohort study)	US; (n = 12) Age (30.1 ± 13.7 years); T1D duration (20.1 ± 14.0 years).	Self-reported (Researcher- developed questionnaire) How many days/ week do you do ≥60 minutes PA?	Total PA levels (n = 10) Moderate: 8 participants (80.00%). Vigorous: 2 participants (20.00%). Daily PA levels 4.70 ± 1.42 days/week.
(Flotynska et al., 2022)	Observational (Prospective cohort study)	Poland; (n = 99) Age 26 [IQR 22, 31] years; T1D duration newly diagnosed.	Self-reported (Type not stated – assessed PA frequency across various timeframes).	Total PA levels (n = 99) Less active 48 participants (48.48%). More active 51 participants (51.52%). Threshold of PA levels Less active: < 2.5 times/week; More active: ≥ 2.5 times/week.

(Golka et al., 2021)	Observational (Prospective cohort study)	Germany; (n = 177) Age (43.6 ± 11.7 years); T1D duration (18.7 ± 12.6 years).	Self-reported (Researcher developed questionnaire).	Daily PA levels (n = 35) Travel on foot/bike 180 ± 180 minutes. Daily sedentary activities (weekday; n = 27) Use of computer 48 ± 36 minutes. Watching TV 108 ± 60 minutes. Reading 30 ± 36 minutes. Sitting in the car 18 ± 30 minutes. Other activities 18 ± 42 minutes. Daily sedentary activities (weekend; n = 27) Use of computer 78 ± 84 minutes. Watching TV 144 ± 108 minutes. Reading 60 ± 54 minutes.

				Sitting in the car 24 ± 42 minutes. Other activities 42 ± 90 minutes.
(Honda et al., 2020)	Observational (Cross-sectional study)	Japan; (n = 42) Age 44.0 [IQR 33.3, 56.8] years; T1D duration 11.0 [IQR 3.1, 18.8] years.	Self-reported (IPAQ-SF).	Daily sedentary time (n = 42) 360 [IQR 276, 480] minutes.
(Jabbour et al., 2022)	Observational (Cross-sectional study)	Qatar; (n = 102) Age 24 [IQR 18, 28] years; T1D duration 14 [IQR 11, 19] years.	Self-reported (IPAQ-SF).	Total PA levels (n = 102) Walking: 46.1 ± 3.1 minutes/week. MVPA: 50.5 ± 10.3 minutes/week. Vigorous PA: 30.5 ± 5.3 minutes/week. Daily sedentary time (n = 135) 408.0 ± 159.6 minutes.
(Jayawardene et al., 2017)	Experimental (Randomised crossover design)	Australia; (n = 12) Age (40 + 13 years); T1D duration: (24 ± 9 years).	Self-reported (Type not stated).	Daily PA (n = 12) PA (<30 minutes): 7 participants (58.33%). PA (30 – 60 minutes): 5 participants (41.67%). PA (> 60 minutes): 0 participants (0%).

(Keshawarz et al., 2018)	Observational (Prospective cohort study)	US; (n = 44) Age (49 ± 9 years); T1D duration (36 ± 8 years).	Self-reported (Type not stated).	Total PA levels (n = 44) MVPA: 274 ± 188 minutes/week.
(Koca et al., 2019)	Observational (Cross-sectional study)	Turkey; (n = 150) Age (31.07 ± 8.83 years); T1D duration (10.70 ± 6.90 years).	Self-reported (IPAQ-SF).	Total PA levels (n = 150) Low: 47 participants (31.33%). Moderate: 54 participants (36.00%). Vigorous: 49 participants (32.67%).
(Kowal et al., 2024)	Observational (Cross-sectional study)	Poland; (n = 43) Men (n = 25); age (27.84 ± 9.44 years); T1D duration (13.40 ± 8.81 years). Women (n = 18); age (28.15 ± 12.55 years); T1D duration (13.44 ± 9.10 years).	Self-reported (IPAQ-SF).	Total PA levels Men (n = 25) 1668.5 ± 1228.5 MET-minutes/week. Women (n = 18) 1181.9 ± 1056.7 MET-minutes/week.
(Lee et al., 2020a)	Experimental (Randomised crossover design)	Australia; (n = 12) Age 53 [IQR 42, 57] years; T1D duration 28 [IQR 18, 38] years.	Self-reported (Type not stated).	Daily PA levels (n = 12) PA (<30 minutes): 3 participants (25%). PA (30 – 60 minutes): 7 participants (58.33%). PA (>60 minutes): 2 participants (16.67%).

(Lee et al., 2020b)	Experimental (Randomised crossover design)	Australia; (n = 12) Age (40.5 ± 10.0 years); T1D duration (15.8 ± 12.2 years).	Self-reported (Type not stated).	Total PA levels (n = 12) 29 ± 36 minutes. Threshold of PA levels Reported less than 150 minute/week of moderate exercise in past six months.
(Lehmann et al., 1997)	Experimental (Non-randomised study)	Zurich; (n = 10) Age 33 [IQR 22, 48] years; T1D duration (11 ± 7 years).	Self-reported (Recorded PA in logbook).	Total PA levels (n = 10) Baseline: 195 ± 176 minutes/week. Post 3 months: 356 ± 164 minutes/week.
(Martínez-Ramonde et al., 2014)	Observational (Prospective pilot cohort study)	Spain; (n = 19) Age (21.9 ± 4.2 years); T1D duration: recent onset.	Self-reported “Participants reported their PA routines, including exercise types, durations, and perceived intensity”.	Total PA levels (n = 19) Sedentary: 11 participants (57.89%). Regular activity: 8 participants (42.11%). Threshold of PA levels Sedentary: No PA at onset, continuing with the same habits; Regular exercise (≥ 5 hours/week) before and after T1D onset.
(McCarthy et al., 2016)	Observational (Secondary cross-sectional study)	US; (n = 7135) Age (37.14 ± 17.00 years); T1D duration (19.50 ± 13.50 years).	Self-reported (Researcher-developed questionnaire) Question: In a typical	Total PA levels (n = 7135) PA 0: 848 participants (11.88%).

			week, how many days do you do at least 30 minutes PA?"	PA 1: 3928 participants (55.07%). PA 2: 2377 participants (33.19%). <u>Threshold of PA levels</u> 30 minutes of PA; PA 0 (no PA); PA 1 (1 – 4 days/week); PA 2 (≥ 5 days/week).
(Melin et al., 2013)	Observational (Cross sectional study)	Sweden; (n = 292) Age (41.0 + 11.6 years); T1D duration (21.1 ± 12.1 years).	Self-reported (Type not stated).	<u>Total PA levels</u> (n = 36) Inactive: 36 participants (12.33%). <u>Threshold of PA levels</u> Inactive: one time per week of 30 minutes moderate activity.
(Melin et al., 2014)	Observational (Cross sectional study)	Sweden; (n = 196) Age (41.30 ± 11.70 years); T1D duration (21.10 ± 12.20 years).	Self-reported (Type not stated).	<u>Total PA levels</u> (n = 19) Inactive: 19 participants (9.69%). <u>Threshold of PA levels</u> Inactive: one time per week of 30 minutes moderate activity.
(Melin et al., 2021)	Observational (Cross sectional study)	Sweden; (n = 292) Age (Mix 18 – Max 59) years; T1D duration (Min 1 – Max 55) years.	Self-reported (Type not stated).	<u>Total PA levels</u> (n = 275) PA 1: 31 participants (11.27%). PA 2: 59 participants (21.45%). PA 3: 86 participants (31.27%). PA 4: 99 participants (36.00%). <u>Threshold of PA levels</u>

				At least 30 of moderate PA; PA 1: (< 1 time/week), PA 2: (1 – 2 times/week), PA 3: (3 – 5 times/week), PA 4: (daily).
(Moser et al., 2017)	Experimental (Cross-sectional study)	UK; (n = 64) Age (34 ± 8 years); T1D duration (17 ± 9 years).	Self-reported (IPAQ-SF).	Total PA levels (n = 64) 3086 ± 2736 MET-minutes/week.
(Murillo et al., 2024)	Observational (Cross-sectional study)	Spain; (n = 232) Age (37.6 ± 12.4 years); T1D duration (16.0 ± 10.1 years).	Self-reported (IPAQ-SF).	Total PA levels (n = 232) 2202 ± 1839 MET-minutes/week.
(Notkin et al., 2021)	Observational (Prospective cohort study)	Denmark; (n = 12) Age 36.5 [IQR 26.5, 45.5 years); T1D duration (16.0 ± 9.3 years).	Self-reported (Reported weekly PA in diary).	Total PA levels (n = 12) 167.0 ± 82.5 minutes/week.
(Nystrom et al., 2022)	Experimental (Randomised crossover design)	Sweden; (n = 142) Group 1 (CGM then SMBG) (n = 69); Age 46.7 (SD 13.0) years; T1D duration 23.4 (SD 11.9) years. Group 2 (SMBG then CGM) (n = 73); Age 42.6 (SD 12.2) years; T1D duration 21.0 (SD 11.7) years.	Self-reported (IPAQ-SF).	Total PA levels Group 1 (n = 61) 3628 (SD 4524) MET-minutes/week. Group 2 (n = 73) 3158 (SD 3389) MET-minutes/week.

(Reddy et al., 2019)	Experimental (Randomised crossover design)	US; (n = 10) Age (33 ± 6 years); T1D duration (18 ± 10 years).	Self-reported (Type not stated).	<u>Total PA levels</u> (n = 10) 66 ± 42 minutes/day. <u>Threshold of PA</u> Reported exercise of < 150 of moderate intensity for last six months.
(Richardson et al., 2023)	Observational (Prospective cohort study)	US; (n = 563) Age (37 ± 9 years).	Self-reported (Assessed leisure and occupational PA).	<u>Total PA levels</u> (n = 563) Moderate: 180 [IQR 90, 300] minutes/ week. Vigorous: 150 [IQR 60, 305] minutes/ week. MVPA: 333 [IQR 125, 630] minutes/week.
(Riddell et al., 2021)	Experimental (RCT)	US; (n = 44) Age 35 (SD 15) years; T1D duration 16 [IQR 9, 24] years.	Self-reported (IPAQ-SF).	<u>Total PA levels</u> (n = 39) Low: 4 participants (10.26%). Moderate: 13 participants (33.33%). Vigorous: 22 participants (56.41%).

(Rooijackers et al., 2017)	Experimental (Randomised crossover design)	Netherland; (n = 20) T1D with NAH (n = 10) Age (23.9 ± 4.4 years); T1D duration (10.7 ± 4.5 years). T1D with IAH (n = 10) Age (25.7 ± 5.8 years); T1D duration (13.9 ± 8.1 years).	Self-reported (Type not stated).	Total PA levels T1D with NAH (n = 10) 258 ± 174 minutes/week. T1D with IAH (n = 10) 294 ± 222 minutes/week.
(Sadarangani et al., 2019)	Observational (Cross-sectional study)	US; (n = 101) Age (34.4 ± 12.3 years); T1D duration (16.5 ± 9.5 years).	Self-reported (Global physical activity questionnaire)	Total PA levels (n = 101) 180 (SD 390) minutes/week. Threshold of PA levels LTPA > 4 METs.
(Soulimane et al., 2022)	Observational (Prospective cohort study)	16 European countries; (n = 2313); Age (23 ± 9 years); T1D duration (14 ± 9 years).	Self-reported (Type not stated; assessed PA frequency and intensity).	Total PA levels (n = 2313) Moderate: 330 ± 612 minutes/week. Vigorous: 138 ± 402 minutes/week. Threshold of PA levels Moderate (1 – 2 times/week) and Vigorous (1 – 3 times/month) activities, then converted to minutes/week.

(Stotl et al., 2019)	Observational (Cross-sectional study)	Slovenia; (n = 109) Age 38 (SD 10) years; T1D duration 22 (SD 10) years.	Self-reported (Global PA questionnaire).	<u>Total PA levels</u> (n = 109) Moderate: 688.20 (SD 711.13) minutes/ week. Vigorous: 418.16 (SD 649.45) minutes/ week. <u>Threshold of PA levels</u> Vigorous PA duration = sum of work and recreation; moderate PA duration = sum work, recreation, and transport activities.
(Tan et al., 2022)	Observational (Cross-sectional study)	Turkey; (n = 32) Age (31.3 ± 8.7 years); T1D duration: (Mean 15.46 years).	Self-reported (IPAQ-SF).	<u>Total PA levels</u> (n = 32) 1610 ± 1908 MET- minutes/week.
(Tikkanen-Dolenc et al., 2017)	Observational (Prospective cohort study)	Finland; (n = 2099) Age (38.8 ± 12.2 years); T1D duration (21.9 ± 12.4 years).	Self-reported (LTPA).	<u>Total PA levels</u> (n = 2099) 1032 [IQR 402, 2028] MET-minutes/ week.
(Tikkanen-Dolenc et al., 2020)	Observational (Prospective cohort study)	Finland; (n = 1612) Age (37.0 ± 11.9 years); T1D duration (18.9 ± 11.7 years).	Self-reported (LTPA).	<u>Total PA levels</u> (n = 1612) Inactive: 482 participants (29.90%). Moderately active: 833 participants (51.67%). Active: 297 participants (18.42%).

(Turčinović et al., 2023)	Observational (Retrospective cohort study)	Croatia; (n = 71) Age (41.7 ± 13.4 years); T1D duration (no longer than 10 years).	Self-reported (IPAQ-LF).	<u>Total PA levels</u> (n = 71) 5746.80 ± 3634.25 MET-minutes/week. <u>Sedentary time (average)</u> 270.70 ± 153.96 minutes/week.
(Van Mark et al., 2019)	Observational (Retrospective cohort study)	Germany; (n = 56,250) Age 36.8 [IQR 20.3, 54.6] years; T1D duration 12.4 [IQR 6.0, 22.9] years.	Self-reported (Type not stated).	<u>Total PA levels</u> (n = 23,310) Inactive: 23,310 participants (41.43%). <u>Threshold of PA levels</u> Inactive: 30 minutes of moderate activities (<1 time/week).
(Waden et al., 2007)	Observational (Cross-sectional study)	Finland; (n = 1028) Age (36.4 ± 11.5 years); T1D duration (21.3 ± 11.7 years).	Self-reported (LTPA).	<u>Total PA levels</u> (n = 1028) Inactive: 254 participants (24.71%). Moderately active: 588 participants (57.20%). Active: 186 participants (18.09%).
(Yardley et al., 2019)	Experimental (Randomised crossover design)	Canada; (n = 12) Age (52.7 ± 7.9 years); T1D duration (36.2 ± 12.7 years).	Self-reported (Godin LTPA).	<u>Total PA score</u> (n = 12) 48.2 ± 41.5 points.

(Zaccaria et al., 2023)	Observational (Cross-sectional study)	Italy; (n = 90) Age 49.0 [IQR 41.0, 55.8] years; T1D duration 21.0 [IQR 14.3, 34.0] years.	Self-reported (IPAQ-LF).	Total PA levels (n = 90) Low: 19 participants (21.11%). Moderate: 37 participants (41.11%). Vigorous: 34 participants (37.78%).
(Zielińska et al., 2018)	Observational (Cross-sectional study)	Poland; (n = 209) Age (30 ± 11 years); T1D duration (12 ± 8 years).	Self-reported (IPAQ-SF).	Total PA levels (n = 209) Low: 15 participants (7.18%). Moderate: 48 participants (22.97%). Vigorous: 146 participants (69.86%).

IPAQ-SF: International Physical Activity Questionnaire short form; **IPAQ-LF:** International Physical Activity Questionnaire long form; **MET:** metabolic equivalent of task; **CGM:** continuous glucose monitoring**; SMBG:** self-management blood glucose; **IQR:** interquartile range; **SD:** standard deviation.

4.A.3.4 Moderators of Physical Activity

Seven studies have shown that factors such as age, sex, BMI, diabetes duration, education levels, and employment status influence the levels of PA in individuals with T1D. Three studies indicated that age had an impact on PA levels, with two studies indicating a decrease in PA participation with age, with higher participation among younger participants (Duda-Sobczak et al., 2018; Brugnara et al., 2023) and one study reporting increased inactivity frequency with age (45 to 80 years) (Bohn et al., 2015). Additionally, four studies compared PA levels between sex, with three reporting men as more physically active than women, while one study found the opposite. For instance, a study by Brugnara and colleagues (Brugnara et al., 2023) found that men engaged in more intense PA, while a study by McCarthy and colleagues (McCarthy et al., 2016) indicated that men achieved significantly higher levels of PA than women (37% versus 30%; $p < 0.0001$). Similarly, a study reported that women were often inactive compared to men (66.0% versus 60.5%; $p < 0.0001$) (Bohn et al., 2015). However, a study revealed that men were more inactive (Tikkanen-Dolenc et al., 2020).

Body mass index was noted in two studies to have an inverse relationship with PA levels, indicating that participants with lower BMI tended to engage more in PA (Bohn et al., 2015; Jabbour et al., 2022). Moreover, the findings suggest that T1D duration serves as moderator impacting PA levels. A study by Duda-Sobczak and colleagues (Duda-Sobczak et al., 2018) indicated that T1D duration is negatively correlated with PA levels ($Rs = -0.15$), implying that individuals with longer T1D tend to engage in lower levels of PA. One study reported that participants with higher education levels (e.g., bachelor's degree) were more likely to engaged in weekly PA of less than 150 minutes compared to those with a high school or diploma (McCarthy et al., 2016). Similarly, employment status

serves as a determining factor for PA levels. A study by McCarthy and colleagues (McCarthy et al., 2016) found that those individuals who were working full-time or part-time or were student more likely to engage in weekly PA of less than 150 minutes compared to those who were retired.

4.A.3.5 Quality Assessment

For the experimental studies, the quality assessment was performed using the RoB2 tool in two RCTs and eight crossover design studies (**Appendix A.4.1** for RCTs, and **Appendix A.4.2** for crossover design). The overall risk of bias was considered ‘low risk’ of bias in one RCT and two crossover design studies. However, one RCT study and six crossover design studies was assessed as having ‘some concern’ of bias due to lack of information about randomisation concealment, blinding of outcome assessors, deviations from the intended intervention (e.g., revising the study protocol for administering carbohydrate pre-exercise due to low plasma glucose concentrations), and lack of information regarding the pre-specified analysis plan. For the non-randomised studies, the quality assessment was also conducted using the ROBINS-I tool in one non-randomised experimental study and the overall risk of bias was evaluated as ‘low risk’ of bias (**Appendix A.5.1**).

For observational studies, the quality assessment was conducted using the NOS in 15 cohort studies, one case-control study, and 26 cross-sectional studies (**Appendix A.6**). The quality assessment of 15 cohort studies was rated as high quality and low risk of bias (score 7 – 9) (**Appendix A.6.1**), as well as the case control study with a nine score (high quality) (**Appendix A.6.2**). Additionally, the 26 cross sectional studies were rated as moderate to high quality (score 5 – 9), which corresponds to a low to moderate risk (**Appendix A.6.3**).

4.A.4 Discussion

To our knowledge, this is the first review to comprehensively analyse PA and SBs among adults with T1D using both objective and self-reported measures. A total of 42 observational studies (prospective and retrospective cohort, cross-sectional and case-control) and 11 experimental studies (RCTs, randomised crossover design, and non-randomised designs) were identified that measured PA and SBs. Findings from the present review reveal that a notable difference between objective and self-reported measures of PA. Studies using device-based measures have shown that a significant proportion of adults with T1D (72.46%; n = 463) fail to meet the recommended daily step count of 10,000 steps, with some individuals (n = 23) exhibiting predominantly SBs, spending up to 69.80% of their day in sedentary activities and limited time across all PA intensities (~29.5%), whereas other studies using also device-based measures found that 112 adults with T1D met the PA guidelines. Conversely, studies using self-reported measure of PA reported markedly varying results in adults with T1D. In these studies, 2369 participants met or exceeded the PA guidelines, and 2087 participants met the PA recommendations through moderate and vigorous activities or a combination of them during leisure time, while a significant number of participants 23,403 were reported being inactive, and in another study, 12,216 participants were found not to engage in any PA. Thus, despite meeting or exceeding the PA guidelines, adults with T1D may be classified as inactive and engage more in SB.

4.A.4.1 Objective Measures

A total of nine studies were included, all reporting device-based PA measures, with one also examining sedentary time. Metrics such as steps per day, minutes per day or per week, and other metrics.

Objective measurements of PA in four studies involving adults with T1D highlight significant variability in daily step counts. These studies revealed that of a total of 639 adults, 463 (72.46%) failed to achieve the target of 10,000 steps per day, while 176 (27.54%) achieved the target. The recommendation to achieve 10,000 steps per day is commonly promoted among general adult population (Wattanapisit and Thanamee, 2017). Encouraging increased MVPA, achieving 10,000 daily steps serves as a target, with individuals setting time goal and calculating their daily step requirements to monitor progress toward guidelines (U.S. Department of Health and Human Services, 2018). The energy expenditure from walking 10,000 steps per day three days a week is comparable 30 minutes of moderate-intensity PA on most days, meeting the 1000 kcal per week threshold for reduced cardiovascular mortality (Warburton et al., 2010). For example, a study by Choi and colleagues (Choi et al., 2007) reported that walking 10,000 steps results in an energy expenditure of 300 to 400 calories in adults, which can be achieved through an active lifestyle, including a daily 30-minute walk.

Preliminary evidence suggests that a goals of 10,000 steps per day may not be sustainable for older adults and those with chronic diseases, who typically take fewer than 5000 steps per day (Tudor-Locke and Myers, 2001). However, as noted by Tudor-Locke and Bassett (Tudor-Locke and Bassett, 2004) even incremental increases in daily steps can provide health benefits such as lower blood pressure and improved cholesterol levels. A study in adults with T1D found that taking 7000 to 10,000 steps per day increased T1R by ~2%, important for managing T1D, compared to days with fewer than 7000 steps (Turner et al., 2024). Therefore, simple and practical interventions that focus on gradual increases in PA and reducing sedentary time, rather than a goal of 10,000 steps, can be more effective in promoting health benefits those with T1D. Step count is

a preferred metric for monitoring the number of steps taken throughout the day, using wearable activity trackers, pedometers, or smart phone applications (Sylvia et al., 2014). These devices provide information on steps, calories, and activity time (Bassett et al., 2017), but they do not capture the intensity, frequency and duration of activity (Freedson and Miller, 2000; Trost, 2001). Therefore, other metrics are used in clinical research to obtain more detailed measures of PA.

Additionally, the findings from the present review also measured total PA and SBs using different objective measures, showed that 112 adults with T1D met the recommended PA guidelines of at least 150 minutes of moderate-intensity PA, achievable through 30-minute on at least five days a week (GOV.UK, 2011; World Health Organisation, 2020). However, one of the included studies found that adults with T1D spent the majority of their time being sedentary (69.8%), with limited engagement in PA across all levels of intensity (~30%). These findings suggest that, despite meeting the PA recommendations, adults with T1D still spend a considerable amount of time in SBs. Our findings are consistent with a recent study in 29 adolescents with T1D, which reported that participants engaged in an average of ~20 minutes per day of MVPA and spent ~69% of waking hours sedentary, based on ActiGraph measure (Tilden et al., 2023).

4.A.4.2 Self-reported Measures

4.A.4.2.1 Total Levels of Physical Activity and Sedentary Behaviours

A total of 46 observational and experimental studies were included, reporting PA and SBs in adults with T1D using various self-reported measures. These studies used a wide range of self-reported assessment tools, including various type of questionnaires with different recall periods (e.g., some focusing on the past week

while others focused on a typical week or even extended to the past months or longer). The categorisation and reporting thresholds also varied, such as duration and frequency (e.g., minutes per week, minutes per day, or days per week) and intensity levels with varying cut-off points for low, moderate, and vigorous activities. Some studies used subjective definitions (e.g., ‘sedentary’ as ‘inactive’ or ‘no PA’). Thus, these variations complicate direct comparisons of PA and SBs across studies due to lack standardisation. Additionally, weekly MET-minutes and PA scores classified participants as active or inactive based on pre-defined thresholds, which varied across studies, resulting in significant variability in data collection methods.

4.A.4.2.1.1 Total Levels of Physical Activity Assessed by the IPAQ

Physical activity levels among adults with T1D demonstrated considerable variation across the included studies. The average weekly activity using the IPAQ was ranged from 1181.94 to 2202.00 MET-minutes (moderately active; n = 351), 1782.00 to 2772.00 MET-minutes (moderately to physically active; n = 254), and 3086.00 to 5746.80 MET-minutes (physically active; n = 269). This analysis shows that many adults with T1D are moderately active (600 – 3000 MET-minutes per week), followed by physically active (> 3000 MET-minutes per week).

4.A.4.2.1.2 Total Levels of Physical Activity Assessed using Alternative Self-reported Tools

Across three reviewed studies, a total of 2335 adults with T1D met the recommended PA guidelines. Moderate-intensity PA ranged from 167 to 330 minutes per week, MVPA ranged from 195 to 356 minutes per week, and vigorous-intensity PA ranged from 138 ± 402 minutes per week, all of which met the weekly PA guidelines. While 114 adults with T1D failed to meet the guidelines

for moderate-intensity PA with an average ranged from 29 to 50 minutes per week. However, two studies involving 3304 participants reported an average weekly activity ranging from 250 to 294 minutes, suggesting that many likely met or exceeded PA guidelines, depending on the intensity of activity but the studies did not specify the intensity.

4.A.4.2.1.3 Quantifying Leisure Time Activities

Physical activity during leisure time in adults with T1D varied across five studies. Moderate-intensity PA was reported in three studies, with averages ranging from 180.00 to 688.20 minutes per week (n = 707). Vigorous-intensity PA was reported in two studies, with averages ranging from 150.00 and 418.16 minutes per week (n = 672). MVPA was reported in three studies, with averages of 180 and 333 minutes per week among a total of 708 participants. Collectively, these findings suggest that a significant proportion of adults with T1D have met or exceeded the WHO guidelines of 150 – 300 minutes per week for moderate-intensity PA or 75 – 150 minutes per week for vigorous-intensity PA or a combination of them (World Health Organisation, 2020), depending on the specific intensity of activity reported.

4.A.4.2.2 Proportion of Participants Classified as Active or Inactive

4.A.4.2.2.1 Proportion of Participants by Physical Activity Intensity

The findings from the IPAQ questionnaire that measured the levels of PA over the past seven days in five studies including 509 adults with T1D demonstrated that 17.09% (n = 87) were classified as having low-intensity PA, 32.02% (n = 163) as moderate-intensity PA, and 50.88% (n = 259) as vigorous-intensity PA. A recent study of 592 adolescents with T1D found that 6.80% of the sample performed low activity, 20.90% engaged in moderate activity, and 72.30%

participated in vigorous activity (Gómez-Peralta et al., 2023). This finding is consistent with our findings, which indicate higher participation in vigorous-intensity PA. However, the reliance on self-reported data raises concerns about potential overestimation, as participants may overstate their activity levels, emphasising the limitations of self-reported tools in accurately assessing PA intensity.

Additionally, studies included in the review using alternative self-reported tools found that 98.30% (n = 23,403) of participants were physically inactive (less than once a week of at least 30-minute of PA or exercise occasionally). However, five studies reported leisure time activities in term of both intensity and frequency. In term of intensity, 28.61% (n = 771) individuals were classified as inactive, 52.71% (n = 1421) as moderately active, and 18.66% (n = 503) as physically active (including those engaged in MVPA and vigorous activities). For frequency, 29.34% (n = 7387) of individuals were moderately active (1 – 4 days per week or 1 – 2 times per week) and 22.20% (n = 5589) were physically active (> 4 times per week or > 2 times per week). This data suggests promising levels of PA among adults with T1D; however, a significant proportion of individuals spend a large portion of their waking hours being sedentary.

4.A.4.1.2 Sedentary Behaviours

Limited studies have examined time spent in SBs, with five reporting this behaviour in minutes per day or minutes per week, and three studies reporting no PA. Adults with T1D spent an average of ~351 minutes per day (~6 hours) in SB (n = 567). While one study reported an average of 270 minutes per week (~39 minutes per day) in sitting time, which suggest a lower amount of time spent in sitting during the day and may underestimate the actual time spent in sitting. As such, it may be important to examine within-week variations in PA as this may

help better inform interventions designed to target low levels of PA and high levels of sedentary time. Notably, a large proportion of adults with T1D, 48.48% (12,216 of 25,200) individuals, reported not engaging in any PA. This emphasises the need for further interventions to reduce sitting time, including incorporating activity breaks throughout the day.

4.A.4.3 Contrasting Objective and Self-reported Physical Activity Assessments

Results from objective and self-reported measures revealed a notable difference in PA levels. The objective assessment indicated that 72.46% (463 of 639) adults with T1D did not reach the recommended 10,000 steps per day, and 23 individuals spent an average of 69.80% of their time in SBs with relatively low levels of PA. However, the self-reported assessment showed considerable variability. For example, studies measuring weekly PA found that 707 adults with T1D met or exceeded the PA guidelines for moderate-intensity PA, and 672 met the guidelines for vigorous-intensity PA. While studies reporting the proportion of individuals participated in PA found that 23,403 engaged in less than once a week or only occasionally, with at least 30 minutes per session.

The aforementioned data highlight the potential for overestimation in self-reported measures, emphasising the need for more literature using objective assessments to accurately represent PA behaviour in this population. This overestimation of PA using self-reported tools has previously been shown in individuals with and without diabetes (Schaller et al., 2016; Nelson et al., 2019; Prince et al., 2020; Finn et al., 2022). The self-reported PA data obtained through questionnaires are susceptible to biases, including inaccurate memory recall and social desirability biases (Pober et al., 2006).

4.A.4.4 Moderators of Physical Activity Levels

In this review, we examined the potential factors that influence levels of PA in adults with T1D, including sex, age, BMI, diabetes duration, education levels, and employment status. Our findings showed that women are less active than men, possibly due to hormonal fluctuations during the menstrual cycle, which can affect blood glucose and insulin needs and act as a barrier to exercise (Toor et al., 2023) and they may also feel less energetic or more fatigued during certain phases of their menstrual cycle, impacting their activity levels. Men also tend to be more active due to testosterone, which makes their muscles stronger and increases their endurance, encouraging them to participate in more activities (Handelsman et al., 2018).

Data from the reviewed study indicates that younger individuals are more likely to engage in PA than older age, as those aged 45 to < 85 have been reported to be physically inactive (less than once a week). This difference may be attributed to the loss of muscle mass and strength, as well as an increase in fat mass (Westerterp, 2018). According to the UK government, there is a decline in PA with age; ~69% of individuals aged 16 to 24 years are active, compared to only 39% of those aged 75 years and over (GOV.UK, 2022a). Additionally, one study included in this review found that adults with higher BMI were less likely to engage in PA, with a significant number of participants (n = 11,357) not engaging in any PA, possibly due to sedentary lifestyle. This aligns with the findings of the Cassidy and colleagues study, which revealed that obese adults (BMI ≥ 35 kg/m^2) were two to three times more likely to report low levels of PA compared to non-obese adults (Cassidy et al., 2017).

Diabetes duration was also a factor that impact the levels of PA. Our findings show that adults with a longer duration of T1D participated less in PA.

However, the large proportion of individual with T1D did not achieve the PA recommendations, due to glycaemic barriers, such as fear of hypoglycaemia and glucose management around exercise (Brazeau et al., 2008; Lascar et al., 2014). Education levels were also influenced by PA levels, as the included study showed that individuals with a bachelor's degree are more likely to engage in less than 150 minutes per week of PA compared to those with a high school diploma education, possibly due to lifestyle or occupation. For example, those with a high school diploma may have a job or a daily routine that involves more PA compared to individuals with a bachelor's degree, who may have more sedentary occupations or lifestyle. A study by Kantomaa and colleagues (Kantomaa et al., 2016) found that higher education is associated with higher sedentary time especially during weekdays.

Furthermore, a study included in this review suggest that PA levels are influenced by employment status, as individuals with part-time or full-time jobs, or who were students, were less active compared to those who were retired. A study by Mein and colleagues (Mein et al., 2005) supports our findings that individuals who are not working, including those who are retired, tend to engage in higher levels of PA compared to those who work full or part-time. Retirement can offer individuals the chance to participate in PA more than those who are occupied with full-time or part-time employment, as the demands of work often limit opportunities for PA. While retirement may provide more opportunities for PA, it's important to note that the 2005 study predates advancements like closed-loop systems, suggesting that if PA levels remain lower than the general population, factors beyond glycaemic control – such as psychological or social barriers – may play a larger role.

4.A.4.5 Study Strengths and Limitations

The main strength of the current review is it included analysis of PA and SBs in adults with T1D using both objective and self-reported measures. It is important to note that objective and self-reported measures offer different information; for instance, objective measures consistently capture bodily movement at a specific threshold, while self-reported measures reflect the behaviours as perceived by the respondent, providing more contextual information. Furthermore, there are several methodological strengths in this review; studies were identified through comprehensive search of published studies in the area and were conducted in a range of databases. The broad definition of search terms applied across multiple databases enabled searching and identification across many potential studies.

Despite the numerous strengths, this approach has several limitations that warrant consideration. The main limitation in this review is that the studies use different methods to process and report data across different recording time periods, making comparison across studies difficult. To improve comparability between studies in the future, standardisation of data collection methods and reporting is necessary to enable more accurate global comparisons. The variety of objective and self-reported measures used to assess PA levels also limited comparison between studies. Even if they used the same questionnaire or accelerometers, they had different thresholds that likely affected the comparison between measures. Moreover, only nine studies reported SBs, using both objective (one studies) and self-reported measures (eight studies). This may hinder the ability to draw robust conclusions or generalise findings regarding SBs in adults with T1D. Lastly, the omission of term ‘driving’ is a limitation, as it may influence the quantification of PA and SBs in individuals with T1D.

4.A.5 Conclusion

This systematic review suggests that adults with T1D may have lower levels of PA and higher levels SB, as indicated by both objective and self-reported measures. However, these findings should be interpreted with caution due to variability in study methodologies and data sources. Surprisingly, there is limited evidence from studies using objective measures (i.e., more reliable, accurate, and valid) compared to self-reported measures, which rely on participants reporting their own SB (Prince et al., 2008). Thus, our findings indicate that prioritising interventions to increase PA and reduce SBs is crucial for improving diabetes management and lowering the risk of complications among individuals with T1D. Specifically, the interrupted sitting approach represents a potentially effective strategy for mitigation in this population.

4.B Meta-analysis

What do we know? Physical activity and SBs influence glucose responses, with some studies reporting improvements in glycaemia post-exercise while other reported no effect or even worsening glycaemia.

Key issues: The differing in response may be due to factors such as variation in exercise intensity and durations, timing of the exercise, baseline glycaemic control, and study protocol.

Chapter aims: This meta-analysis aims to evaluate the impact of a single bout of aerobic exercise and long-term aerobic training on glycaemia. Additionally, it sought to determine how different exercise intensities and durations affect glycaemia in adults with T1D.

Chapter implications: The findings and conclusions of this analysis will uniform the direction and design of the subsequent studies in the PhD thesis, particularly, in understanding the optimal exercise intensities and durations for improving glycaemia in adults with T1D.

4.B.1 Introduction

Acute exercise, defined as a single bout of intense PA performed with a relatively short time frame, plays an important role in the regulation of glycaemia in individuals with T1D by enhancing glucose uptake and improving insulin sensitivity for up to 72 hours (Colberg et al., 2010; Bird and Hawley, 2017). However, the potential of exercise-induced hypoglycaemia presents a significant challenge in this population, requiring a careful balance PA and glucose management (Riddell and Perkins, 2009). Consequently, a significant proportion of individuals with T1D may be reluctant to engage in exercise due to concerns about managing their glycaemia effectively (Brazeau et al., 2008). While long-

term exercise training (chronic exercise) characterised by sustained and regular PA over an extended period duration, has emerged as critical factor influencing various health parameters, including long-term improvements in glycaemic control (HbA1c) (Bird and Hawley, 2017).

Despite the well-established nature of current guidelines, uncertainties persist regarding the exact impact of exercise on glucose control in individuals with T1D. Understanding is hindered by heterogeneity in study characteristics, including population demographics (e.g., children, adolescent, or adults) and exercise modalities. Previous systematic reviews and meta-analyses have addressed the impact of exercise on glucose control in individuals with T1D, highlighting its significant role in disease management such as improving the HbA1c levels and quality of life in adolescent with T1D (Patience et al., 2023). A meta-analysis conducted by Tonoli and colleagues (Tonoli et al., 2012) found that acute aerobic exercise results in a larger decrease in venous blood glucose concentrations immediately following the exercise (change in venous blood glucose concentrations immediately post-exercise) with the overall estimated effect of −4.17 mmol/L (95% CI: −4.57 to −3.76) in individuals with T1D. The same review reported the impact of long-term aerobic exercise training on venous blood glucose concentrations (change in HbA1c levels over a period of two to three months), findings a small but significant overall estimated effect of −0.23% (95% CI: −0.44 to −0.02) in 171 individuals with T1D (Tonoli et al., 2012). Another systematic review and meta-analysis found that acute aerobic exercise tests led to an overall decreased in the blood glucose concentrations during the exercise session by −3.1 mmol/L (95% CI: −3.4 to −2.8), which had a mean duration of 46 ± 21 minutes, with running resulting a larger decrease (−4.1 mmol/L [95% CI: −4.7 to −2.4]) compared to cycling (−2.7 mmol/L [95% CI: −3.0 to −2.4]; $p <$

0.0001) (Eckstein et al., 2023). Moreover, a systematic review and meta-analysis found that high intensity exercise in a mean overall blood glucose concentrations decreased of −1.3 mmol/L (95% CI: −2.3 to −0.2) (McClure et al., 2023). When performed after an overnight fast, exercise increased blood glucose concentrations by +1.7 mmol/L (95% CI: 0.4 to 3.0), whereas postprandial exercise decreased blood glucose concentrations by −2.1 mmol/L (95% CI: −2.8 to −1.4), with a statistically significant difference between groups ($p < 0.0001$) (McClure et al., 2023).

Based on the findings regarding the impact of acute exercise and long-term exercise training on glycaemia in individuals with T1D, several gaps in the literature can be identified. One meta-analysis reported the effects of acute and long-term exercise training on venous blood glucose concentrations across all individuals with T1D, including children, adolescents, and adults (Tonoli et al., 2012). Another meta-analysis specifically examined the impact of different types of acute aerobic exercise on the magnitude of blood glucose fluctuations in adolescents and adults (Eckstein et al., 2023). An actual gap remains in understanding the effects of acute and long-term aerobic exercise training specifically with adult population, particularly when focusing solely on aerobic exercise. Additionally, a third meta-analysis focused on the effect of high-intensity PA on blood glucose concentrations, highlighting the difference between fasting and postprandial states (McClure et al., 2023). Although the review by McClure and colleagues (McClure et al., 2023) has primarily focused on the effects of high-intensity acute exercise on blood glucose concentrations, particularly differentiating between fasting and postprandial states, they often overlook the broader impact of both acute exercise and long-term aerobic exercise training, including moderate-intensity PA and high-intensity PA, on overall glucose control

in individuals with T1D. Thus, our review fills this gap by comprehensively examining how these varying intensities and exercise durations influence glucose control in adults with T1D.

Numerous studies on exercise and T1D have been used different classification tools to measure exercise intensity, such as VO_{2max}, lactate threshold, HR_{max} (Zinman et al., 1984; Lehmann et al., 1997; Wróbel et al., 2018). Generally, engaging in short-duration, high-intensity exercise has a tendency to cause an increase in blood glucose concentrations during exercise, whereas participating in long-duration, moderate-intensity exercise rises the likelihood of experiencing low blood glucose concentrations, both during the activity and in the 12 to 24 hours afterward (Murillo et al., 2022). However, what constituted moderate or vigorous-intensity PA varied in these studies, and it is important to note that the impact of high-intensity interval training on blood glucose concentrations varies among studies.

Some studies report a significant increase in blood glucose concentrations after an acute, single session of high-intensity interval training, reaching approximately 70 mg/dL (Potashner et al., 2019; Riddell et al., 2019a), and some studies indicate only a minor effect on glycaemia (Scott et al., 2019b). Differences in exercise intensity, type and duration of exercise, timing of activity relative to meals and insulin administrations, individual fitness levels, and baseline glycaemic control may contribute to differences in study outcomes. Consequently, accurately predicting the impact on blood glucose concentrations becomes challenging, making it difficult to formulate consistent recommendations based on current findings. This uncertainty highlights the need for further research to clarify how exercise intensity affects blood glucose concentrations in those with T1D (Tonoli et al., 2012; Kennedy et al., 2013).

Despite of the previous findings, there is a lack of meta-analyses that specifically examine the impact of both a single bout of aerobic exercise and long-term aerobic exercise training on glycaemia in adults with T1D, taking into consideration different intensities and durations of exercise. Although resistance training and high-intensity interval training benefits glycaemia, aerobic exercise is the most studied and commonly performed in T1D. Its association with greater glycaemic variability, making it particularly relevant for investigation. Therefore, this meta-analysis focuses on adults with T1D. Specifically, its objectives are to: 1) assess the effects of a single bout of aerobic exercise on glycaemia and determine whether different intensities influence plasma glucose or capillary glucose concentrations, and 2) evaluate the effects of long-term aerobic exercise training on HbA1c levels and fasting glucose concentrations, as well as the impact of exercise duration on HbA1c.

4.B.2 Methods

The methodological details are comprehensively outlined in Part A, **section 4.A.2**; thus, only the specific aspects related to the meta-analysis are presented in this section.

4.B.2.1 Search Strategy and Data Sources

Search strategy techniques, electronic search terms for PA, SBs and T1D were explained in detail in **section 4.A.2.2** of this chapter. The search was revised and updated to include studies conducted between July 2022 to May 2024, but no studies were included, as none met the inclusion criteria reported in **Table 4.3**.

In this meta-analysis, studies needed to fulfil the following criteria, taking into consideration the PICOs principles, with a main focus on glycaemia as the primary outcome. All searches were limited to studies published in English, with

no restrictions on publication year. The PRISMA flow diagram, illustrating the selection of included studies was presented in **Figure 4.1**.

Table 4.3 Inclusion Criteria for Selected Studies

PICOs principles	Inclusion criteria
Population	Adults with T1D, free of other diseases or infections.
Intervention/Exposure	-
Comparisons	No advice, free-living, standard of care, or lower levels of PA or sedentary time.
Outcomes	Glycaemia (e.g., HbA1c, plasma glucose, capillary glucose, and fasting plasma glucose concentrations) pre- and post-exercise.
Study design	Experimental studies.

4.B.2.2 Data Extraction

Three researchers (AA, MH, MZ) independently screened the study title and abstracts according to the review protocol. Any disagreements were resolved through discussion. The full texts of the studies were then independently reviewed by one researcher AA. Data extraction was performed independently by one researcher AA and confirmed by second and third researcher (MH, MZ). The extraction criteria of studies were applied by using the inclusion criteria on the title, abstract, and/or full text. The effect of a single bout and long-term aerobic exercise training on glycaemia were distinguished in the analyses.

The following data were extracted from included studies: study characteristics such as the first author and year of publication, study design, sample size, intervention details, and participant characteristics (e.g., age, sex, diabetes duration). Additionally, descriptions of the exercise testing protocol and intervention (e.g., exercise frequency, intensity, and duration), intervention length, exercise modality, and study outcomes were also extracted. The outcome measures of included studies were extracted as means and its variance (i.e.,

mean difference, SD, or SE) for pre- and post-intervention HbA1c (%) and fasting plasma glucose (mmol/L), plasma glucose (mmol/L), and capillary glucose (mmol/L). In cases where data were presented in alternative units (e.g., mg/dL), they were converted to mmol/L using the following formula: divide the glucose value in mg/dL by 18 (Diabetes UK, 2023). Additionally, to convert HbA1c levels from mmol/mol to %, multiply total HbA1c value in mmol/mol by 0.0915, then multiply the result by 2.25 (Heinemann and Freckmann, 2015). A meta-analysis was conducted, requiring at least two comparable studies for inclusion.

If glycaemia outcome data were not explicitly reported in the full text but were presented graphically, the graphs were digitised using the Web Plot Digitizer tool (Drevon et al., 2017). If the data could not be obtained successfully, the study was omitted from the meta-analysis. Additionally, if the exercise mode in the study involved combined aerobic, resistance, or flexibility training, the study was excluded. However, one study reported that participants engaged in 45 minutes of aerobic exercise followed by 45 minutes of resistance training (Yardley et al., 2012). Glycaemia in this study was measured at the start of and immediately post-aerobic exercise, so we included data from the initial 45 minutes of aerobic exercise. For long-term aerobic training studies, the weekly exercise duration in minutes was calculated by multiplying the exercise duration per session in minutes by the exercise frequency per week. Furthermore, given our objective to assess the impact of exercise interventions on glycaemia and observe changes from the pre-exercise state, studies that did not report glycaemia measurements pre-exercise sessions were excluded.

4.B.2.3 Quality Assessment of Included Studies

Eligible studies were independently assessed for methodological quality by one researcher AA. For the RCTs and crossover design studies, the RoB2 tool was

used (Higgins et al., 2019; Sterne et al., 2019), while for the non-randomised studies, the ROBINS-I tool was used (Sterne et al., 2016).

4.B.2.4 Subgroup Analysis

For the exercise intensity it was apparent that differences existed in how exercise intensities were classified in the included studies (e.g., low-, moderate-, MVPA, and vigorous-intensity PA), as they used varying thresholds and classifications. For the subgroup analysis of exercise intensity, these were re-classified based on the exercise intensities outlined in the guidelines of the American College of Sports Medicine (ACSM) using VO_{2max}, HR_{max} or the lactate threshold (outlined in **Table 4.4**).

Subgroup analyses for the HbA1c outcomes were also performed based on exercise intensity for long-term aerobic exercise training using the same classification of exercise intensity as reported in **Table 4.4**. Additionally, subgroup analyses were also conducted based on weekly exercise duration, categorised according to the median value as ≤ 135 minutes per week versus > 135 minutes per week for the HbA1c outcomes. This duration was calculated by multiplying the duration of each exercise session by the frequency of sessions per week. The median exercise duration across six studies was 135 minutes, despite the recommendation of at least 150 minutes of MVPA per week (Thompson, 2009; Carral et al., 2013). Furthermore, another subgroup analyses were performed for the HbA1c outcomes based on the length of exercise training, categorised as 12 weeks duration and 16 weeks duration, as these were the most commonly reported time points in the included studies. Whereas no subgroup analysis was performed for a single bout of aerobic exercise, as the exercise intensity was classified as moderate intensity in all six studies.

Table 4.4 Classification of Exercise Intensity across Different Measurement

	Parameters		
	%VO_{2max}	**%HR_{max}**	**%HRR**
Definition	Maximum amount of O_2 individual can consume during exercise.	Highest number of beats the heart can pump during exercise.	Difference between HR_{max} and resting HR. (HRR= HR_{max}–HR_{rest})
Intensity domain			
Very low	< 37	< 57	< 30
Low	37 – 45	57 – 63	30 – 39
Moderate	46 – 63	64 – 76	40 – 59
Vigorous	64 – 90	77 – 95	60 – 89
Near maximal	≥ 91	≥ 96	≥ 90

Table data adapted from the ACSM guidelines (Pollock et al., 1998). **%VO_{2max}**, percentage of maximal oxygen uptake; **%HR_{max}**, percentage of maximum heart rate; **%HRR**, percentage of heart rate reserve.

4.B.2.5 Data Analysis

Meta-analyses were conducted using Review Manager (RevMan; version 5.4.1; The Cochrane Collaboration, 2020) to compare the mean difference in glycaemia pre- and post-exercise, performed by one researcher (AA). Random effects models were computed to calculate pooled effect sizes. Meta-analyses for continuous outcomes were completed using the mean, SD, and total sample size from each study. The SEM values were converted to SD using the formula: SD = SEM X $\sqrt{sample\ size}$. Heterogeneity of effect sizes was evaluated using the I^2 test as recommended by Higgins and colleagues and was expressed as a percentage (%) and can be quantified as low, moderate, and high, with upper limits of 25%, 50%, and 75%, respectively (Higgins et al., 2003; Ioannidis et al., 2007). The levels up to 50% were considered acceptable for pooling the study findings (Higgins and Green, 2011b). For I^2 above 50%, results were interpreted with caution, for example, by conducting subgroup analysis (to determine

whether specific characteristics of studies such as intervention types, population differences, or study designs could explain the observed variability). Publication bias was assessed through the examination of statistical test, such as Egger's regression test (Egger et al., 1997) using the Jamovi software.

4.B.3 Results

4.B.3.1 Studies Retrieved

The total number of studies suitable for meta-analysis was 14. The detailed flow diagram illustrating the literature search and screening process is provided in Part A of this chapter, **Figure 4.1**.

4.B.3.2 Characteristics of Included Studies

Studies were published between 1982 to 2020 and the total number of adults with T1D included in these studies was 159 individuals. Their ages ranged from 22 to 53 years, while the diabetes duration varied from 9 to 36 years. For studies looking at the effects of a single bout of aerobic exercise, glycaemia was assessed before and immediately after exercise. In the case of long-term aerobic exercise training, glycaemia was evaluated both at baseline and at the end of exercise interventions. The characteristics of included studies examining the impact of exercise interventions on glycaemia are presented in **Tables 4.5** and **4.6.**

Table 4.5 Effects of Acute Aerobic Exercise on Glycaemia in Adults with Type 1 Diabetes

Study, year	Study design	Participants characteristics	Age (years)	T1D duration (years)	Glycaemia (mmol/L)	Intervention
(Bally et al., 2015)	Randomised crossover design	(n = 10) 10 males	26.3 ± 3.5	12.9 ± 5.2	Plasma glucose Pre: 5.60 ± 4.99 Post: 6.80 ± 6.98	A 90-minute of moderate activity (50% VO_{2peak}).
(Guelfi et al., 2005)	Randomised crossover design	(n = 7) 4 males | 3 females	21.6 ± 4.0	8.6 ± 5.0	Capillary glucose Pre: 11.0 ± 2.3 Post: 6.6 ± 1.1	A 30-minute of moderate activity (40% VO_{2peak}).
(Trovati et al., 1988)	Randomised crossover design	(n = 6) 6 males	26.0 ± 7.4	11.0 ± 4.0	Plasma glucose Pre: 5.50 ± 2.45 Post: 4.50 ± 1.96	A 45-minute of moderate activity (48 ± 4% VO_{2max}).
(Trovati et al., 1992)	Non-randomised design	(n = 6) 6 males	27.2 ± 8.3	12.6 ± 3.7	Plasma glucose Pre: 5.90 ± 2.94 Post: 4.60 ± 2.45	A 45-minute of moderate activity (50% VO_{2max}).
(Yardley et al., 2012)	Randomised crossover design	(n = 12) 10 males | 2 females	31.8 ± 15.3	12.5 ± 10.0	Plasma glucose Pre: 9.1 ± 2.4 Post: 5.5 ± 2.4	A 45-minute of moderate activity (60% VO_{2peak}).
(Yardley et al., 2013)	Randomised crossover design	(n = 12) 10 males | 2 females	31.8 ± 15.3	12.5 ± 10.0	Plasma glucose Pre: 9.2 ± 3.4 Post: 5.8 ± 2.0	A 45-minute of moderate activity (60% VO_{2peak}).

(Yardley et al., 2019)	Randomised crossover design	(n = 12) 5 males | 7 females	52.7 ± 7.9	36.2 ± 12.7	<u>Plasma glucose</u> Pre: 6.1 ± 1.0 Post: 4.2 ± 2.5	A 45-minute of moderate activity (60% VO_{2peak}).
(Yardley, 2020b)	Randomised crossover design	(n = 12) 6 males | 6 females	34.0 ± 9.0	19.0 ± 12.7	<u>Capillary glucose</u> Pre: 9.9 ± 3.1 Post: 9.5 ± 3.4	A 45-minute of moderate activity (50% VO_{2peak}).

All glycaemia data presented as mean ± SD. Postprandial plasma glucose concentrations and capillary blood glucose concentrations reported pre-exercise (at 0 minutes) and post-exercise (immediately at the end of exercise). **VO_{2max}:** maximal oxygen consumption**;** **VO_{2peak}:** peak oxygen uptake.

Table 4.6 Effects of Chronic Aerobic Exercise on Glycaemia in Adults with Type 1 Diabetes

Study, year	Study design	Participants characteristics	Age (years)	T1D duration (years)	Glycaemia	Intervention
(Fuchsjager-Mayrl et al., 2002)	Non-randomised design	(n = 18) 7 males | 11 females	42.0 ± 10.0	20.0 ± 10.0	HbA1c (%) Pre: 7.30 ± 0.85 Post: 7.50 ± 1.16	Length of training 16 weeks. A 50-minute of vigorous activity (60 – 70% HRR) thrice weekly.
(Lee et al., 2020b)	Randomised crossover design	(n = 12) 6 males | 6 females	40.5 ± 10.0	15.8 ± 12.2	HbA1c (%) Pre: 8.63 ± 0.66 Post: 8.10 ± 1.04	Length of training 12 weeks. A 33-minute of vigorous activity (85 – 95% HR_{peak}) thrice weekly.
(Lehmann et al., 1997)	Non-randomised design	(n = 20) 13 males | 7 females	33.0 ± 7.7	11.0 ± 7.0	HbA1c (%) Pre: 7.60 ± 4.47 Post: 7.50 ± 4.02 Fasting plasma glucose (mmol/L) Pre: 8.30 ± 13.41 Post: 8.30 ± 16.09	Length of training 12 weeks. A 45-minute of MVPA (50 – 70% VO_{2max}), at least thrice weekly.
(Wallberg-Henriksson et al., 1982)	Non-randomised design	(n = 9) 9 males	35.0 ± 2.0	12.0 ± 1.0	HbA1c (%) Pre: 10.4 ± 2.1 Post: 11.3 ± 1.5	Length of training 16 weeks. A 60-minute of vigorous activity (exercise started at 50 W and increased by 50 W every 6-minute until exhaustion) thrice weekly.

Wrobel et al., 2018	RCT	(n = 10) 10 males	35.0 ± 6.0	22.0 ± 8.0	HbA1c (%) Pre: 7.44 ± 0.70 Post: 7.12 ± 0.70	Length of training 12 weeks. A 60-minute of vigorous activity (75% VO_{2max}) twice a week.
(Zinman et al., 1984)	Non-randomised design	(n = 13) 7 males | 6 females	30.0 ± 1.8	14.3 ± 3.2	HbA1c (%) Pre: 10.70 ± 1.08 Post: 10.30 ± 2.89 Fasting plasma glucose (mmol/L) Pre: 10.80 ± 5.41 Post: 11.20 ± 6.13	Length of training 12 weeks. A 45-minute of MVPA (60 – 85% HR_{peak}) thrice weekly.

All glycaemia data presented as mean ± SD. The HbA1c and fasting plasma glucose concentrations reported at baseline and post-exercise (at the end of training). **W:** watts; **VO_{2max}:** maximal oxygen consumption**; HR_{peak}:** peak heart rate.

4.B.3.3 Outcomes

4.B.3.3.1 A Single Bout of Aerobic Exercise and Glycaemia

4.B.3.3.1.1 Plasma Glucose Concentrations

A meta-analysis was conducted on six experimental studies (n = 58) that examined the difference in plasma glucose concentrations pre- and immediately post-exercise. Mean effect sizes of the studies ranged from −3.60 mmol/L to 1.20 mmol/L. Results of the analysis showed a significant decrease in plasma glucose concentrations immediately post-exercise (−2.24 mmol/L [95% CI: −3.28, −1.20]; $p < 0.0001$), with low heterogeneity ($I^2 = 17\%$), **Figure 4.B.1**. Publication bias was absent, as indicated by the Egger's regression test ($p = 0.24$). Subgroup analysis for exercise intensity was not conducted due to the consistent use of moderate-intensity PA across studies.

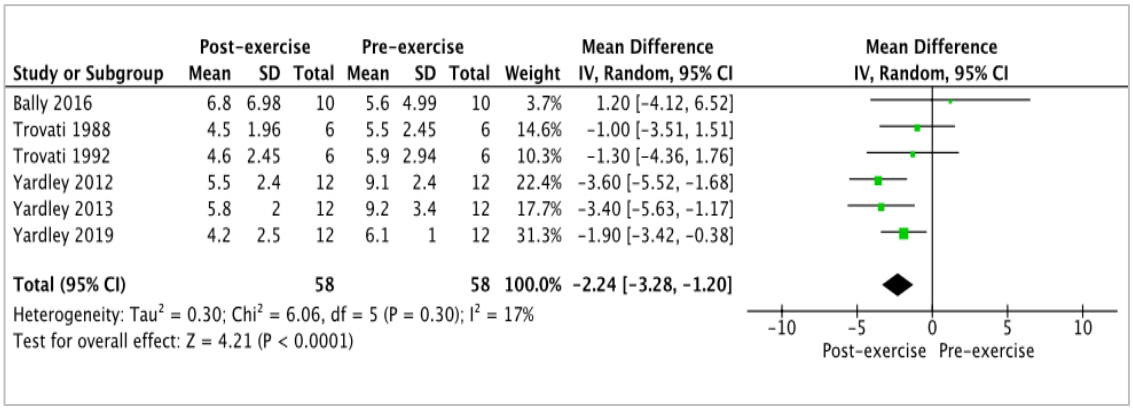


Figure 4.2 Forest Plot of Six Studies (n = 58) on Acute Aerobic Exercise and Plasma Glucose Concentrations in Type 1 Diabetes (Random-Effects Model)

4.B.3.3.1.2 Capillary Blood Glucose Concentrations

A meta-analysis was performed on two experimental studies (n = 19) to assess the difference in capillary blood glucose pre- and immediately post-exercise (at 45 minutes). The analysis indicated that there was no significant difference in capillary blood glucose concentrations immediately post-exercise, with a mean difference of (−2.50 mmol/L [95% CI: −6.42, 1.41]; $p = 0.21$; **Figure 4.3**). This

meta-analysis shows high heterogeneity (I^2 = 83%; p = 0.01), indicating that the variability in effect sizes across studies is likely due to difference between studies, such as exercise duration (e.g., 30-minute versus 45-minute) rather than random chance. Given the inclusion of only two studies on capillary blood glucose concentrations, no subgroup analysis was performed.

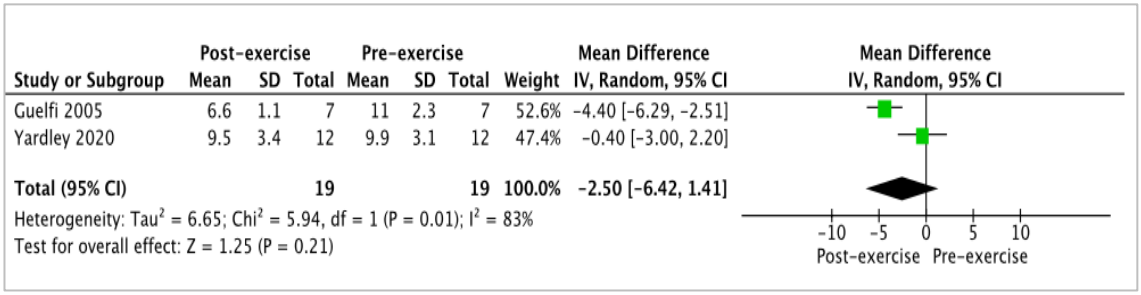


Figure 4.3 Forest Plot of Two Studies (n = 19) on Acute Aerobic Exercise and Capillary Glucose Concentrations in Type 1 Diabetes (Random-Effects Model)

4.B.3.3.2 Long-term Aerobic Exercise Training and Glycaemia

4.B.3.3.2.1 Glycated Haemoglobin Levels

Six experimental studies including 82 adults with T1D were included, all of which reported HbA1c levels. Exercise interventions focused on aerobic activities such as running, cycling, and walking, with sessions occurring two or three times per week and interventions lasting between 12 and 16 weeks. The mean effect sizes across individual studies ranged from −0.53 to 0.90%. The results of the analysis showed no significant difference in the HbA1c levels pre-exercise (baseline) and post-exercise durations (12 and 16 weeks), with a mean difference of −0.18% (95% CI: −0.55, 0.18; p = 0.33; I^2 = 0%; **Figure 4.4**). No heterogeneity or potential publication bias was evident, as indicated by the Egger's regression test (p = 0.52).

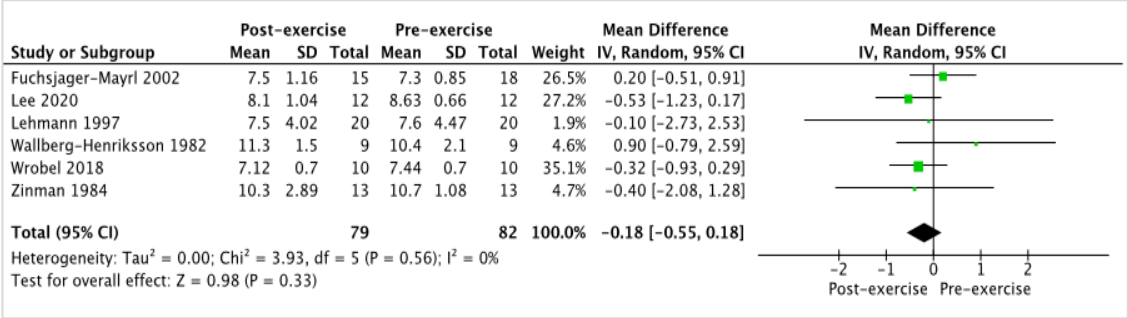


Figure 4.4 Forest Plot of Six Studies (n = 82) on Long-Term Aerobic Exercise and Glycated Haemoglobin in Type 1 Diabetes (Random-Effects Model)

Despite the overall effect of the meta-analysis for a long-term aerobic exercise training on the HbA1c levels not being significant (**Figure 4.4**), subgroup analyses were conducted to investigate whether the effect size varied based on exercise intensity (e.g., MVPA versus vigorous-intensity PA), weekly exercise durations (e.g., ≤ 135 minutes per week versus > 135 minutes per week), and length of training (12 weeks versus 16 weeks).

Subgroup analysis of long-term aerobic exercise training, including MVPA, did not reveal a statistically significant difference in HbA1c levels pre- and post-training, with a mean difference of −0.31% (95% CI: −1.73, 1.10; p = 0.85; I^2 = 0%). Similarly, subgroup analysis comparing MVPA, and vigorous-intensity PA showed no significant difference in HbA1c (mean difference: −0.15%; 95% CI: −0.59, 0.29; p = 0.50; I^2 = 22%). The subgroup analyses for exercise intensity are presented in **Figure 4.5.**

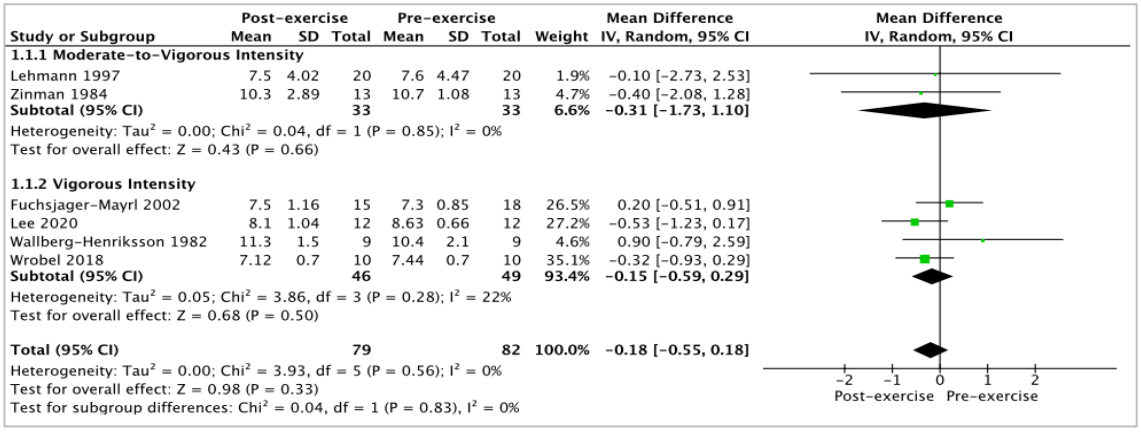


Figure 4.5 Forest Plot of Long-term Aerobic Exercise and Glycated haemoglobin in Type 1 Diabetes, with Subgroup analysis by Exercise intensity (Random-Effects Model)

Additionally, subgroup analyses for long-term aerobic exercise training, including exercise duration of ≤ 135 minutes did not show a statistically significant difference of −0.40% (95% CI: −0.84, 0.04; p = 0.07; I^2 = 0%). Similarly, for the weekly exercise duration of > 135 minutes, the mean difference was 0.30% (95% CI: −0.35, 0.96; p = 0.36; I^2 = 0%), **Figure 4.6**.

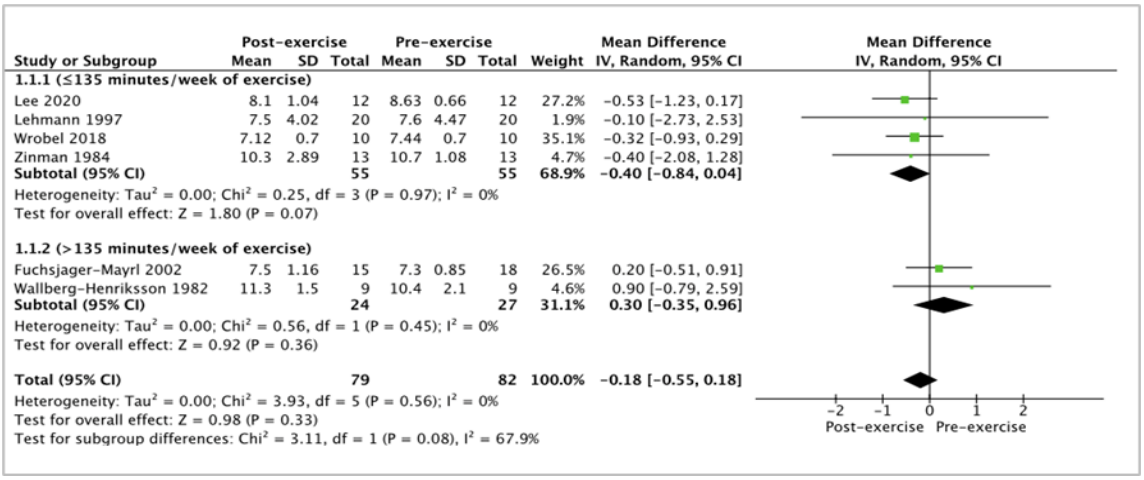


Figure 4.6 Forest Plot of Long-Term Aerobic Exercise and Glycated haemoglobin in Type 1 Diabetes, with Subgroup analysis by Weekly Exercise (Random-Effects Model)

Furthermore, subgroup analyses for long-term aerobic exercise training, including 12 weeks exercise intervention, did not reveal a significant difference of −0.40% (95% CI: −0.84, 0.04; p = 0.07; I^2 = 0%). Similarly, for the 16 weeks

exercise intervention, the mean difference was 0.30% (95% CI: −0.35, 0.96; *p* = 0.36; I^2 = 0%), **Figure 4.7**.

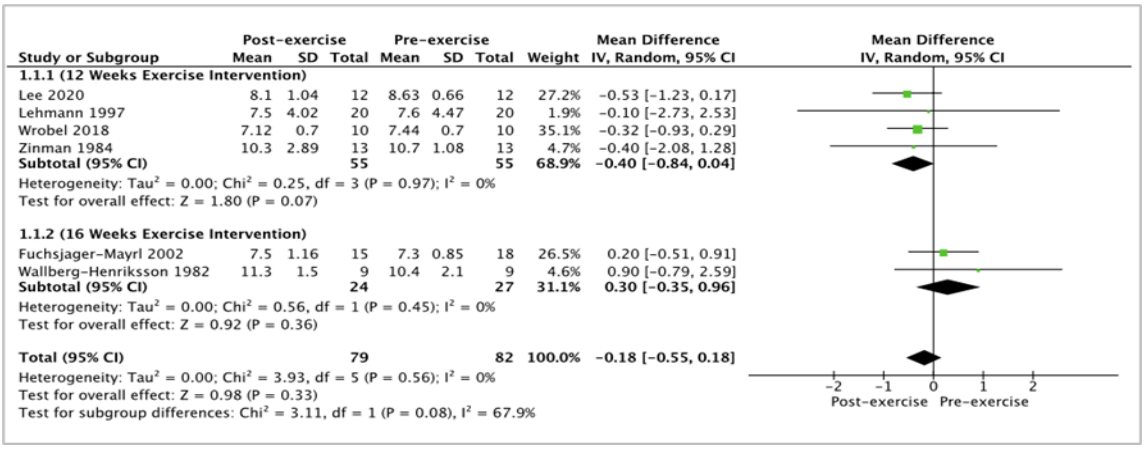


Figure 4.7 Forest Plot of Long-Term Aerobic Exercise and Glycated haemoglobin in Type 1 Diabetes, with Subgroup analysis by Exercise Intervention Duration (Random-Effects Model)

4.B.3.3.2.2 Fasting Plasma Glucose Concentrations

A meta-analysis was conducted on two experimental studies (n = 33) to evaluate the difference in fasting plasma glucose concentrations between baseline and following long-term aerobic exercise training. The results of the analysis showed no significant difference in fasting plasma glucose concentrations pre- and post-exercise training, with a mean difference of 0.32 mmol/L (95% CI: −3.68, 4.32; *p* = 0.87; I^2 = 0%; **Figure 4.B.7**). As only two studies reported fasting plasma glucose concentrations, no subgroup analysis was performed.

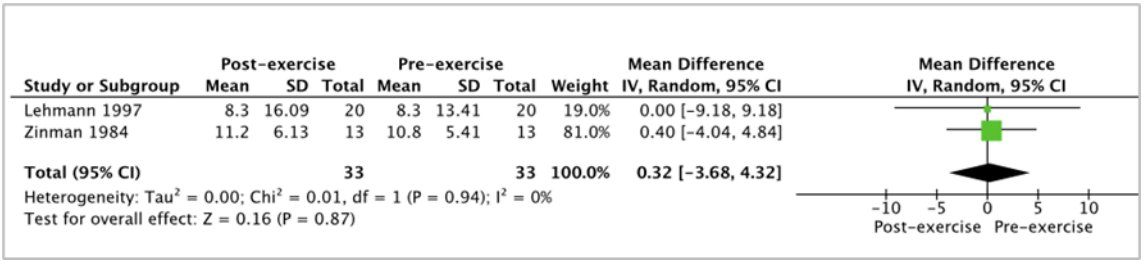


Figure 4.8 Forest Plot of Two Studies (n = 33) on Long-Term Aerobic Exercise and Fasting Glucose Concentrations in Type 1 Diabetes (Random-Effects Model

4.B.3.4 Quality Assessment for Included Studies

For the randomised studies, the quality assessment was using the RoB2 tool in

one RCT and eight crossover deign studies **(Appendix A.7)**. The overall risk was considered ‘some concerns’ for the one RCT study and seven crossover studies due to lack of information on randomisation concealment. Nevertheless, one crossover study was assessed as having a ‘low risk’ of bias. For the non-randomised study, the quality assessment for one study was indicated as a ‘low risk’ of bias using the ROBINS-I tool **(Appendix A.8).**

4.B.4 Discussion

The present meta-analysis aimed to examine the impact of a single bout of aerobic exercise and long-term aerobic exercise training on glycaemia in adults with T1D. Fourteen experimental studies involving 159 adults with T1D were meta-analysed. Findings demonstrate that a single bout of exercise results in a significant improvement post-exercise in plasma glucose concentrations only. In addition, long-term aerobic training did not result in significant differences in either HbA1c levels or fasting plasma glucose concentrations post-training. Additionally, subgroup analyses indicated that exercise intensity, weekly exercise duration, or length of exercise training did not influence the HbA1c levels.

4.B.4.1 Effect of a Single Bout of Aerobic Exercise on Glycaemia

In total, eight controlled trials (seven randomised and one non-randomised) involving 77 adults with T1D were conducted to assess the difference in plasma glucose concentrations and capillary blood glucose concentrations following a single bout of aerobic exercise. Our results confirm that a single bout of aerobic exercise reduces plasma glucose concentrations by −2.24 mmol/L (95% CI: −3.28, −1.20; $p < 0.0001$) immediately post-exercise, with low heterogeneity observed ($I^2 = 17\%$). Low heterogeneity across the studies is likely due to the consistency in study design, population characteristics, and intervention

protocols. For example, when studies have similar methodologies, such as consistent participant inclusion criteria, standardised measurement techniques, and comparable intervention durations, the variation in outcomes is minimised, resulting in lower heterogeneity. After considering the findings regarding the positive influence of a single bout of aerobic exercise on plasma glucose concentrations, it is important to highlight that the intensity of exercise used in these studies was moderate. This moderate-intensity PA, defined as approximately 50 – 60% of VO_{2max} and VO_{2peak} based on the ACSM guidelines (Pollock et al., 1998), consistently resulted in improvement in plasma glucose concentrations.

Our findings suggest that a single bout of aerobic exercise is more effective intervention for reducing plasma glucose concentrations in adults with T1D compared to healthy individuals with a mean difference of −0.05 mmol/L, 95% CI: 0.22, 0.13; p = 0.002) (Frampton et al., 2021). This highlights the potential of acute aerobic exercise as a valuable approach for improving glucose control in T1D. Additionally, our findings correspond with research demonstrating a decrease of -5.4 mmol/L in postprandial plasma glucose concentrations during aerobic exercise session in adolescents with T1D (Särnblad et al., 2021). The larger mean difference of 5.4 observed in adolescent with T1D compared to 2.24 in adults suggests that age may play a significant role in the efficiency of acute exercise as glucose-lowering intervention, highlighting the potential for greater benefits in younger individuals with T1D.

Mechanistically, a single bout of exercise has been shown to cause immediate increases in glucose uptake into the skeletal muscle, both during and for several hours post-exercise, leading to improved insulin sensitivity and decreased blood glucose concentrations (Bird and Hawley, 2017; Zheng et al.,

2020). Furthermore, exercise promotes glycogen depletion within muscle cells, promoting subsequent replenishment during post-exercise recovery phase (Soo et al., 2023). Over the longer term, exercise induces adaptations such as increased muscle mass and enhanced insulin sensitivity, contributing to sustained improvements in glucose control (Bird and Hawley, 2017). Consequently, these highlight the significance of regular exercise training in optimising metabolic responses and maintaining glucose regulation, particularly in those with T1D.

The present meta-analysis reported no significant difference in capillary blood glucose concentrations following a single bout of aerobic exercise in adults with T1D ($p > 0.05$). The concentration of glucose found in capillary blood glucose, frequently used by individuals with diabetes to independently monitor their blood glucose concentrations (Walker, 2004). Capillary glucose measurements can be constituted as a valuable alternative to venous blood glucose measurements in population-based studies (Kruijshoop et al., 2004). High heterogeneity was observed ($I^2 = 83\%$; $p = 0.01$), but only two studies with varying methodologies were included in the meta-analysis.

5.B.4.2 Effect of Long-term Aerobic Exercise Training on Glycaemia

In total six experimental studies (2 randomised and 4 non-randomised) involving 82 adults with T1D were analysed to assess the difference in HbA1c levels post-exercise training. Our analysis found no significant difference in HbA1c levels following long-term aerobic exercise training ($p > 0.05$). However, a meta-analysis included 12 studies with a total of 171 participants with T1D (children, adolescent, and adults) found that the structured exercise (both aerobic and resistance exercises) were associated with the mean difference of −0.23% (95% CI: −0.44, −0.02) (Tonoli et al., 2012). This indicates that regular aerobic exercise

can lead to a meaningful improvement in chronic glycaemic control in T1D, particularly when the training is sustained over a longer period. The lack of a significant effect in our review, which included only 85 adults, may be due to the small sample size, older participant age, and possibly lower baseline HbA1c levels, all of which reduce the likelihood of detecting meaningful changes compared to studies involving younger or more diverse populations.

Subgroup analyses based on exercise intensity, weekly exercise duration, and exercise intervention duration did not reveal a statistically significant difference in HbA1c levels. A possible reason for the non-significant results in HbA1c levels could be attributed to the small sample size of participants in the six included studies, which may limit the sufficient power to detect significant difference in HbA1c levels. Additionally, other factors such as methodological differences (participants age, gender, and diabetes duration) and variability in study designs (randomised versus non-randomised study design). In a recent systematic review and meta-analysis encompassing 76 studies, the relationship between 24-hour movement behaviours, particularly PA, and glycaemic control was investigated, revealing a significant favourable association between PA and HbA1c (−0.22% [95% CI: −0.35, −0.08]; p = 0.001) in adolescents with T1D (Patience et al., 2023). Additionally, subgroup analysis for exercise intensity (e.g., low-, moderate-, and vigorous-intensity PA, as well as MVPA) demonstrated a favourable association with HbA1c levels (Patience et al., 2023). Our findings differ likely due to the smaller number of studies (14 versus 76), which may reduce statistical power, as well as differences in study design and participant characteristics.

Numerous studies have measured changes in fasting plasma glucose concentrations response to exercise interventions. An individual study by Asuako

and colleagues (Asuako et al., 2017) in 12 participants with diabetes reported that eight weeks aerobic training decreased fasting plasma glucose concentrations by 4.16 mmol/L (from 9.56 to 5.40). However, our meta-analysis of two studies found no significant difference in fasting plasma glucose concentrations following long-term aerobic exercise training in 33 adults with T1D ($p > 0.05$). This lack of significance might be due to attributed to methodological difference such as exercise intensity and participants characteristics.

4.B.4.3 Study Strengths and Limitations

The current meta-analysis has several strengths, including experimental studies that evaluated the metabolic effects of exercise interventions in the context of both acute aerobic exercise and chronic aerobic training. Exercise intensity in the included studies was carefully standardised according to the guidelines set by the ACSM across various measurements domains. This helped ensure consistency and comparability among the different research findings.

Despite this, the limitations of the current meta-analysis must be mentioned. Small sample studies were included, which may limit the statistical power to detect effect. The lack of variation in exercise intensity limits the ability to perform subgroup analyses for acute aerobic exercise, which can provide insights into how different intensities might affect glycaemia differently. Additionally, the differences in the exercise duration in the acute exercise studies could also be viewed as a limitation. Some of the outcomes could not undergo subgroup analysis because there were only two studies included for each glycaemic outcome (e.g., capillary blood glucose concentrations and fasting plasma glucose concentrations). Selection bias may be present, as certain studies did not clearly report the allocation concealment.

4.B.5 Conclusion

This meta-analysis demonstrates a beneficial effect of acute aerobic exercise on plasma glucose concentrations, consistent with previous studies findings. However, it did not indicate a significant effect on capillary blood glucose concentrations, and no impact was observed on HbA1c or fasting plasma glucose concentrations following chronic aerobic exercise training. As such, future research should employ longer follow-up periods, use standardised exercise protocols and incorporate CGM to more accurately evaluate the relationship between exercise and glucose control in individuals with T1D.

4.B.4 Chapter Summary

- Part A of our systematic review aimed to quantify the amount of PA and SBs that adults with T1D undertaken. Our findings revealed that adults with T1D are generally more physically inactive and spend more time in SBs. This highlights a significant area of concern, as increased SB are associated with various adverse health outcomes. Additionally, age, sex, BMI, education levels, and employment status influence the levels of PA.
- Part B of our review focused on conducting a meta-analysis to assess the impact of acute exercise and chronic aerobic exercise training on glycaemia in adults with T1D. The analysis demonstrated a mean reduction of 2.24 mmol/L in plasma glucose concentrations immediately post-exercise in adults with T1D. Furthermore, the analysis did not observe significant differences in HbA1c levels and fasting plasma glucose concentrations pre- and post-chronic aerobic exercise training. This remained even when studies were sub-grouped by exercise intensity (MVPA versus vigorous-intensity PA, weekly exercise duration (≤ 135 minutes per week versus > 135 minutes per week), and exercise intervention duration (12 weeks duration versus 16 weeks duration).
- It is noteworthy that this review did not include studies specifically reporting the impact of SBs on low levels of PA on glycaemia. Unfortunately, such data were absent in the research reviewed, potentially due to a lack of studies in the area.

Chapter 5 – Characterising the Impact of Daily Activities on Glucose Control in Adults with Type 1 Diabetes: An Observational Study

What do we know? Activities of daily living, including recreational activities, contributing significantly to overall daily PA.

Key issues: There is a need to develop specific self-management guidelines for individuals with T1D to safely engage in activities of daily living, as current guidelines focus predominantly on structured exercise. However, there is no empirical research assessing the glucose demands of daily living activities in individuals with T1D.

Chapter aims: To characterise the impact of objectively measured daily activities and SBs on the glucose control, and to explore the relationships between self-reported and objective measures of sedentary time in adults with T1D.

Chapter implications: Understanding how daily activities affect the blood glucose concentrations provides practical insights for managing T1D. Building on the quantified levels of PA and SBs and their glycaemic impact from Chapter 4, this chapter highlights the importance of everyday activities. It sets the stage for Chapter 6, which explores how interrupting prolonged sitting with low-intensity PA can further optimise glucose control.

5.1 Introduction

The management of T1D presents unique challenges, particularly in maintaining glucose control. Unlike T2D, where insulin production is impaired but still present (Reed et al., 2021), individuals with T1D must carefully balance insulin

administration with their activity levels (Riddell et al., 2017). This balance is important because PA can significantly impact blood glucose concentrations, often increasing the risk of hypoglycaemia (Younk et al., 2011). Despite advances in diabetes research, the specific glucose demands and risks associated with various daily activities for T1D individuals remain under-characterised.

To improve glucose control, current guidelines and recommendations are predominantly focused on exercise, recommending at least 150 minutes of moderate-intensity PA, 75 minutes of vigorous-intensity PA, or a combination of them per week, with no more than two consecutive days without activity (Colberg, 2008; Colberg et al., 2016; World Health Organisation, 2020). No guidance is currently provided for low-intensity PA or activities on daily living. Individuals with T1D typically aim to lead a normal lifestyle and participate in daily activities; however, they often struggle to maintain optimal blood glucose concentrations due to the demanding routine of constant monitoring, insulin administration, and managing carbohydrate intake alongside PA (Tong et al., 2022). The CGM may enhance glucose control in individuals with T1D by providing real-time glucose readings, which aid in preventing glucose fluctuations (Rodbard, 2016). Integrating CGM with wearable activity devices allows for personalised management strategies, improving individual outcomes by linking PA, SB, and glucose control. This information can aid individuals with diabetes and healthcare professionals make informed decisions regarding diabetes management (McMillan et al., 2018; McMillan et al., 2020; Zaharieva et al., 2023).

Several recent studies have explored the impact of PA on glycaemia using various wearable devices integrated with CGM measures across different population (El Fatouhi et al., 2022; Gal et al., 2022). A study by Gal and colleagues (Gal et al., 2022) involved 52 youth with T1D, who were divided into

two groups based on their PA levels during free-living conditions (less active: engaged in less than 200 MET-minutes per day of PA, and more active: achieved 600 or more MET-minutes per day of PA), as measured by the CGM and PA trackers. In the more active group, participants showed better glucose control with an average mean blood glucose concentration of 10.1 ± 1.8 mmol/L, spending 49% of their time in a target range and 19% in hyperglycaemia (> 13.9 mmol/L), while less active group had a higher average mean glucose concentration of 12.8 ± 4.1 mmol/L, with only 26% in TIR and 37% in hyperglycaemia (Gal et al., 2022). Notably, both groups spent a minimum amount of time in hypoglycaemia, and no significant increase in hypoglycaemia (< 3.9 mmol/L) was observed in either group (Gal et al., 2022). Additionally, in 85 adults without diabetes it was found that an increase of 1000 steps per day led to a decrease in mean blood glucose concentration by 0.01 mmol/L the following day under free-living conditions (El Fatouhi et al., 2022).

Despite existing research, gaps persist in our understanding of how the interplay between daily activities such as SBs, low-intensity PA, and MVPA affects glucose control in adults with T1D. Previous studies have highlighted that SB and PA (e.g., low-intensity PA and MVPA) are interconnected within a 24-hour cycle, emphasising the need for comprehensive measurement and analysis methods to capture interactions of these behaviours (Rosenberger et al., 2019). Previous research has also shown that meeting integrated movement behaviour guidelines, which include recommendations for SB and PA, is associated with better health outcomes, such as reduced stress and improved overall well-being (Kastelic et al., 2021). However, there is a lack of empirical research assessing time spent in SBs among adults with T1D using objective measures such as accelerometry. According to our systematic review and meta-analysis (Chapter

4, Part A), existing studies predominantly rely on self-reported data, which may lead to overestimation or underestimation due to their limited validity relative to device-based measures (Shephard, 2003). Addressing these gaps is crucial as it might provide further insight for personalised management strategies, enhances glucose control, and mitigates the risk of diabetes-related complications.

Therefore, in the present chapter we employed device-based measures for PA (GENEActiv) and SBs (ActivPAL) along with a CGM to assess the impacts of daily activity levels on CGM metrics in adults with T1D. Furthermore, we explored the associations of sedentary time between self-reported measure (IPAQ) and device-based measures (GENEActiv and ActivPAL) to better understand the reliability of different assessment measures.

5.2 Methods

5.2.1 Study Design

This was a single-centre observational study conducted at the School of Food Science and Nutrition, University of Leeds, between September 2023 and February 2024. It was approved by the NHS Research Ethics Committees of reference number 23/PR/0500. Eligible participants provided signed written consent before participating, as shown in **Appendix B, Table B.1**.

5.2.2 Eligible Criteria and Assessment

To be eligible for the study, participants had to meet the following criteria: 1) be male or female between 18 and 70 years old, diagnosed with T1D, and treated with a stable insulin regimen for at least six months, defined as no major changes in insulin type (CSII or MDIs) or significant dose adjustments beyond routine modifications; 2) have a clinical diagnosis of T1D with a duration of at least five years. Participants were not eligible if they: 1) were pregnant or had overt

diabetes complications (e.g., end-stage renal failure requiring dialysis); 2) had recent diabetic ketoacidosis (within the last six months) or hypoglycaemia unawareness, as assessed by the Clarke method (Clarke et al., 1995).

5.2.3 Participant Recruitment

Participants were recruited through various advertisements, including university channels (i.e., university mailing lists, website, and local notice boards on campus), local NHS general practitioners and dental clinics, gyms, as well as local and national diabetes charities, and individuals who had previously taken part in research and had consented to be contacted about future research. An initial phone call and WhatsApp were made available to interested participants to discuss the study, address any questions, and collect their contact information for sending a study information pack.

5.2.4 Study Protocol

Participant information sheet and medical screening questionnaire were used to assess participant medical history (e.g., free from hypoglycaemia unawareness and overt diabetes complications, no recent history of diabetic ketoacidosis within the last six months), as shown in **Appendix B, Tables B.2 and B.3**. These were sent by the researcher to interested participants to assess eligibility. If a participant is found eligible, a preliminary visit either in person or online was scheduled. Following confirmation of eligibility at this meeting, participants wore three devices continuously for 14 days: a CGM device to measure blood glucose continuously (FreeStyle Libre Pro iQ (Abbott Diabetes Care), a wrist-worn accelerometer to measure PA (GENEActiv; Activinsights Ltd, Cambridge, UK), and a thigh-worn accelerometer to measure SBs (ActivPAL; PAL Technologies Ltd, Glasgow, Scotland). The duration of 14-day was chosen to capture variations

in daily activity patterns and glycaemic metrics over a representative period, according for both weekdays and weekends.

5.2.4.1 Preliminary Visit

All eligible participants were required to attend a medical screening session at the university laboratory for clinical assessments. If a face-to-face visit was not feasible, an online option was provided. During the laboratory visit, the researcher recorded participants medical history data, including age, sex, diabetes duration, and insulin therapy. Anthropometric measurements including body mass and height using an electronic body mass scale with stadiometer (Seca 764, GmbH & Co. KG, Hamburg, Germany) were also collected during the laboratory visit, while for the online visit, height and body mass were self-reported.

During both the in-person and the online visits, participants were required to complete a consent form and two validated questionnaires – the IPAQ-LF (**Appendix B, Table B.4**) (Cleland et al., 2018) and the BAPAD-1 (**Appendix B, Table B.5**) (Dube et al., 2006; Brazeau et al., 2012a) – to assess PA status and perceived barriers to engaging in PA. For the online visit, electronic versions of the documents and a personalised link were provided to participants to upload the completed consent form, IPAQ-LF and BAPAD-1 questionnaires to a secure University server (Microsoft OneDrive). Subsequently, participants were fitted with a CGM sensor for continuous glucose scanning, along with GENEActiv and ActivPAL devices to record SBs and PA levels throughout the study period. If participants underwent the online preliminary visit, instructions on fitting the sensor and accelerometers were provided during an online meeting, in which a researcher (AA) guided the participant through the placement and procedures for fitting the devices via Microsoft Teams or Zoom. Participants were instructed to return the CGM and accelerometer devices either in person or via post using a

prepaid envelope at the end of the 14-day study period. Eligible participants were instructed to maintain their usual diet and daily routines during the 14-day study.

5.2.5 Measures

5.2.5.1 Anthropometric

Participants body mass and height were measured by the researcher (AA) during the laboratory visit. Body mass and height were measured with participants wearing light clothing and no shoes, using an electronic weighing scale with stadiometer (Seca 764, GmbH & Co. KG, Hamburg, Germany; **Figure 2.1**), and the BMI was calculated as body mass (kilogram) divided by the square of height (meters). While for online visit, the researcher asked participants to self-report their height and body mass.

5.2.5.2 Continuous Glucose Monitoring

Details on activating the sensor, proper placement, and data retrieval instructions are outlined in Chapter 2, **section 2.2.3**. The sensor remained in place for 14 days and was then removed and returned to the researcher. Blood glucose was continuously measured during the study period using a CGM sensor fitted on the back of the upper arm of participants during the preliminary visit.

5.2.5.3 Accelerometry

5.2.5.3.1 GENEActiv

Specific information regarding the GENEActiv and usage protocol is provided in Chapter 2, **section 2.2.4.1**. GENEActiv accelerometer tracks the intensity and duration of PA by detecting and recording movements. The researcher configured the GENEActiv accelerometer using the GENEActiv software, and the participants wore the device continuously on their non-dominant wrist for 14

consecutive days following the preliminary visit. Afterwards, the participants returned the device either by post or in person.

5.2.5.3.2 ActivPAL

ActivPAL setup and usage details summarising the information covered in Chapter 2, **section 2.2.5.1**. The accelerometer was worn on the thigh continuously for 14 days following the preliminary visit and then returned to the researcher either by post or in person. The ActivPAL accelerometer provides detailed information about a person's PA patterns, including sitting/lying, standing, and sit-to-stand postures (Aminian and Hinckson, 2012).

5.2.5.4 Self-reported Physical Activity Questionnaire

More information about the IPAQ-LF is provided in Chapter 2, **section 2.2.4.2**. The IPAQ-LF self-reported measure was completed by the participants during the preliminary visit to establish a baseline assessment of participants PA levels that provides valuable insight into participants activity patterns and behaviours.

5.2.5.5 24-hour Food Diary Assessment

Participants were asked to complete a weighed food diary for three days of their choosing during the 14-day CGM measurement period, and to submit the diary at the end of each day. These data were collected via Myfood24 https://www.myfood24.org/, which is a validated online dietary assessment tool used to measure the 24-hour food diary (Wark et al., 2018). This period included two non-consecutive weekdays and one weekend day, as it is typical when attempting to measure habitual intake using a self-report tool (Thompson and Byers, 1994; Willett, 2012). While under-reporting is a known limitation of self-reported food diaries, dietary intake was collected for context rather than detailed analysis and was not systematically validated (i.e., not checked for accuracy

using objective methods). On the day that the participant chose to report their food diary, a link was sent by the researcher at 9 am. Myfood24 instruction document was also provided to all participants during the preliminary visit to enhance the accuracy of the information reported.

Myfood24 incorporates various methods, including an optional quick list, food search feature, reminder for forgotten items, and a final review before diary submission (Carter et al., 2015). Participants could search for and add specific brands of food or drink where possible, or non-branded (generic) equivalents when an exact match could not be found, as well as select portion sizes from pictures the reflect the amount consumed or drunk, use the recipe builder, and review and submit their diary. Subsequently, the data is extracted and downloaded into two Microsoft Excel files (participant summary and participant breakdown). The participant summary file includes ID, diary date, total energy (kcal/kJ), macronutrients, micronutrients, and water (Albar et al., 2015).

5.2.6 Sample size

The sample size (n = 40) was determined using a critical value of 1.96 corresponding to a 95% CI and a significant level (*p*-value) of 0.05. With a SD of 5 mmol/L and a margin of error of one mmol/L, the sample size was calculated to ensure adequate power to detect statistically significant difference in TIR as the primary outcome, as well as in secondary outcomes including mean blood glucose concentrations, TAR, TBR, and glycaemic variability. The sample size calculation was based on the following formula:

$$\frac{\left(Z_{1-\frac{\alpha}{2}}\right)^{2*}(\mathrm{p})(\mathrm{q})}{(d)^2}$$

$Z_{1-\frac{\alpha}{2}}$ = Critical value and a standard value for the corresponding level of

confidence (1.96 = 95% CI; p = 0.05).

σ^2 = SD of 5 mmol/L.

d = margin of error (1 mmol/L).

5.2.7 Statistical Analysis

Out of the 47 participants deemed to be eligible, 40 individuals completed the 14-day measurement period included in the analysis. Seven participants were excluded from the analysis due to incomplete data, with five individuals failing to meet the wear time criteria for the CGM, two for the GENEActiv.

Correlation and General linear model analyses (GLMs) were conducted on data collected from the 40 completers. Mean daily CGM metrics were calculated using the manufacture software over the 14-day period, and included mean blood glucose concentrations, TIR, TAR, TBR, and the glycaemic variability. PA was analysed using the average time in minutes per day for low-, moderate-, and vigorous-intensity PA measured by the GENEActiv device, while SBs were analysed using the average time in minute per day for standing, sitting, lying, seated transport, and sit-to-stand transitions measured by the ActivPAL. This enabled us to retrospectively align the GENEActiv device data across different PA intensities and the ActivPAL device data across different SBs, and to match daily glucose concentrations from the CGM monitor to their corresponding activities for each day of the two tracking weeks. Kolmogorov-Smirnov test was used to assess the data normality. GLMs were employed to determine the effect of various PA levels and SBs on CGM metrics, while considering covariates such as age, sex, BMI, diabetes duration, bolus insulin, and TDD of insulin over a 14-day period. Additionally, Pearson correlation analysis (r) was conducted to explore the relationships between sedentary time obtained from objective measures (GENEActiv and ActivPAL) and the self-

reported measure (IPAQ-LF), with correlations calculated to quantify the strength and direction of the linear relationships between sedentary time from each measure. Statistical analyses were performed using SPSS (IBM SPSS statistics, version 29), and *p*-values of < 0.05 were considered statistically significant.

5.3 Results

5.3.1 Participants Characteristics and Insulin Usage

Table 5.1 presents the baseline characteristics and insulin usage of the participants. The mean age of the participants was 46.00 ± 14.49 years, with a majority being female (62.50%). The mean disease duration since diagnosis with T1D was 22.05 ± 15.02 years. Participants had an average body mass of 75.14 ± 13.08 kg; a height of 168.65 ± 9.27 cm; a BMI of 26.54 ± 5.11 kg/m^2; bolus insulin of 20.52 ± 15.60 units, and TDD of insulin 40.22 ± 24.43 units.

Table 5.1 Participants Characteristics and Insulin Usage

Baseline Characteristics	**All data (n = 40)**
Age (years)	46.00 ± 14.49
Sex Male (%)	15 (37.50)
Female (%)	25 (62.50)
Length of diagnosis (years)	22.05 ± 15.02
Body mass (kg)*	75.14 ± 13.08
Height (cm)*	168.65 ± 9.27
BMI (kg/m^2)	26.54 ± 5.11
Bolus insulin (IU)	20.52 ± 15.60
TDD of insulin (IU)	40.22 ± 24.43

BMI: body mass index; **TDD**: total daily dose; **IU:** units. Continuous data are presented as mean ± SD, categorical data are presented as number (%).

**:* The body weight and height of 13 participants were measured, while 27 participants self-reported their body mass and height.

Mean CGM metrics for 14 days are presented in **Table 5.2**. The mean blood glucose concentrations were 8.74 ± 2.23 mmol/L, with TIR (3.9 – 10.0

mmol/L) at 66.01 ± 18.57%. Hyperglycaemia (TAR 1 > 10.0 mmol/L) was 19.35 ± 8.94% and (TAR 2 > 13.9 mmol/L) was 9.65 ± 14.39%. Hypoglycaemia (TBR 1 < 3.9 mmol/L) was 4.07 ± 4.27% and (TBR 2 < 3.0 mmol/L) was 0.90 ± 2.11%. Additionally, the glycaemic variability was 32.48 ± 6.95%. The mean wear time for the devices was as follows: 13.75 ± 1.13 days for CGM, 13.75 ± 0.78 days for GENEActiv, and 13.73 ± 0.93 days for ActivPAL, **Table 5.2**.

Table 5.2 Continuous Glucose Monitoring Metrics and Devices Wear Time Over a 14-day Period

Variables	**All data (n = 40)**
CGM Metrics (14 days)	
Mean blood glucose (mmol/L)	8.74 ± 2.23
TIR (%)	66.01 ± 18.57
TAR 1 (%)	19.35 ± 8.94
TAR 2 (%)	9.65 ± 14.39
TBR 1 (%)	4.07 ± 4.27
TBR 2 (%)	0.90 ± 2.11
Glycaemic variability (%)	32.48 ± 6.95
Wear Time Compliance	
CGM (days)	13.75 ± 1.13
GENEActiv (days)	13.75 ± 0.78
ActivPAL (days)	13.73 ± 0.93
Total devices	13.74 ± 0.95

CGM: Continuous glucose monitoring; **TIR:** Time in range; **TAR**: Time above range; **TBR:** Time below range. Continuous data are presented as mean ± SD.
*: The body mass and height of 13 participants were measured, while 27 participant**s** self-reported their body mass and height.

5.3.2 Quantifying Physical Activity and Sedentary Behaviours

5.3.2.1 Objective Measures

Physical Activity and SBs from the GENEActiv and the ActivPAL measures are presented in **Table 5.3**. During the 14-day study period, analysis of the GENEActiv data indicated that individuals performed an average of 260.25 ±

206.50 minutes per day of low-intensity PA, 92.22 ± 75.90 minutes per day of moderate-intensity PA, and 2.50 ± 6.13 minutes per day of vigorous-intensity PA. This suggests that participants were active, especially with low- and moderate-intensity PA. Sedentary time was also measured using the GENEActiv, with an average of 705.97 ± 1166.65 minutes per day.

Sedentary behaviours measured by the ActivPAL during the study period indicated that individuals spent an average of 244.42 ± 108.42 minutes per day of standing, 511.67 ± 177.40 minutes per day of lying, 457.19 ± 158.81 minutes per day of sitting, and 75.55 ± 98.47 minutes per day of seated transport, and 45.41 ± 19.86 sit-to-stand transitions per day. Total sedentary time including sitting and seated transport averaged 548.14 ± 150.34 minutes per day.

5.3.2.2 Self-reported Measures

Data collected from the IPAQ-LF questionnaire are presented in **Table 5.3**, and indicated that on average participants engaged in 564.30 ± 657.04 MET-minutes per week of low-intensity PA, 285.50 ± 422.71 MET-minutes per week of moderate-intensity PA, and 723.00 ± 1035.83 MET-minutes per week of vigorous-intensity PA. These results demonstrate that participants engaged in more vigorous-intensity PA compared to low- and moderate-intensity PA. Total sedentary time was also reported using the IPAQ-LF, with an average of 337.50 ± 161.00 minutes per day.

Table 5.3 Quantification of Physical Activity and Sedentary Behaviours using Objective and Self-reported Measures

Variables	**All data (n = 40)**
GENEActiv measure	
Low-intensity PA (minutes/day)	260.25 ± 206.50
Moderate-intensity PA (minutes/day)	92.22 ± 75.90
Vigorous-intensity PA (minutes/day)	2.50 ± 6.13

Sedentary time (minutes/day)	705.97 ± 1166.65
ActivPAL measure	
Standing (minutes/day)	244.42 ± 108.42
Lying time (minutes/day)	511.67 ± 177.40
Sit to stand transitions (per day)	45.41 ± 19.86
Sitting time (minutes/day)	457.19 ± 158.81
Seated transport time (minutes/day)	75.55 ± 98.47
Sedentary time (minutes/day)	548.14 ± 150.34
IPAQ (self-reported measure)	
Low-intensity PA (MET-minutes/week)	564.30 ± 657.04
Moderate-intensity PA (MET-minutes/week)	285.50 ± 422.71
Vigorous-intensity PA (MET-minutes/week)	723.00 ± 1035.83
Sedentary time (minutes/day)	337.50 ± 161.00
Data are presented as mean ± SD.	

5.3.3 Association between Objective and Self-reported Measures of Sedentary Time

Correlation analyses were conducted to examine the associations between objective measures (GENEActiv and ActivPAL) and self-reported measure (IPAQ) of sedentary time, **Table 5.4**. The results showed no significant correlation between GENEActiv and ActivPAL (r = 0.22; p = 0.17). Additionally, no significant correlations were found between GENEActiv and IPAQ (r = 0.14; p = 0.39), or between ActivPAL and IPAQ (r = 0.04; p = 0.82).

Table 5.4 Pearson's Correlations between Objective and Self-reported Measures of Sedentary Time

GENEActiv & ActivPAL		**GENEActiv & IPAQ**		**ActivPAL & IPAQ**	
r	***P*-value**	***r***	***p*-value**	***r***	***P*-value**
0.22	0.17	0.14	0.39	0.04	0.82

***r*:** Pearson's Correlation**.** Pearson's significant correlations at $p < 0.05$.

5.3.4 Association between Physical Activity and Continuous Glucose Monitoring Metrics

To assess whether activities of low-, moderate-, or vigorous-intensity PA (as measured by the GENEActiv measure) were associated with glucose control over a 14-day period, three multiple regression analyses were conducted. In each analysis, a specific CGM metric (e.g., mean blood glucose concentrations, TIR, TAR, TBR, and glycaemic variability) was regressed with low-, moderate-, and vigorous-intensity PA as predictors, **Table 5.5**. Model 1 explored the unadjusted relationships, Model 2 was adjusted for age, sex, BMI, and diabetes duration, while Model 3 included further adjustments for bolus insulin and TDD of insulin.

For the mean 24-hour blood glucose concentrations, in Model 1, moderate-intensity PA was found to be a significant predictor (B = 0.001; p = 0.01). This model indicated that for every additional minute per day of moderate-intensity PA, there was an estimated increase of 0.001 mmol/L in the mean blood glucose concentrations. However, low and vigorous activities were found not to predict mean 24-hour blood glucose concentrations ($p > 0.05$). After adjusting for age, sex, BMI, and diabetes duration in Model 2, vigorous-intensity PA indicated as a significant predictor of mean 24-hour blood glucose concentrations (B = −0.02; p = 0.01), suggesting that for each one-minute increase per day of such activity, mean blood glucose concentrations decrease by 0.02 mmol/L. However, moderate-intensity PA was no longer significant ($p > 0.05$), and low-intensity PA remained non-significant ($p > 0.05$). Additionally, in Model 2, a statistically significant association was observed between sex and mean 24-hour blood glucose concentrations, with males having higher mean blood glucose concentrations compared to females, by approximately 0.08 mmol/L (p = 0.01). Age, BMI, diabetes duration were not significant predictors of mean 24-hour blood

glucose concentrations ($p > 0.05$). In Model 3, none of the predictors were found to be significant for mean 24-hour blood glucose concentrations ($p > 0.05$).

For TIR, moderate-intensity PA was found to be significant predictor in Model 1 (B = −0.10; $p = 0.04$), suggesting that each additional minute per day of such activity was associated with a 0.10% reduction in TIR. Conversely, low- and vigorous-intensity PA did not show significant effects on TIR ($p > 0.05$). In Model 2, vigorous-intensity PA was a significant predictor, with an estimated increase of 2.92% in the TIR for each additional minute per day of vigorous-intensity PA ($p = 0.01$). Low- and moderate-intensity PA were not significant ($p > 0.05$). Age was also a significant predictor with an estimated increase of 0.58% in TIR for each one-year increase in age ($p = 0.01$), and age remained significant in Model 3 (B = 0.52; $p = 0.03$). In Model 3, vigorous-intensity PA tended to be associated with TIR but didn't reach significance ($p = 0.07$).

For hyperglycaemia (> 10.0 mmol/L) none of the predictors observed significant associations in Model 1, Model 2, and Model 3 ($p > 0.05$). While for hyperglycaemia (> 13.9 mmol/L) in Model 1, moderate-intensity PA was found to be a significant predictor (B = 0.01; $p = 0.02$), indicating that for every additional minute per day of such activity, there was an estimated increase of 0.01% in hyperglycaemia. However, low- and vigorous-intensity PA were found not to predict hyperglycaemia (> 13.9 mmol/L; $p > 0.05$). In Model 2, vigorous-intensity PA indicated as a significant predictor of hyperglycaemia (> 13.9 mmol/L; B = −0.31; $p = 0.01$), suggesting that for each one-minute increase per day of such activity, hyperglycaemia decrease by 0.31%. In Model 3, none of the predictors showed a significant association with hyperglycaemia (> 13.9 mmol/L; $p > 0.05$).

For hypoglycaemia (< 3.9 mmol/L and < 3.0 mmol/L) none of the predictors across the three Models were significant predictors ($p > 0.05$). For the glycaemic

variability, in Model 1, none of the PA levels were significant predictors for glycaemic variability ($p > 0.05$). In Model 2, age emerged as a significant predictor, with an estimated decrease of 0.23% in glycaemic variability for each one-year increase in age ($p = 0.02$) and remained significant in Model 3 (B = −0.22; $p = 0.04$), while all other predictors had $p > 0.05$ in both Model 2 and 3.

Table 5.5 Unadjusted and Adjusted Models for Physical Activity Levels Predicting Continuous Glucose Monitoring Metrics

CGM metrics	Mean glucose (mmol/L)	TIR (3.9 – 10.0) mmol/L	TAR 1 (> 10.0) mmol/L	TAR 2 (> 13.9) mmol/L	TBR 1 (< 3.9) mmol/L	TBR 2 (< 3.0) mmol/L	Glycaemic variability%
			B (*p*-value)				
			Model 1				
Low-intensity (minutes/day)	< 0.001 (0.11)	−0.05 (0.10)	< 0.0001 (1.00)	0.01 (0.09)	0.001 (0.69)	0.001 (0.32)	0.01 (0.56)
Moderate-intensity (minutes/day)	0.001 **(0.01)**	−0.10 **(0.04)**	0.02 (0.56)	0.01 **(0.02)**	−0.002 (0.40)	−0.002 (0.33)	0.01 (0.65)
Vigorous-intensity (minutes/day)	−0.01 (0.20)	1.50 (0.14)	−0.44 (0.40)	−0.16 (0.12)	0.02 (0.71)	−0.01 (0.81)	−0.37 (0.36)
			Model 2				
Age (year)	−0.002 (0.17)	0.58 **(0.01)**	−0.26 (0.05)	−0.04 (0.13)	−0.02 (0.09)	−0.01 (0.46)	−0.23 **(0.02)**
Gender: Male	0.08 **(0.01)**	−10.64 (0.06)	2.77 (0.37)	1.20 (0.05)	−0.57 (0.11)	−0.18 (0.57)	−1.04 (0.67)
Female	0	0	0	0	0	0	0
BMI (kg/m^2)	0.002 (0.58)	−0.83 (0.14)	< 0.001 (1.00)	0.05 (0.38)	0.02 (0.58)	0.04 (0.16)	−0.07 (0.78)
Diabetes duration (year)	−0.002 (0.08)	0.29 (0.20)	−0.15 (0.24)	−0.04 (0.13)	0.02 (0.11)	−0.01 (0.66)	0.03 (0.76)
Low-intensity (minutes/day)	< 0.0001 (0.62)	−0.01 (0.73)	−0.02 (0.26)	0.002 (0.54)	< 0.001 (0.78)	< 0.001 (0.74)	−0.003 (0.82)
Moderate-intensity (minutes/day)	< 0.001 (0.12)	−0.04 (0.39)	−0.02 (0.43)	0.01 (0.18)	−0.003 (0.29)	−0.003 (0.23)	−0.02 (0.45)

Vigorous-intensity (minutes/day)	−0.02 **(0.01)**	2.92 **(0.01)**	−1.05 (0.08)	−0.31 **(0.01)**	0.09 (0.19)	−0.02 (0.69)	−0.40 (0.38)
Model 3							
TDD (IU)	0.002 (0.26)	−0.37 (0.31)	0.20 (0.32)	0.06 (0.12)	−0.02 (0.34)	−0.01 (0.73)	0.12 (0.45)
Bolus insulin (IU)	−0.001 (0.63)	0.24 (0.64)	−0.12 (0.66)	−0.04 (0.44)	0.02 (0.51)	−0.01 (0.83)	−0.07 (0.75)
Age (year)	−0.001 (0.27)	0.52 **(0.03)**	−0.22 (0.09)	−0.03 (0.24)	−0.03 (0.07)	−0.01 (0.60)	−0.22 **(0.04)**
Gender: Male	0.05 (0.18)	−5.53 (0.40)	−0.09 (0.98)	0.41 (0.54)	−0.31 (0.45)	−0.16 (0.66)	−2.74 (0.36)
Female	0	0	0	0	0	0	0
BMI (Kg/m^2)	−0.003 (0.45)	−0.08 (0.92)	−0.42 (0.31)	−0.06 (0.42)	0.05 (0.27)	0.06 (0.12)	−0.32 (0.34)
Diabetes duration (years)	−0.001 (0.42)	0.12 (0.64)	−0.05 (0.72)	−0.01 (0.69)	0.02 (0.34)	−0.01 (0.37)	0.09 (0.43)
Low-intensity (minutes/day)	< 0.0001 (0.58)	−0.01 (0.68)	−0.02 (0.31)	0.002 (0.44)	< 0.001 (0.91)	0.001 (0.64)	−0.002 (0.87)
Moderate-intensity (minutes/day)	< 0.001 (0.14)	−0.04 (0.43)	−0.02 (0.39)	0.01 (0.19)	−0.003 (0.32)	−0.003 (0.28)	−0.02 (0.42)
Vigorous-intensity (minutes/day)	−0.01 (0.08)	2.11 (0.07)	−0.59 (0.36)	−0.19 (0.11)	0.05 (0.49)	−0.05 (0.43)	−0.13 (0.80)

Note. Mean blood glucose and PA levels were averaged over a period of 14 days.

Dependent variable: Glycaemic metrics measured by continuous glucose monitoring (CGM).

B: Regression coefficient. Significant association at $p < 0.05$.

Model 1 includes three predictors of PA levels (low, moderate, and vigorous).

Model 2 includes three predictors (low, moderate, vigorous) adjusted for age, sex, BMI, and diabetes duration.

Model 3 includes three predictors (low, moderate, vigorous) adjusted for age, sex, BMI, diabetes duration, and insulin requirements.

5.3.5 Association between Sedentary Behaviours and Continuous Glucose Monitoring Metrics

To determine whether SBs such as standing, lying down, siting, seated transport time and sit-to-stand transitions using ActivPAL influenced blood glucose over a 14-day period, three multiple regression analyses were performed. In each analysis, a particular CGM metric was regressed with SB metrics, **Table 5.6**. Model 1 examined the unadjusted relationship, whereas Model 2 adjusted for age, sex, BMI, and diabetes duration. Model 3 incorporated additional adjustments for bolus insulin and TDD of insulin.

In the unadjusted model, none of the SBs, including standing, lying down, sitting, seated transport time, and sit-to-stand transitions, were associated with mean 24-hour blood glucose concentrations ($p > 0.05$). In Model 2, lying down time was a significant predictor (B = 0.001; $p = 0.03$), indicating that for each additional minute spent in lying down, there was an estimated increase of 0.001 mmol/L in mean 24-hour blood glucose concentrations. Time spent in lying down remained significant in Model 3 (B = 0.001; $p = 0.01$). However, standing, sitting time, seated transport time, and sit-to-stand transitions were not found to predict mean 24-hour blood glucose concentrations ($p > 0.05$), in Model 2 and Model 3. In Model 3, BMI was a significant predictor (B = −0.01; $p = 0.03$), suggesting that with each unit increase in BMI, there was an estimated decrease of 0.01 mmol/L in mean 24-hour blood glucose concentrations. Conversely, age, sex, diabetes duration, bolus insulin, and TDD of insulin did not show significant associations ($p > 0.05$).

For TIR, hyperglycaemia (> 10.0 mmol/L and > 13.9 mmol/L), and glycaemic variability, none of the three models demonstrated statistically

significant associations ($p > 0.05$). For the hypoglycaemia (< 3.9 mmol/L) none of the models observed statistically significant associations ($p > 0.05$). However, hypoglycaemia (< 3.0 mmol/L) in the unadjusted model, sit-to-stand transitions per day was a significant predictor (B = 0.02; $p = 0.03$), suggesting that with each additional sit-to-stand transition per day there was an estimated increase of 0.02% in hypoglycaemia. While none of the Model 2 and Model 3 showed significant associations ($p < 0.05$).

Table 5.6 Unadjusted and Adjusted Models for Sedentary Behaviours Predicting Continuous Glucose Monitoring Metrics

CGM metrics	**Mean glucose** (mmol/L)	**TIR** (3.9 – 10.0 mmol/L)	**TAR 1** (> 10.0 mmol/L)	**TAR 2** (> 13.9 mmol/L)	**TBR 1** (< 3.9 mmol/L)	**TBR 2** (< 3.0 mmol/L)	**Glycaemic variability%**
			B (*p*-value)				
			Model 1				
Standing (minute)	< 0.001 (0.70)	0.01 (0.89)	−0.01 (0.86)	< 0.001 (0.92)	< 0.001 (0.97)	−0.002 (0.59)	−0.003 (0.92)
Sitting time (minute)	< 0.001 (0.44)	0.05 (0.49)	−0.03 (0.39)	−0.001 (0.76)	−0.001 (0.90)	−0.001 (0.70)	−0.02 (0.37)
Seated transport (minute)	< 0.001 (0.77)	−0.02 (0.65)	0.01 (0.70)	0.001 (0.44)	0.001 (0.66)	0.002 (0.30)	0.02 (0.22)
Lying time (minute)	< 0.001 (0.20)	−0.14 (0.60)	−0.02 (0.62)	0.003 (0.22)	< 0.001 (0.95)	0.01 (0.05)	−0.01 (0.66)
Sit-to-stand transition (per day)	0.001 (0.45)	−0.21 (0.31)	−0.02 (0.83)	0.01 (0.53)	−0.001 (0.95)	0.02 **(0.03)**	−0.05 (0.48)
			Model 2				
Age (year)	< 0.001 (0.77)	0.40 (0.15)	−0.20 (0.16)	−0.01 (0.56)	−0.03 (0.07)	0.01 (0.41)	−0.18 (0.10)
Gender: Male	0.05 (0.08)	−5.43 (0.38)	2.57 (0.43)	0.35 (0.13)	−0.41 (0.25)	−0.36 (0.21)	−0.40 (0.87)
Female	0	0	0	0	0	0	0
BMI (Kg/m^2)	−0.002 (0.60)	−0.49 (0.45)	0.13 (0.70)	0.02 (0.47)	0.53 (0.18)	0.02 (0.44)	0.05 (0.85)
Diabetes duration (years)	−0.002 (0.14)	0.20 (0.44)	−0.09 (0.53)	−0.01 (0.15)	0.02 (0.13)	−0.01 (0.59)	0.07 (0.52)

Standing (minute)	< 0.001 (0.33)	−0.07 (0.51)	0.03 (0.57)	0.01 (0.23)	−0.01 (0.93)	−0.003 (0.47)	−0.01 (0.86)
Sitting time (minute)	< 0.001 (0.53)	−0.01 (0.87)	< 0.001 (0.99)	0.002 (0.45)	−0.01 (0.31)	−0.002 (0.51)	−0.02 (0.43)
Seated transport (minute)	< 0.001 (0.45)	−0.02 (0.60)	0.01 (0.68)	0.002 (0.23)	−0.001 (0.83)	0.001(0.35)	0.01 (0.44)
Lying time (minute)	0.001 **(0.03)**	−0.14 (0.11)	−0.02 (0.73)	0.01 (0.11)	−0.01 (0.10)	0.004 (0.27)	−0.03 (0.32)
Sit-to-stand transition (per day)	< 0.001 (0.87)	0.05 (0.84)	−0.14 (0.27)	−0.01 (0.48)	−0.003 (0.82)	0.02 (0.08)	−0.09 (0.32)
Model 3							
TDD (IU)	0.002 (0.17)	−0.45 (0.23)	0.34 (0.09)	0.01 (0.29)	−0.03 (0.29)	−0.02 (0.38)	0.12 (0.43)
Bolus insulin (IU)	−0.001 (0.83)	0.19 (0.72)	−0.26 (0.35)	−0.01 (0.79)	0.02 (0.53)	0.01 (0.56)	−0.03 (0.98)
Age (year)	<0.0001 (0.99)	0.33 (0.20)	−0.16 (0.23)	−0.01 (0.57)	−0.03 (0.05)	0.01 (0.43)	−0.16 (0.14)
Gender: Male	0.03 (0.33)	−0.89 (0.89)	−0.48 (0.88)	0.20 (0.42)	−0.20 (0.62)	−0.32 (0.33)	−1.67 (0.51)
Female	0	0	0	0	0	0	0
BMI (Kg/m^2)	−0.01 **(0.03)**	0.49 (0.51)	−0.42 (0.28)	−0.02 (0.44)	0.09 (0.06)	0.04 (0.26)	−0.25 (0.41)
Diabetes duration (years)	−0.001(0.34)	0.06 (0.81)	−0.001(0.99)	−0.01 (0.33)	0.02 (0.27)	−0.01 (0.42)	0.11 (0.31)
Standing (minute)	0.001(0.17)	−0.08 (0.40)	0.03 (0.52)	0.01 (0.16)	−0.01 (0.40)	−0.003 (0.47)	−0.001 (0.99)
Sitting time (minute)	<0.001 (0.37)	−0.02 (0.78)	−0.002 (0.96)	0.002 (0.39)	−0.004 (0.36)	−0.002 (0.52)	−0.02 (0.52)

Seated transport (minute)	<0.001 (0.35)	−0.03 (0.57)	0.01 (0.75)	0.002 (0.21)	<0.001 (0.90)	0.002 (0.34)	0.02 (0.41)
Lying time (minute)	0.001 **(0.01)**	−0.15 (0.09)	−0.02 (0.67)	0.01 (0.10)	−0.01 (0.13)	0.004 (0.35)	−0.03 (0.38)
Sit-to-stand transitions (per day)	<0.001 (0.88)	0.04 (0.85)	−0.14 (0.23)	−0.01 (0.42)	−0.003 (0.83)	0.02 (0.07)	−0.09 (0.32)

Note. Mean blood glucose and PA levels were averaged over a period of 14 days.

Dependent variable: CGM metrics. **B:** Regression coefficient. Significant association at $p < 0.05$.

Model 1 includes three predictors of SBs (standing, sitting, seated transport, lying, and sit-to-stand transition).

Model 2 includes three predictors (low, moderate, vigorous) adjusted for age, sex, BMI, and diabetes duration.

Model 3 includes three predictors (low, moderate, vigorous) adjusted for age, sex, BMI, diabetes duration, and insulin requirements (basal insulin and TDD).

5.4 Discussion

This study aimed to characterise the impact of objectively measured daily activities and SBs on glucose responses in adults with T1D. Our findings indicated that moderate-intensity PA was associated with a slight increase in 24-hour mean blood glucose concentrations (0.001 mmol/L), a 0.10% decrease in TIR, and a 0.01% rise in hyperglycaemia (> 13.9 mmol/L). Conversely, vigorous-intensity PA was linked to a reduction in mean blood glucose concentrations (0.02 mmol/L), a 2.29% increase in TIR, and a 0.31% decrease in hyperglycaemia (> 13.9 mmol/L). However, hyperglycaemia (> 10.0 mmol/L) and hypoglycaemia were not observed any association with daily activities. Additionally, SBs influenced glucose responses: lying time was positively associated with a 0.001 mmol/L increase in mean 24-hour blood glucose concentrations (Model 2 and 3), while sit-to-stand transitions per day (Model 1) were linked to a 0.02% increase in hypoglycaemia (< 3.0 mmol/L).

5.4.1 Quantifying Daily Activities using Device and Self-reported Measures

5.4.1.1 Physical Activity Levels

Based the present findings, participants engaged in an average of 260.25 ± 206.50 minutes of low-intensity PA, 92.22 ± 75.90 minutes of moderate-intensity PA and 2.50 ± 6.13 minutes of vigorous-intensity PA per day (GENEActiv). This level of activity aligns with public health recommendations, such as those from the WHO, which suggests at least 150 minutes of moderate-intensity PA per week for adults (~21.4 minutes per day) (World Health Organisation, 2020). However, minimal engagement was shown in vigorous activities such as running or cycling, which offer substantial health benefits such as improved

cardiovascular fitness and glucose control in this population (Guelfi et al., 2005; Chimen et al., 2011). Our findings, along with data from studies included in the systematic review in Chapter 4 (Part A), suggest that individuals with T1D, on average, meet or exceed PA recommendations when measured using objective devices such as accelerometers.

The self-reported data using the IPAQ measure showed that participants reported engaging in an average of 564.30 ± 657.04 MET-minutes per week of low-intensity PA, 285.50 ± 422.71 MET-minutes per week of moderate-intensity PA, and 723.00 ± 1035.83 MET-minutes per week of vigorous-intensity PA over the last seven days. When converted into minutes per week, participants self-reported that they were spending most of their time in low-intensity PA (~171 minutes per week), followed by vigorous-intensity PA (~90 minutes per week) and then moderate-intensity PA (~71 minutes per week). As such, participants reported that they were meeting the PA guidelines for vigorous-intensity PA but not for moderate-intensity PA (World Health Organisation, 2020). However, it is important to note that large differences were seen between self-reported and device-measured PA, with the self-reported PA levels indicating higher levels of vigorous-intensity PA compared to GENEActiv device. This discrepancy is suggestive of over-reporting of PA levels using the IPAQ questionnaire, which may be attributed to participants reliance on memory and tendency to overestimate their PA levels. Indeed, previous studies have shown that self-reported PA data can often be inflated due to recall bias and social desirability bias (Sallis and Saelens, 2000; Prince et al., 2008).

Remarkably, the self-reported and objective measures of PA indicated that the majority of activities were of low-intensity PA. Given current recommendations for those with diabetes to limit sedentary time and incorporating frequent

episodes of low-intensity PA (Bull et al., 2020), it is plausible that interventions focused on promoting low-intensity PA would be effective and feasible for this population.

5.4.1.2 Sedentary Behaviours

The total sedentary time reported from two objective measures and self-reported questionnaire. Participants spent an average of 705.97 ± 1166.65 minutes per day (~12 hours) using the GENEActiv, 548.14 ± 150.34 minutes per day (~9 hours) using ActivPAL, and 337.50 ± 161.00 minutes per day (~6 hours) according to the IPAQ. Recently, the Canadian Society of Exercise Physiology recommended that adults between the ages of more than 18 years should limit their sedentary time to less than eight hours per day, focusing on reducing recreational screen time (< 3 hours per day) and incorporating regular breaks throughout the day (Singh and Sharma, 2022). These data highlight an important discrepancy between the objective and self-reported measures, with the objective measures indicating that sedentary time exceeded the eight-hour daily limit, while the self-reported measure indicated individuals were below the eight-hour per day limit. The self-reported data moderately consistent with the study reported in Chapter 4, which indicated 408.00 ± 159.60 minutes per day (~6 hours) spent in sedentary time using the same questionnaire (Jabbour et al., 2022). This underestimation from self-reported measure highlights the importance of using objective measures for a more accurate assessment of SB.

The present findings also indicated that participants spent an average of 244.42 ± 108.42 minutes per day standing, 511.67 ± 177.40 minutes per day lying down, 457.19 ± 158.81 minutes per day sitting, and 75.55 ± 98.547 minutes per day in seated transport (as measured using the ActivPAL device). Additionally, participants in our study averaged 45.41 ± 19.86 sit-to-stand transitions per day.

This measure is critical as it reflects the pattern of breaking up prolonged sitting periods, which has been shown to have metabolic and cardiovascular benefits (Healy et al., 2008b). As such, detailed postural data from ActivPAL further confirm that the large proportion of time is spent either sitting or lying down. In the systematic review presented in previous chapter, one of the included studies involving 23 participants found that adult with T1D spent about 70% of their time in SBs (< 2 METs), with significantly less time devoted to PA as measured using a multi-sensory device (Valletta et al., 2014). Our findings, along with the finding from study in Chapter 4 (Part A), indicate that adults with T1D spend a substantial amount of their day performing sedentary activities.

Based on the findings from the present study, it is evident that while adults with T1D meet the recommended PA guidelines, they also accumulate significant amounts of sedentary time. This phenomenon is referred to as the 'Active Couch Potato', and it has been suggested that meeting PA guidelines alone may not be sufficient to mitigate the risks associated with prolonged SB (Owen et al., 2010; Craft et al., 2012; Biswas et al., 2015). The high levels of sedentary time observed in this population highlights the need for further behavioural strategies to reduce or break up sedentary time for optimal health.

5.4.2 Association between Physical Activity and Glucose Control

Moderate-intensity PA was associated with 24-hour mean blood glucose concentrations, TIR, and hyperglycaemia (> 13.9 mmol/L), but the magnitude of effect was small and potentially of limited clinical significance. Regression analysis indicated that for every additional minute per day of moderate-intensity PA, 24-hour mean blood glucose concentrations increased by 0.001 mmol/L, TIR decrease by 0.10%, and hyperglycaemia increased by 0.01%. However, these associations did not remain consistent across Model 2 and 3 when covariates

were added, with these predictors no longer being significant when age, sex, BMI, diabetes duration, bolus insulin, and TDD were controlled. Our study findings contradict with the anticipated results, which may be attributed to various environmental factors such as dietary intake (as consumption of carbohydrate-rich foods can lead to elevated blood glucose concentrations post-meal, potentially compounded by the body`s response to PA), individual responsiveness to insulin, and the complex interplay of counter-regulatory hormone release during moderate-intensity PA on glucose regulation (Riddell et al., 2017; Fitzpatrick et al., 2022). A study by Dijk and colleagues (Van Dijk et al., 2013) found that daily activities, such as 15-minute bouts of post-meal strolling, did not significantly reduce hyperglycaemia (> 10.0 mmol/L) or alter the mean 24-hour blood glucose concentrations in males with T2D. Another study by Tanzila and colleagues (Tanzila et al., 2020) found that engaging in moderate activities for 30 minutes once a week for four weeks did not significantly affect blood glucose concentrations in individuals with T2D (p = 0.29). While a study in individuals with T1D using CGM indicates that moderate-intensity aerobic exercise in the afternoon led to reduced blood glucose concentrations, leading nocturnal hypoglycaemia, which results from increased glucose utilisation by muscle and enhanced insulin sensitivity during activity (Maran et al., 2010). The risk of late-night hypoglycaemia following exercise is likely due to depletion of glycogen stores (McMahon et al., 2007).

Additionally, the present study found that vigorous-intensity PA was associated with 24-hour blood glucose concentrations, TIR, and hyperglycaemia (> 13.9 mmol/L). Here for every additional minute per day of vigorous activity, there was a decrease in mean 24-hour blood glucose concentrations by ~0.02 mmol/L, a decrease in hyperglycaemia (> 13.9 mmol/L) by 0.31%, and an

increase in TIR by 2.92%. These associations were still evident in Model 2 after adjusting for age, sex, BMI, and diabetes duration, but not in Model 3 when further adjusted for bolus insulin and TDD. This suggests that specific components of an individual's insulin regimen, such as TDD, or bolus insulin usage, may mediate the relationship between PA levels and CGM metrics. The observed decrease in effects in the fully adjusted model may be due to the limited sample size and the complexity of the model, which could hide the true impact of PA on glucose control. Previous research in T2D indicated that a single vigorous-intensity exercise session resulted in decreased hyperglycaemia, measured as the proportion of time spent above 10 mmol/L in the 24-hour post-exercise period, compared to non-exercising control day (4.5 ± 4.4% versus 15.2 ± 12.3%; p = 0.04, respectively) (Gillen et al., 2012). These findings consistent with our results, which demonstrated that vigorous-intensity PA lowered mean blood glucose concentrations, reduced hyperglycaemia, and consequently improved the TIR. Prior research suggests that engaging in vigorous-intensity PA can be beneficial in managing diabetes due to its physiological benefits, including improved cardiovascular fitness and metabolic process, despite the need to consider risks such as hypoglycaemia and hyperglycaemia and contraindications like uncontrolled diabetes (MY, 1992).

Our study findings indicating that moderate-intensity PA may negatively affect glucose control, while vigorous-intensity PA improves the CGM metrics. However, a study by Riddell and colleagues (Riddell et al., 2017) reported that moderate-intensity PA generally decreases blood glucose concentrations, while vigorous-intensity PA can cause initial increase in blood glucose concentrations, but there is still a risk of hypoglycaemia post-exercise. This may be due to stress hormones: for example, stress associated with daily tasks, especially those

perceived as moderate but sustained (e.g., working on a tight deadline), can elevate stress hormones such as cortisol and adrenaline, which raise blood glucose concentrations (Horton and Beisel, 1994). While during vigorous-intensity PA, a rapid spike in stress hormones increases blood glucose concentrations through glycogenolysis and gluconeogenesis, but as hormone concentrations decline post-activity and muscles continue using glucose, blood glucose concentrations ultimately decrease (Marliss and Vranic, 2002).

Hypoglycaemia risk has been highlighted in previous research examining the impact of moderate- and vigorous-intensity PA on blood glucose concentrations in individuals with T1D (Davis et al., 1997; Bachmann et al., 2016), which may be attributed to excess delivery of exogenous insulin, inadequate carbohydrate consumption, and increased duration of such exercise intensity (Younk et al., 2011). However, in this study, hypoglycaemia was not shown to be associated with any predictors. Age and sex considered as a covariate, were found to be significantly associated with CGM metrics, indicating their potential influence on glucose regulation in the study population. The mean age for the study population was 46.00 ± 14.49 years. Increasing age was associated with increasing TIR by ~0.52% after adjusting for covariates (Model 2 and 3) and reducing glycaemic variability ~0.22% (Model 2 and Model 3). These findings suggest that older adults may have developed more effective strategies for managing their diabetes, which could contribute to better glucose control, higher TIR, and reduced glycaemic variability. This may be due to their greater experience with the disease and more established routines in their daily lives. However, older people are more vulnerable to hypoglycaemia, as age impairs the counter-regulatory responses and increases the prevalence of hypoglycaemia unawareness (Kilvert and Fox, 2015). Additionally, sex specifically males, was

associated with increasing mean 24-hour blood glucose concentrations by 0.08 mmol/L. This finding related to sex difference in glucose responses may be attributed to hormonal differences (e.g., testosterone), behavioural factors (e.g., dietary intake and levels of PA), and sample demographics (e.g., difference in participant age, diabetes duration, and insulin regimens). Recent research revealed a positive correlation between testosterone concentrations in individuals with T1D and eGDR levels (r = 0.33; p = 0.04) (Simonienė et al., 2020).

5.4.3 Sedentary Behaviours and Glucose Control

Lying time was associated with increase in mean 24-hour blood glucose concentrations, with each additional minute spent in lying down estimated to increase mean 24-hour blood glucose concentrations by ~0.001. The effect size of a 0.001 mmol/L increase in mean 24-hour blood glucose concentrations per unit of lying time, with adjustment for covariates in Models 2 and 3, may be small but is clinically significant. Even minor increases in mean blood glucose concentrations can contribute to long-term complications in diabetes management. Evidence from a recent study in individuals with prediabetes and diabetes shows that replacing 30 minutes of sedentary time with low-intensity PA can reduce all-cause mortality by up to 11% (Zhu et al., 2023), emphasising the significant health benefits of even modest reductions in SB, particularly for improving long-term glucose management and reducing complications in diabetes. This suggests that limiting SBs, should be considered as a part of diabetes care to help maintain optimal glucose control and prevent adverse health outcomes. Therefore, it is recommended to limit the amount of time being sedentary to promote better health and overall well-being (Bull et al., 2020).

Our finding is consistent with previous study demonstrating that lying time can contribute to increase blood glucose concentrations and other metabolic

markers associated with metabolic syndrome (Asante et al., 2020). Sit-to-stand transition was associated with a 0.02% increase in hypoglycaemia (< 3.0 mmol/L), attributed to heightened insulin sensitivity and increased energy expenditure, which could potentially lead to lower blood glucose concentrations (Healy et al., 2008b). One study demonstrated that a single sit-to-stand transition results in an increased in energy expenditure by 1.49 ± 0.20 kcal per minute and the energy cost was calculated to be 0.32 kcal (Judice et al., 2016). Increased energy expenditure affects hypoglycaemia by enhancing glucose uptake by muscles, which coupled with increased insulin sensitivity, reduces blood glucose concentrations more rapidly (Caron et al., 2016). SBs such as lying time can increase the blood glucose concentrations by reducing LPL activity, decreasing the insulin-regulated glucose transporter (GLUT4), and impairing insulin sensitivity (Tremblay et al., 2010; Park et al., 2020). Collectively, these factors contribute to decrease glucose uptake by cells and increase blood glucose concentrations.

Additionally, higher BMI was associated with a decrease in mean 24-hour blood glucose concentrations by 0.01 mmol/L. Higher BMI is often associated with IR (Wondmkun, 2020), potentially leading to increased blood glucose concentrations. However, individuals with a higher BMI may compensate by injecting more insulin, leading to reduced blood glucose concentrations (Brod et al., 2009).

5.4.4 Objective and Self-reported Measures for Sedentary Time

To our knowledge, this is the first study to specifically investigate the relationship between self-reported and objectively measured sedentary time in individuals with T1D, with findings indicating that there were no significant associations between the two device-measured estimates sedentary time. The lack of

correlation suggests that the two objective measures may capture sedentary time differently. This difference may be due to differences in sensor placement (ActivPAL on the thigh and GENEActiv on the wrist), the algorithms used to interpret the data to process and classify movement data, or sensitivity to detecting certain types of movement (Arif and Kattan, 2015; Davoudi et al., 2021).

The present findings also demonstrated that there were no associations between the device-measured and self-reported estimates of sedentary time. This is consistent with previous studies, with Urda and colleagues (Urda et al., 2017) finding a positive but weak association between self-reported sedentary time (Paffenbarger Physical Activity Questionnaire and ActivPAL; $r = 0.25$; $p = 0.10$), and between the Occupational Sitting and Physical Activity Questionnaire and ActivPAL during work hours ($r = 0.10$; $p = 0.52$) in 44 healthy individuals. Sedentary time was also significantly under-reported using self-report compared to the ActivPAL data in this study (3.06 ± 2.76 hours per day; $p = 0.001$) (Urda et al., 2017), which is in line with a recent review suggests that self-report measure tend to underestimate sedentary time in comparison to objective measure (Prince et al., 2020).

5.4.5 Study Strengths and Limitations

The key strength of this study is the free-living context, combined with objective device-based measures including GENEActiv, ActivPAL, and CGM over a 14-day period, which enhances the validity and reliability of findings to provide a deeper understanding of the impact of PA levels and SBs on CGM metrics in adults with T1D. Additionally, incorporating confounding variables such as age, sex, diabetes duration, BMI, and insulin treatments, into the analysis strengths the study by improving the validity and reliability of the findings.

There are some limitations to this study. One limitation may be heterogeneity among participants in HbA1c levels, which could introduce confounding variables affect result consistency and generalisability. Furthermore, the free-living design of the study provides a real-world context but may introduce limitations due to the lack of control over participant behaviours and environments outside of research setting. Future research should consider those limitations, to provide a better understanding of the interactions influencing glucose control in this population, potentially leading to tailored interventions an improved management strategies for individuals with T1D.

5.5 Conclusion

In conclusion, our findings indicate that moderate-intensity PA was associated with poorer glucose control, as evidenced by increased 24-hour mean blood glucose concentrations, hyperglycaemia (> 13.9 mmol/L), and decreased TIR of glucose. Conversely, vigorous-intensity PA appears to have a beneficial impact on glucose control. Lying time was also associated with higher 24-hour mean blood glucose concentrations, while more frequent sit-to-stand transitions were associated with a greater incidence of hypoglycaemia (< 3.0 mmol/L). Additionally, no significant correlations between the GENEActiv, ActivPAL, and IPAQ data for sedentary time were seen, with sedentary time under-reported using the self-reported IPAQ relative to the GENEActiv and ActivPAL. As this research indicates that SBs may significantly influence glucose control in individuals with T1D, future research should examine the impact of specific interventions designed to break up these SBs on glucose control.

5.6 Chapter Summary

1) Physical Activity (GENEActiv) and CGM Metrics

- Mean blood glucose concentrations and hyperglycaemia (> 13.9 mmol/L) were unfavourably associated with moderate activity but favourably associated with vigorous activity. Additionally, TIR was favourably associated with vigorous activity.
- Hypoglycaemia was not significantly associated with daily activities, suggesting that daily activities did not have a detectable impact on hypoglycaemia events.
- Age was favourably associated with better glucose control, as indicated by increased TIR and decreased glycaemic variability. Furthermore, males exhibited higher blood glucose concentrations compared to females.

2) Sedentary Behaviours (ActivPAL) and CGM metrics

- Lying time was associated with an increase in 24-hour mean blood glucose concentrations. Additionally, sit-to-stand transitions per day were associated with an increase in hypoglycaemia (< 3.0 mmol/L).
- Body mass index was negatively associated with mean blood glucose concentrations.

3) Association between Objective and Self-reported Measures of Sedentary time

- There was no significant association in sedentary time between GENEActiv and ActivPAL, GENEActiv and IPAQ, and ActivPAL and IPAQ ($p > 0.05$).

Chapter 6 – Interrupting Prolonged Sitting Time with Frequent Short Activity Breaks and Glucose in Adults with Type 1 Diabetes: A Randomised Crossover Trial

What do we know? Individuals with T1D are often physically inactive and more sedentary (Chapter 4) due to concerns about manage glucose fluctuations from exercise (Chapter 3). Chapter 5 characterise the impact of daily activities on glucose control, revealing that vigorous-intensity PA improves glucose control, moderate-intensity PA leads to poorer control, increased lying time raises mean blood glucose concentrations, and frequent sit-to-stand transitions increase the risk of hypoglycaemia. Thus, interrupting prolonged sitting time with low-intensity PA could benefit their glucose control, as has been observed in individuals with or at risk of T2D (Chapter 1).

Key issues: Studies on individuals with T2D have been shown that interrupted prolonged sitting intervention led to improvements in whole-day glycaemia; however, these findings are limited to individuals with T2D and have yet to be examined in those with T1D.

Chapter aims: To examine the effect of frequent, short bouts of low-intensity PA on glucose control over 48 hours and to determine if these interruptions in prolonged sitting influence glucose control at different times of the day in adults with T1D.

Chapter implications: The interrupted prolonged sitting intervention could improve glucose control, and thus inform clinical guidelines, encourage regular activity breaks for SBs, and enhance our understanding of the impact of SBs on glucose metabolism and quality of life.

6.1 Introduction

Physical activity is a key component of diabetes management and is recommended for individuals with diabetes due to its significant impact on glucose control and overall health (Chimen et al., 2011; Colberg et al., 2016). Regular PA, particularly MVPA, is known to be a cost-effective public health intervention, yet individuals with chronic conditions are often less active and more sedentary due to concerns about potential risks and benefits (Dempsey et al., 2020). Spending more time being sedentary has a greater negative impact on health (Chau et al., 2013; Cooper et al., 2014), regardless of the amount of PA the person engages in otherwise (Biswas et al., 2015). The recommended levels of PA may pose challenges for glucose management in many individuals with T1D, preventing them from participating in PA. Therefore, it is important to evaluate whether low-intensity PA is associated with health benefits.

The WHO has stated that 60 to 85% of individuals worldwide lead sedentary lifestyles, making it one of the most serious public health problems (World Health Organisation, 2020). A new guideline has been released to limit SB with any intensity including low-intensity PA at least every 30 minutes throughout the day, due to its health benefits (World Health Organisation, 2020). Growing evidence indicates that interrupted prolonged sitting with frequent short bouts of activity can enhance acute postprandial and whole-day glucose concentrations, with glycaemic improvement including nocturnal to following morning hyperglycaemia (Healy et al., 2008b; Dempsey et al., 2016a; Dempsey et al., 2016b; Dempsey et al., 2017b). This improvement is either due to enhanced insulin sensitivity and/or a greater reliance on insulin independent contraction-mediated glucose disposal (Bergouignan et al., 2016; Dempsey et

al., 2017b). However, this data is still preliminary and mainly applies to individuals with or at risk of developing T2D.

In the context of T1D, many individuals struggle to meet the PA guidelines and tend to spend more time being sedentary compared with those without T1D. For example, a survey of 18,028 adults with T1D found that around 60% of individuals with T1D did not achieve the recommended levels of PA (Bohn et al., 2015). This finding is consistent with some (Van Mark et al., 2019; Tikkanen-Dolenc et al., 2020), but not all previous studies (Jensen et al., 2016; Keshawarz et al., 2018). Many individuals with T1D report fear of hypoglycaemia and lack of knowledge about the effects of exercise on glucose control as main barriers to participating in MVPA (Lascar et al., 2014; Kennedy et al., 2018). Interestingly, few of them mention this fear when asked about lower intensity PA such as walking (Campbell et al., 2017c). Despite many individuals with T1D engage in little-to-no exercise, they are often willing to increase participation in lower intensity activities and are eager to learn how to reduce their SBs (Campbell et al., 2017c; Yardley and Campbell, 2020a). However, there is limited information available for individuals with T1D or the healthcare professional who support them regarding effective strategies to reduce sedentary time and potential impact of these strategies on hypoglycaemia (Campbell et al., 2017c; Yardley and Campbell, 2020a). Reducing sitting time through less intensive PA is viewed as more achievable and a logical starting point.

Evidence about interrupting prolonged sitting time with frequent, short low-intensity activity breaks and its impact on blood glucose concentrations in individuals with T2D has been well-documented, but the body of evidence for T1D is limited. Most of the recommendations regarding PA for T1D are based on conclusions driven from studies on T2D (Pilacinski and Zozulińska-Ziółkiewicz,

2014). Therefore, there is a need to evaluate the effect of reducing prolonged sitting time on blood glucose concentrations in individuals with T1D. The aim of this chapter was to assess the impact of interrupting prolonged sitting time with frequent, short bouts of low-intensity PA on 48 hours, as well as to determine whether the interrupted sitting (SITLESS intervention) influences glucose control at different times of the day during the 48 hours post-intervention, in adults with T1D using CGM to test the hypothesis that frequent bouts of low-intensity activity breaks during prolonged sitting are associated with improved glucose control without an increased risk of hypoglycaemia in adults with T1D.

6.2 Methods

6.2.1 Study Design

Data presented in this chapter are aggregated from two separate laboratories: the University of Leeds (n = 8) and the University of Sunderland (n = 32), with identical experimental procedures. Only eight participants were recruited at the University of Leeds due to COVID-19 restrictions and difficulties in recruiting clinically vulnerable individuals with T1D. These data were collected using identical methodologies between sites and were combined for the analyses in this chapter to assess the impact of the SITLESS intervention on glucose control in adults with T1D. The study was a RCT adopting two conditions – crossover design conducted between May 2022 to December 2022. The study received ethical approval from the National Health Service Health Research Authority (London – Surrey Research Ethics Committee; Ref 20/LO/0650) and was prospectively registered (ISRCTN13641847). Participants completed an initial screening visit and two laboratory-based experimental visits each of which were interspersed by at least one week apart to minimise the carryover effects, as PA

increases insulin sensitivity for up to 48 hours following activity cessation (Mikines et al., 1988). Experimental conditions were randomly assigned using a computerised random-number generator www.randomization.com to undergo two experimental conditions: prolonged uninterrupted sitting (SIT) versus interrupted sitting (SITLESS).

6.2.2 Study Participants

Individuals with T1D who currently treated on a stable insulin regimen consisting of CSII or MDIs of a combination of rapid-acting and long-acting insulin were recruited from local advertisements in diabetes websites (i.e., Diabetes UK Form), social media (i.e., Facebook, Twitter) or NHS General Practitioner (i.e., Shakespeare medical practice). The participants information sheet, providing detailed information about the study, was given to all potential participants prior to enrolment and is available in **Appendix C, Table C.2**. Participants were eligible if aged between 18 to 60 years with a duration of diabetes more than two years on enrolment and classified as inactive as per international PA guidelines (Colberg et al., 2016), specifically, this consisted of failing to achieve a minimum of 150 minutes of MVPA per week. Participants were required to be familiar with carbohydrate-counting method for determining mealtime insulin dose and were free from hypoglycaemia unawareness, as assessed by completing a validated hypoglycaemia unawareness questionnaire (Clarke questionnaire, which comprises eight questions, where each question scored indicates awareness (A) or reduced awareness (R)) (Clarke et al., 1995). Participants were excluded if they were: pregnant, performed 150 minutes of MVPA or more per week, had severe functional limitations (e.g., back pain, walking difficulties), and overt diabetes complications (excluding background retinopathy). The medical

screening questionnaire used in the study was provided in **Appendix C, Table C.3.** All participants provided written informed consent (**Appendix C, Table C.1**).

6.2.3 Study Protocol and Experimental Conditions

6.2.3.1 Preliminary Visit

Anthropometric measurements, including body mass and height, were taken using an electronic scale (Seca 764, Germany; **Figure 2.1**, Chapter 2). The CGM (FreeStyle Libre Pro, Abbott, UK) was inserted into the subcutaneous tissue on the back of upper arm to continuously measure interstitial glucose concentrations. Furthermore, participants were required to abstain from exercise, caffeine, and alcohol for 48 hours prior to each experimental condition, as these may influence blood glucose concentrations by increasing the incidence of hypoglycaemia (Turner et al., 2001; Metcalf et al., 2014; Zaharieva et al., 2016).

For standardisation of glucose control prior to each laboratory visit, a standardised mixed macronutrient meal was provided to all participants to be consumed at home in the evening each visit (details of nutritional composition of the standardised meals are shown in **Table 6.1**). Following the evening meal, participants were instructed to avoid further food intake including caloric beverages, except for extremes of glucose readings managed as appropriate with corrective insulin boluses for hyperglycaemia and glucose supplementation for hypoglycaemia, to ensure a fasted state upon arrival to experimental visit.

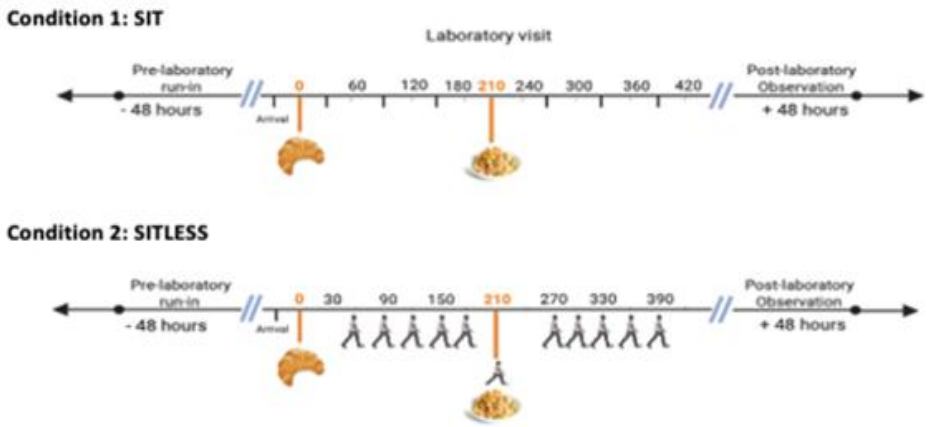
6.2.3.2 Experimental Conditions

The scheme of the experimental conditions is shown in **Figure 6.1**. On the morning of each experimental visit, study personnel contacted participants to ensure fasting status and confirm blood glucose concentrations within the range of 4 – 12 mmol/L, to avoid any confounding influence of hypoglycaemia,

hyperglycaemia, or illness. Experimental visits were re-arranged if participants experienced one or more sustained hypoglycaemic or hyperglycaemic episodes. Thereafter, participants attended a dedicated laboratory on a morning (~08:00 am) following an overnight fast. On both experimental visits, participants consumed a standardised mixed-macronutrients breakfast (at 0-hour) and lunch (at 3.5-hour), within a 20-minute period. Both meals were sought to replicate a typical Western diet that is representative of what people typically consume, nutritional composition of the standardised meals was provided in **Table 6.1**. The carbohydrate content of each meal was individualised, equating 1g.carbohydrate.kg.BM-1. Higher protein or fat intake could slow digestion and reduce glucose spikes, potentially lowering the immediate impact of activity breaks, but the carbohydrate-heavy meals reflect real-world glucose challenges in individuals with T1D.

Participants were instructed to administer their usual insulin bolus immediately prior to each meal, the dose of which was calculated using the carbohydrate-counting method, with dose, timing, and site of injection replicated across visits. After breakfast meal, participants commenced the following experimental protocols in a randomised order. 1) SIT condition – participants remained at rest and seated in a reclining chair for the duration of the visit. 2) SITLESS condition – study procedures were replicated, but sitting was interrupted with 3-minute bouts of self-paced, low-intensity walking at 30-minute intervals, commencing 60 minutes after each meal, equating to a total of 36 minutes of PA over seven hours. Three-minute walking bouts were chosen as they are practical for daily routines, help reduce hypoglycaemia risk in T1D, and have shown effectiveness in improving glucose control in individuals with T2D (Dempsey et al., 2016a; Dempsey et al., 2017b).

During each experimental visit, participants had access to the internet and books and were supervised by study personnel. At 3.5 hours post-lunch, participants were discharged from the laboratory with further free-living glycaemic assessment captured remotely by CGM for a further 48 hours. To minimise potential confounding of food intake, participants were provided with an evening and breakfast meal to consume in sequence, replicating eating times within each study condition. Any additional nutritional intake during the subsequent 48-hour observation window was recorded on visit one and subsequently replicated on visit two. All meals provided to the participants consisted of commercially available foods with standardised heating and preparation instructions. During less than seven days washout between experimental conditions, participants resumed their habitual diet and PA patterns.



Study design and protocol for the experimental conditions: participants attended the research laboratory on three separate occasions. Two laboratory-based experimental conditions (SIT and SITLESS) were completed in a randomised order, separated by one week. Breakfast meal was provided upon beginning of the experimental condition (0 hour), and lunch meal at 3.5 hour.

Three-minute bouts of low-intensity walking were completed every 30 minutes across seven hours (equalling 11 X 3-minute bouts of walking), after one hour post-meals in the SITLESS condition. Blood glucose concentrations using CGM were measured continuously during the study period.

Figure 6.1 Scheme of the Experimental Conditions

Table 6.1 Nutritional Composition of Standardised Meals

	Pre-experimental (Evening meal)	**Experimental** (Breakfast meal)	**Experimental** (Lunch meal)	**Post-experimental** (Evening meal)	**Post-experimental** (Breakfast meal)
Energy (Kcal)	724.9 ± 66.5	1042.7 ± 95.7	1244.0 ± 114.0	724.9 ± 66.5	1042.7 ± 95.7
Carbohydrate (g) [%energy]	80.0 ± 7.3 [57.7]	80.0 ± 7.3 [47.0]	80.0 ± 7.3 [42.7]	80 ± 7.3 [57.7]	80.0 ± 7.3 [47.0]
Protein (g) [%energy]	24.7 ± 2.3 [17.8]	17.7 ± 1.6 [10.3]	17.1 ± 1.6 [9.1]	24.7 ± 2.3 [17.8]	17.7 ± 1.6 [10.3]
Fat (g) [%energy]	34.0 ± 3.1 [24.5]	72.6 ± 9.7 [42.7]	90.4 ± 8.3 [48.2]	34.0 ± 3.1 [24.5]	72.6 ± 9.7 [42.7]
Food items	Lasagna with flatbread	Croissant with jam	Vegetable curry with rice	Lasagna with flatbread	Croissant with jam

Note: Meals provided were individualised based on body mass with carbohydrate intake standardised at 1 g of carbohydrate per kilogram of body mass. Insulin dose was calculated using the carbohydrate counting method. Data are presented as mean ± SD.

6.2.3.3 Continuous Glucose Monitoring Measure

Continuous glucose monitoring is a small blinded real-time device that has been proven accurate and safety in T1D across the full range of blood glucose concentrations (Massa et al., 2018). A CGM (FreeStyle Libre Pro) was inserted during the preliminary visit by a trained researcher into the subcutaneous tissue on the anterior of the upper arm to capture interstitial glucose concentrations. The sensor inserted at least 72 hours prior to each data capture window, to ensure adequate sensor initialisation. The sensor was worn for up to 14 days, after which the data was read by a reader held over the sensor using manufacturer software (more details in Chapter 2, **section 2.2.3**).

Data was anonymised with a participant ID (initials of first and last name with participant sequence number). In the study, CGM measured interstitial glucose concentrations every 15 minutes over a 48-hour pre-experimental period, experimental period, and the 48-hour post-experimental period in the SIT and SITLESS conditions. The CGM data for each condition was calculated, including mean blood glucose concentrations; glycaemic variability (< 36%); TIR (3.9 – 10.0 mmol/L). In addition to the hypoglycaemia subdivided into (TBR 1 [3.0 – 3.8 mmol/L] and TBR 2 [< 3.0 mmol/L]); and hyperglycaemia subdivided into (TAR 1 [10.1 – 13.9 mmol/L] and TAR 2 [> 13.9 mmol/L]) (Advani, 2020). TIR, TAR, and TBR were expressed as the percentage of readings in each range per day for each participant.

6.2.4 Statistical Analysis

A repeated-measures two-way ANOVA [Condition X Time] were conducted to examine mean blood glucose concentrations, glycaemic variability, TIR, hypoglycaemia, and hyperglycaemia during different time points in two

experimental conditions. Two levels of condition (SIT and SITLESS) and seven levels of time (pre-48hr period, experimental period [8:00 am – 15:00 pm], and subsequent 48-hour period (free-living period), with the covariate age, gender, and BMI was conducted. A subsequent 48-hour divided into diurnal [day 1 (15:15 – 21:45 pm), day 2 (07:00 am – 21:45 pm), day 3 (07:00 am – 15:00 pm), and nocturnal periods [nocturnal 1 and nocturnal 2 (22:00 pm – 6:45 am)]. Bonferroni-corrected *post-hoc* pairwise comparisons were performed to examine condition and time effects.

Friedman's two-way ANOVAs is the non-parametric test was used for multiple comparisons between different time periods of day (e.g., morning [06:00 – 11:45 am], afternoon [12:00 – 17:45 pm], evening [18:00 – 23:45 pm], and overnight [00:00 – 05:45 am]) for all CGM measures in the SIT and SITLESS conditions. Adjusted significance (*p*-value) was reported to control for multiple comparisons. Statistical analysis was performed using SPSS software (IBM statistics, version 28). Data are presented as mean ± SD. *P*-value (< 0.05) was considered as a statistically significant and a *p*-value between (0.05 and 0.10) considered as marginally significant (Olsson-Collentine et al., 2019). Effect sizes (partial-η2) to measure the difference between the mean of different variables in both experimental conditions.

6.3 Results

Thirty – nine participants with T1D (18 males, 21 females) mean age 28.58 ± 6.33 years and BMI 26.45 ± 3.58 kg/m^2 were recruited and completed two experimental conditions (SIT and SITLESS) in a random order. Glucose measures were collected every 15 minutes, yielding 31,913 glucose readings over a total of 10 days (48-hour pre-experimental period, experimental period,

and subsequent 48-hour period (free-living period) in two experimental conditions) for all study participants. In total, one participant was excluded, due to incomplete data at the experimental period and subsequent 48-hour period (free-living period), which may have been due to sweating, sensor movement, or sensor tip sticking out of the skin (FreeStyle Libre, 2023).

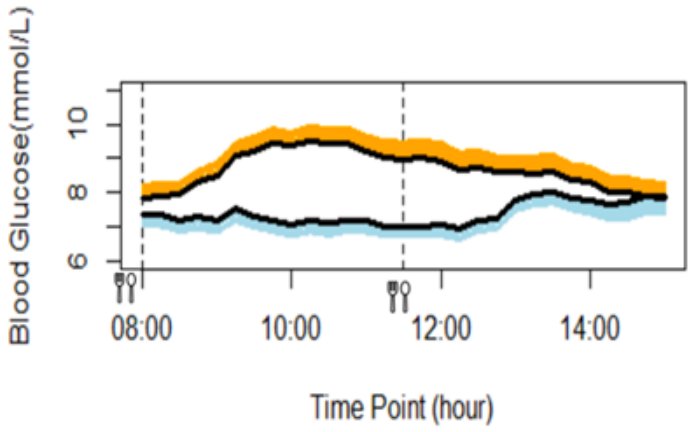
6.3.1 Continuous Glucose Monitoring Data Analysis

Mean blood glucose concentrations are presented in **Figure 6.2 and 6.3**. The mean blood glucose concentrations lowered by 1.27 mmol/L under the SITLESS condition during the experimental period (SIT 8.66 ± 2.98 mmol/L versus SILTESS 7.39 ± 2.39 mmol/L; $p < 0.001$; partial-η2 = 0.984; **Figure 6.2**). In addition, mean blood glucose concentrations reduced by 1.18 mmol/L during 48-hour post-SITLESS (SIT 8.71 ± 3.25 mmol/L versus SITLESS 7.53 ± 2.96 mmol/L; $p < 0.001$; partial-η2 = 0.29; **Figure 6.3**). TIR (3.9 – 10.0 mmol/L) was increased by ~9% under the SITLESS condition (SIT 51.25 ± 21.12% versus SITLESS 60.01 ± 18.25%; $p<0.001$; partial-η2 = 0.41). Hyperglycaemia (> 10.0 mmol/L) reduced by 7% under the SITLESS condition (SIT 14.53 ± 16.16% versus SITLESS 7.20 ± 11.21%; $p < 0.001$; partial-η2 = 0.44).

While there was no time effect for the mean blood glucose concentrations across conditions ($p > 0.05$). For TIR, there was a significant time effect ($p < 0.001$; partial-η2 = 0.96); for example, the pre-48-hour period, the experimental period, and the 48-hour post-experimental period specifically the nocturnal periods were significantly higher than the 48-hour post-experimental periods diurnal periods [day 1 (15:00 – 21:45 pm), day 2 (06:45 am – 21:45 pm), and day 3 (07:00 am – 15:00 pm)], with $p < 0.001$. The 48-hour post experimental periods specifically day 2 period was significantly lower than the pre-48 hours period, the experimental period, and the 48-hour post-experimental nocturnal periods. While

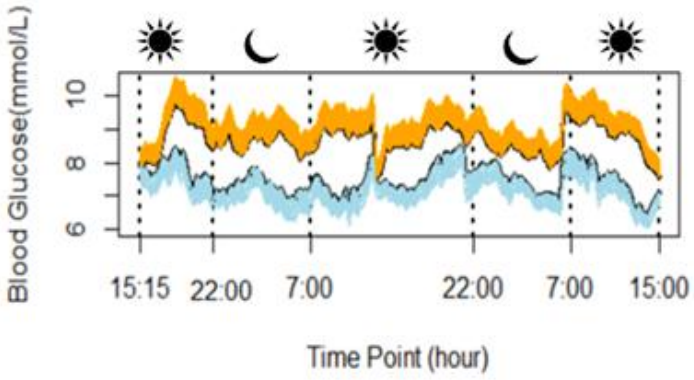
the 48-hour post-experimental period specifically day 2 was significantly higher than day 1 and day 3, $p < 0.001$. In addition, the 48-hour post-experimental period (specifically day 1 and day 3) was significant with all other time periods ($p < 0.001$), while there was no time effect between day 1 and day 3, $p > 0.05$ for TIR. or hyperglycaemia (> 10.1 mmol/L), there was no time effect ($p > 0.05$). Moreover, there were no condition X time interactions for the mean blood glucose concentrations, TIR, and hyperglycaemia (> 13.9 mmol/L), with $p > 0.05$.

The SITLESS intervention did not significantly influence the glycaemic variability, hypoglycaemia exposure irrespective of glucose threshold (< 3.9 mmol/L; < 3.0 mmol/L), and hyperglycaemia (> 13.9 mmol/L) ($p > 0.05$). Age, sex, and BMI did not significantly mediate any of the responses observed $p > 0.05$.



Note – Vertical dashed lines indicate the timing of breakfast (0 minute) and lunch (3.5 hours) meals. Insulin was administered 10 minutes before meals, and low-intensity PA (3 minutes) started one-hour post-meals, every 30 minutes. CGM data are presented as mean ± SEM.

Figure 6.2 Time Changes in Mean Glucose Concentrations during the Experimental Period (from 8:00 am – 15:00 pm)



Note - Vertical dashed lines indicate timing of breakfast (0 minutes) and lunch (3.5 hour) meals. The insulin was administered 10 minutes pre-meals, and the low intensity PA (3-minute) was started one-hour post-meals every 30 minutes. CGM data presented as mean ± SEM.

Figure 6.3 Time Changes in Mean Glucose Concentrations during the Experimental Period (from 8:00 am – 15:00 pm)

6.3.1.1 Time of Day (48-hour Post-experimental Period)

An effect of time of day was identified for the CGM measures (**Table 6.2 and 6.3**). There was no significant difference for the mean blood glucose concentrations in the 48-hour post-experimental period, all time comparisons $p > 0.05$. TIR increased by ~14% under the SITLESS condition during the morning (post-SITLESS) compared to the evening (post-SIT) (SIT (evening) 68.61 ± 23.69% versus SITLESS (morning) 82.73 ± 22.42%; $p = 0.04$). While no significant differences were noticed during the morning (post-SITLESS) compared to the afternoon (post-SIT), and the overnight (post-SITLESS) compared to the evening (post-SIT) for TIR $p > 0.05$.

There was a significant difference in hyperglycaemia (> 10.0 mmol/L) in the 48-hour post-experimental period, as the hyperglycaemia reduced by 15% during the evening (post-SITLESS) compared to the overnight (post-SIT) (SIT (overnight) 23.31 ± 25.57% versus SITLESS (evening) 8.10 ± 12.56%; $p = 0.03$), and by 12% during the evening (post-SITLESS) compared to the evening (post-

SIT) (SIT (evening) 20.41 ± 17.74% versus SITLESS (evening) 8.10 ± 12.56%; p = 0.007). While hyperglycaemia increased by 11% during the evening (post-SIT) compared to the overnight (post-SITLES) (SIT (evening) 20.41 ± 17.74% versus SITLESS (overnight) 9.28 ± 13.78%; p = 0.03). No significant differences were observed during the morning (post-SITLESS) compared to the evening (post-SIT), and evening (post-SITLESS) compared to the afternoon (post-SITLESS) for hyperglycaemia, $p > 0.05$.

The Friedman test reported no significant differences were confirmed in the 48-hour post-experimental period when blood glucose concentrations were fluctuating, below the specific ranges (< 3.9 mmol/L and < 3.0 mmol/L), and above the range of 13.9 mmol/L between times of day, $p > 0.05$. In addition, age, BMI, and sex also were not significantly mediated any of the responses confirmed, $p > 0.05$.

Table 6.2 Summary of Measures of Continuous Glucose Monitoring over a 48-hour Post-phase in SIT Condition

	Daily Average	**Morning** (06:00 – 11:45)	**Afternoon** (12:00 – 17:45)	**Evening** (18:00 – 23:45)	**Overnight** (00:00 – 05:45)
Mean blood glucose concentrations (mmol/L)					
Mean ± SD	8.71 ± 2.90	8.43 ± 2.75	8.70 ± 2.84	9.09 ± 3.47	8.62 ± 2.54
95% CI	[8.26, 9.17]	[7.54, 9.32]	[7.77, 9.62]	[7.97, 10.22]	[7.79,9.44]
Glycaemic variability (%)					
Mean ± SD	27.95 ± 12.93	28.87 ± 12.34	31.06 ± 12.07	26.03 ± 12.14	25.83 ± 14.21
95% CI	[25.90, 29.99]	[24.87, 32.88]	[26.94, 35.18]	[22.09, 29.97]	[21.22, 30.44]
CGM metrics (%)					
TIR (%)	67.52 ± 26.76	69.62 ± 26.45	65.86 ± 24.68	68.61 ± 23.69	66.00 ± 32.25
TBR 1 (%)	3.33 ± 6.15	3.96 ± 7.60	3.95 ± 6.19	2.30 ± 4.66	3.10 ± 6.28
TBR 2 (%)	1.08 ± 3.66	1.34 ± 4.62	1.66 ± 4.85	0.51 ± 1.99	0.80 ± 2.22
TAR 1 (%)	20.20 ± 25.53	18.02 ± 20.48	19.07 ± 17.72	20.41 ± 17.74	23.31 ± 25.57
TAR 2 (%)	8.30 ± 16.97	7.76 ± 16.76	9.52 ± 16.74	8.92 ± 19.36	7.00 ± 15.31

Table 6.3 Summary of Measures of Continuous Glucose Monitoring over a 48-hour Post-phase in SITLESS Condition

	Daily Average	**Morning** (06:00 – 11:45)	**Afternoon** (12:00 – 17:45)	**Evening** (18:00 – 23:45)	**Overnight** (00:00 – 05:45)
Mean blood glucose concentrations (mmol/L)					
Mean ± SD	7.50 ± 2.87	7.27 ± 2.23	7.63 ± 3.06	7.72 ± 3.57	7.39 ± 2.52
95% CI	[7.05, 7.95]	[6.54, 7.99]	[6.64, 8.62]	[6.56, 8.87]	[6.57, 8.20]
Glycaemic variability (%)					
Mean ± SD	22.79 ± 11.43	22.67 ± 13.06	24.64 ± 12.11	23.74 ± 10.37	20.12 ± 9.05
95% CI	[20.99, 24.60]	[18.26, 27.08]	[20.72, 28.57]	[20.38, 27.10]	[17.19, 23.05]
CGM metrics (%)					
TIR (%)	80.06 ± 24.19	82.73 ± 22.42	76.15 ± 25.16	79.56 ± 26.42	81.82 ± 22.94
TBR 1 (%)	3.57 ± 8.09	3.31 ± 8.23	3.96 ± 7.56	3.69 ± 9.42	3.31 ± 7.28
TBR 2 (%)	1.49 ± 5.46	1.55 ± 7.43	1.89 ± 6.10	1.76 ± 4.72	0.75 ± 2.46
TAR 1 (%)	9.70 ± 14.14	8.40 ± 10.47	13.04 ± 18.51	8.10 ± 12.56	9.28 ± 13.78
TAR 2 (%)	4.95 ± 16.19	3.90 ± 14.49	4.91 ± 16.08	6.68 ± 20.13	4.30 ± 13.78

6.4 Discussion

This study is the first to investigate the impact of frequent activity breaks from prolonged sitting time on the glucose control over 48-hour in adults with T1D. We found that the SITLESS intervention improved mean blood glucose concentrations and TIR and reduced hyperglycaemia (> 10.0 mmol/L) during the experimental period, and the improvement in TIR and reduction in hyperglycaemia persisted until the 48-hour post-experimental period. Whereas there were no significant increases in glycaemic variability, hypoglycaemia (< 3.9 mmol/L; < 3.0 mmol/L) and hyperglycaemia (> 13.9 mmol/L) occurred in adults with T1D. These findings build on a growing number of experimental studies in adults with T2D (Dempsey et al., 2016a; Dempsey et al., 2016b; Dempsey et al., 2017b; Paing et al., 2019a) or at risk of T2D (Stringer, 2018; Larsen et al., 2019), and support the extension of current PA guidelines by the ADA regarding interrupted prolonged sitting time (American Diabetes Association, 2020a).

Prolonged sitting has been associated with poor glucose control (Paing et al., 2018) leading to long-term diabetes complications in individuals with T2D (L Kearney and P Thyfault, 2016; Haghighatpanah et al., 2018). Conversely, this study showed that interrupted prolonged sitting time resulted in a decrease in mean blood glucose concentrations by 1.27% compared to uninterrupted prolonged sitting in adults with T1D. The ADA stated that the effect of PA on blood glucose concentrations may last up to 24 hours or longer following PA, making the body more sensitive to insulin (American Diabetes Association, 2023).

Time in range is a key metric of the quality of glucose control and reduces the risk of diabetes-related complications. TIR has been identified by individuals with diabetes as impacting quality of daily life, which was correlated with

favourable outcome HbA1c (Runge et al., 2018). A recent study reported a highly inverse correlation between TIR and HbA1c levels (r = −0.75) when HbA1c levels at the end of clinical trial were compared with the CGM data for at least 14 days for individuals with T1D or insulin-treated T2D (Hirsch et al., 2019). In the present study, we observed a 9% improvement in TIR and a 7% reduction in hyperglycaemia under the SITLESS condition, in adults with T1D. TIR is largely determined by the extent and magnitude of hyperglycaemia, for example, if individual has a TIR of 60%, TBR 8%, then the TAR will be 32% (Advani, 2020). In this study, 79% of participants under the SITLESS condition achieved TIR > 70% and 49% achieved TIR = 100% during their experimental visit, compared to 49% and 23% of participants under the SIT condition, respectively. The international consensus recommendation proposes a target of a TIR > 70% (16 hour and 48 minute per day) for individuals with T1D (Battelino et al., 2019).

The mechanisms for increasing TIR and decreasing hyperglycaemia during and post-SITLESS intervention, consistent with previous studies of similar design in adults with T2D, are the result of increases in the contractile-mediated (insulin-independent) glucose uptake pathway. In addition, another possible mediator is an increased in muscle insulin sensitivity, which has obvious clinical significance in the prevention and treatment of chronic IR in peripheral tissue, which has a direct effect on glucose control (Thyfault, 2008). Bergouignan and colleagues (Bergouignan et al., 2016) found that interrupting prolonged sitting with low-intensity PA activates insulin signaling and increases insulin-mediated glucose uptake. Exercise improves insulin sensitivity in skeletal muscle for three to six hours (Richter et al., 1998) and lowers blood glucose concentrations for up to 24 hours (Colberg et al., 2016). These activities enhance short-term insulin sensitivity and long-term glycaemic control (Mikines et al., 1988; Cartee et al.,

1989). Skeletal muscle, responsible for 60 – 70% of postprandial glucose uptake, is essential for glucose homeostasis and T1D management (Mann et al., 2010; Bergouignan et al., 2016).

6.4.1 Time of Day to Exercise in the 48-hour Post-experimental Period

Mean blood glucose concentrations were comparable across conditions, which may be due to increased carbohydrate intake for fear of hypoglycaemia. Fear of hypoglycaemia generally leads to excess intake of carbohydrate and reduction in insulin dose in individuals with T1D (Riddell and Iscoe, 2006b; Brazeau et al., 2008). One study reported that increased carbohydrate consumption could be a reason why the analysis failed to detect the glucose benefit for the intervention (Kennedy et al., 2013). Time in range was significantly increased by ~14% during the morning (post-SITLESS) compared to the evening (post-SIT) with $p = 0.04$. In light of this, Yardley and colleagues (Yardley, 2020b) found that fasted morning exercise has been shown to improved whole body insulin sensitivity in the 24 to 48 hours post-exercise. In the 48-hour post-experimental period, we observed that a TIR > 70% as recommended from international consensus (Battelino et al., 2019) was achieved by 79% of participants during nocturnal time and 51% of participants during daytime post-SITLESS, compared to 72% of participants and 46% of participants post-SIT, respectively.

Hyperglycaemia (> 10.0 mmol/L) was significantly decreased during the evening and overnight (post-SITLESS) compared to the evening and overnight (post-SIT), with $p < 0.05$. More specifically, the SITLESS intervention had a lower time in hyperglycaemia and a greater TIR for up to a further 48-hour post-experimental period. To support our findings one study with the same study design demonstrated that interrupting seven hours sitting time with low-intensity

walking reduced 22 hours hyperglycaemia including nocturnal-to-following morning, in adults with T2D (Dempsey et al., 2017b).

Importantly, glucose reduction was achieved without a significant increase in hypoglycaemia, glycaemic variability, and hyperglycaemia (> 13.9 mmol/L) (p > 0.05) during the SITLESS and the 48-hour post-SITLESS period. To support our findings, one study conducted the similar study design but in different populations found that hypoglycaemic episodes (< 3.9 mmol/L) and glycaemic variability was not significantly different compared to prolonged sitting condition (Dempsey et al., 2017b). Whereas exercise training studies have shown that MVPA was associated with an overnight and following day hypoglycaemia in individuals with T1D (Metcalf et al., 2014; Hasan et al., 2018), and exercise-induced hypoglycaemia has been identified as a main barrier to exercise in T1D (Brazeau et al., 2008). Hence, inability to effectively self-manage blood glucose concentrations during and post-activity prevents safe participation in activity and contributes to worsening diabetes control (Kennedy et al., 2013). Exercise is often viewed as an unachievable or daunting by many individuals who do not exercise or struggle to meet PA recommendations, translating our data into clinical practice and patient education may help reduce the fear of hypoglycaemia around PA and enable better glucose control when adopting low-intensity PA. Consequently, low-intensity PA can be a logical starting point for inactive individuals with T1D to develop and build upon achievable positive behavioural changes that increase their overall activity levels.

6.4.1.1 Time of Day to Exercise and Glycaemic Parameters

Exercise makes the body more sensitive to insulin, as muscle cells are better able to use any available insulin to take up glucose during and post-activity. This is how the PA/exercise helps improve acute (short-term) glucose, and if a person is

active on a regular basis, can lower chronic (long-term) glycaemic control (HbA1c) (American Diabetes Association, 2023). Previous studies have been shown that the time of day to exercise impacts acute glucose responses in individuals with T1D, as fasted morning exercise reduces exercise induced hypoglycaemia compared to postprandial (afternoon) exercise (Jeffrey Ruegemer et al., 1990; Gomez et al., 2015; Toghi-Eshghi and Yardley, 2019; Yardley, 2020b).

Cortisol and growth hormone are vital hormones in managing hypoglycaemic episodes in individuals with diabetes with a variety of mechanism, including increased hepatic glucose synthesis and decreased peripheral glucose uptake leading to an increase in blood glucose concentrations (Yousefi et al., 2022). To support of this notion, Schmidt and colleagues (Schmidt et al., 1981) reported that morning exercise may increase blood glucose concentrations via circadian-mediated elevations in cortisol and growth hormone. Whereas in the afternoon exercise, growth hormone and cortisol decrease, which increases the risk of developing hypoglycaemia, as a gluconeogenesis (i.e., glucose generate from non-carbohydrate substrates) and glucagon (i.e., a hormone produced by the pancreas that helps regulate blood glucose concentrations (Graf et al., 1999)) concentration decrease (Gomez et al., 2015). As diurnal variations of cortisol concentrations may influence insulin sensitivity during PA, glucose changes during PA are likely in individuals with T1D throughout the day. Another possible explanation for lower the incidence of hypoglycaemia post fasted morning exercise is the absence of insulin dosing prior to exercise (Gomez et al., 2015).

6.4.2 Study Strengths and Limitations

Each experimental condition was conducted in a controlled-laboratory setting to maximise internal validity and minimise the inherent variability of less-controlled

'real world' settings. The crossover trial with strict behavioural supervision, standardised meals, appropriate sample size and high participant retention were among the strengths of our study**.** Moreover, the experimental conditions and subsequent free-living condition were captured using a CGM to report real-time glucose continuously.

However, this study has also some potential limitations. First, the study assessed the effects of one-day exposure to prolonged uninterrupted sitting versus interrupted sitting; thus, implications cannot be assumed to long-term exposures. Second, it examined the activity bouts (3-minute) of fixed length. Third, PA was described as low-intensity PA, but walking for some people could be of moderate-intensity PA based on fitness level. Fourth, walking intensity was not measuring using heart rate or oxygen consumption, limiting the ability to accurately assess the intensity of the activity. Fifth, study results may not be generated to those with diabetes complications. Finally, wearable devices (i.e., CGM sensor) may influence participants eating behaviour during the experimental visits. For example, some participants may experience mild stress or pressure from wearing the sensor, which could influence their appetite or eating pace, even though it would not alter the amount of food consumed due to the standardised meals.

6.5 Conclusion

Interrupting time spent in prolonged sitting with frequent low-intensity PA such as walking improves mean blood glucose concentrations, increased TIR and reduced hyperglycaemia without a significant increase in glycaemic variability and hypoglycaemia in adults with T1D for up to a further 48 hours. This provides the first experimental evidence for the value of frequent low-intensity PA for

improving glycaemia in individuals with T1D. This information advances new strategies for improved T1D self-management around PA that may reduce the risk of future diabetes complications. Whereas in this population, activities of daily living remain challenging for managing glucose control, as shown in the public engagement. Research is needed to determine whether patients can maintain such a strategy in free-living environments over the long-term and whether this translates to reduced risk of long-term diabetes complications and improved the quality of life.

6.6 Chapter Summary

- Interrupted prolonged time spent in sitting with frequent, brief bouts of low-intensity PA has been shown to enhance mean blood glucose concentrations, increase TIR, and decrease hyperglycaemia without a significant increase in hypoglycaemia and glucose fluctuations in T1D.
- During the 48-hour post-experimental period, the SITLESS condition demonstrated improvements in TIR in the morning and reductions in hyperglycaemia (> 10.0 mmol/L) in the evening compared to the SIT condition. However, there was an increase in hyperglycaemia during the evening post-SIT compared to overnight post-SITLESS.
- Mean blood glucose concentrations, hypoglycaemia, and hyperglycaemia (> 13.9 mmol/L) did not show significant effects. Age, BMI, and sex also did not mediate any of the response, confirmed ($p > 0.05$) during the 48-hour post-experimental period.

Chapter 7 – General Discussion

7.1 Thesis Overview

This thesis investigated the effects of PA and SBs on glucose control in individuals with T1D, including quantification of PA and sedentary time using objective device-based measures, their effects of glucose control (CGM metrics), and the acute effects of breaking up sedentary time on glucose control. The main findings from the experimental chapters are summarised below.

- Fear of hypoglycaemia was found to be the main barrier to exercise for individuals with T1D and IR, while those with T1D but without IR identified non-diabetes related barriers such as low fitness level and physical health status excluding diabetes as the main barriers (Chapter 3).
- Adults with T1D were physically inactive and more displayed high levels of SB. Additionally, the findings indicated that higher levels of PA were common among adults who were younger, had a lower BMI and education levels, had a shorter duration of T1D, and were retired (Chapter 4, Part A).
- Acute exercise leads to a significant improvement in plasma glucose concentrations post-exercise (Chapter 4, Part B).
- Moderate-intensity PA was positively associated with 24-hour mean blood glucose concentrations and hyperglycaemia and negatively associated with TIR. In contrast, vigorous-intensity PA was negatively associated with 24-hour mean blood glucose concentrations and hyperglycaemia, and positively with TIR. Sit-to-stand transitions were also positively associated with hypoglycaemia. The effect size of these associations was often small (Chapter 5).
- SITLESS approach (interrupted prolonged sitting with 3-minute bouts of

walking) improved blood glucose concentrations and TIR, and decreased hyperglycaemia (> 10.0 mmol/L) during the experimental period, and the improvement in TIR and the reduction in hyperglycaemia persisted until the 48-hour post-experimental period. However, hypoglycaemia, glycaemic variability, and hyperglycaemia (> 13.9 mmol/L) were not observed during the experimental period or the 48-hour post-experimental period. In addition, there was a 14% increase in TIR during the morning post-SITLESS compared to the evening post-SIT, while hyperglycaemia (> 10.0 mmol/L) decreased during the evening and overnight periods post-SITLESS compared to the same periods post-SIT (Chapter 6).

7.1.1 Perceived Barrier to Exercise in Individual with Type 1 Diabetes with and without Insulin Resistance

In Chapter 3, we analysed the data from two RCTs assessing attitudes toward exercise and quality of life in 85 adults with T1D, 39 of whom had IR. Our findings showed that individuals with IR faced greater barriers to exercise related to glycaemic factors, such as risk of hypoglycaemia and hyperglycaemia, with fear of hypoglycaemia being the highest-rated among predetermined set (BAPAD-1 questionnaire). However, this does not necessarily mean it was the greatest overall barrier. Whereas those without IR experienced barriers not related to diabetes but linked to fitness and physical health status excluding diabetes. Surprisingly, we did not find a difference in quality of life between individuals with T1D when stratified by IR status, as noted previously in comparison to general population, which might be attributable to the small sample size.

Many individuals with T1D struggle to meet the recommended levels of PA and prior research suggest that this could be attributed to a fear of hypoglycaemia

and a lack of knowledge about diabetes management around exercise (Brazeau et al., 2008; Kennedy et al., 2018). Despite this, it has not previously been established whether these barriers are the same in individuals with T1D with or without IR. IR contributes to the challenges for managing T1D, leading to difficulties achieving target blood glucose concentrations (Wolosowicz et al., 2020), which could explain why glycaemic factors are more significant obstacles for those with IR.

The findings highlight the importance of recognising the barriers to exercise faced by individuals with T1D, and the potential need to differentiate between individuals with and without IR. Indeed, to create better management strategies in those with and without IR, it may be prudent to consider factors such as implementing moderate-intensity cardiovascular exercise (e.g., walking) in accordance with PA guidelines, and providing individualised dietary modifications that limit carbohydrate, particularly refined grain products and high-glycaemic index carbohydrate, which are important for weight management and improving glucose control in those with IR (Freeman and Pennings, 2021). While those without IR may benefit from balanced dietary adjustments including carbohydrate intake and regularly exercise, with an emphasis on maintaining glucose control (Reynolds and Mitri, 2024). Additionally, this emphasises the need for specialised intervention to address the specific challenges faced by each group, with the goal of improving participation in PA/exercise.

7.1.2 Systematic Review and Meta-Analysis of Physical Activity, Time Spent in Sedentary Behaviours, and Glucose Control.

The amount of PA and SBs among adults with T1D varies markedly in the literature. There are also limited studies specifically quantifying SBs in individuals

with T1D, such as reading, watching TV, using a computer, sitting in a car, and other behaviours. Therefore, Chapter 4, Part A included a systematic review aimed at quantifying the amount of PA and SBs undertaken by adults with T1D. Importantly, this was the first review to quantify the amount of PA and SBs by adults with T1D using both self-reported and objective measures.

This review included a total of 53 studies and based on both objective and self-reported measures, revealed that while some adults with T1D were physically active, the overall findings indicate that the majority are physically inactive and predominantly sedentary. This finding is consistent with a recent review on youth with T1D, which reported that they tend to be less physically active and more sedentary than their healthy peers (Huerta-Uribe et al., 2023). Significant heterogeneity was seen in the methods used to assess PA and the cut-points used to determine intensities, while self-report measures were found to overestimate PA and underestimate sedentary time relative to device-measured estimates. Additionally, Part A of this chapter also examined the moderators that influence levels of PA in adults with T1D. The findings also suggested that adults with younger age, male sex, lower BMI, shorter diabetes duration, lower education levels, and retirement status tend to engage in higher levels of PA, which may help identify specific target groups for interventions designed to enhance PA (rather than a ‘one-size-fit-all’ approach). A key implication of our findings is the need for more comprehensive research using uniform, device-based methodologies to accurately monitor PA levels and SB in adults with T1D. Standardising the assessment methods would allow for clearer conclusions about the actual amount of PA in this population and facilitate more effective comparisons across studies.

These findings emphasise the significant issue of physical inactivity and

excessive SBs among those with T1D, and this highlights the need for strategies that reduce prolonged sitting and encourage more regular movement throughout the day. Addressing inactivity is vital to improve overall health outcomes and enhance glucose control, as sedentary lifestyles can negatively impact metabolic health (e.g., impaired insulin sensitivity, resulting in high blood glucose concentrations) (Saunders et al., 2012), and increase the risk of diabetes-related complications (e.g., high blood glucose concentrations (chronic hyperglycaemia) can increase the risk of complications such as CVDs including atherosclerosis, coronary artery disease and stroke, as well as microvascular complications (retinopathy and nephropathy)) (Colom et al., 2021).

In Part B of the chapter, the impact of both acute exercise (a single bout of aerobic exercise) and chronic exercise (long-term aerobic exercise training) on glycaemic patterns in adults with T1D was meta-analysed. The type, intensity, and duration of exercise have been shown in the literature to influence glucose regulation (Colberg et al., 2015), with previous studies suggesting that an acute bout of exercise may negatively impact glycaemic control in individuals with T1D. This meta-analysis included 14 studies, with eight focusing on glycaemia concentrations after a single bout of exercise and six examining glycaemia following long-term training. The analysis showed that plasma glucose concentrations decreased following single bouts of moderate aerobic exercise, whereas glycaemic control (HbA1c) did not differ following long-term training. Inconsistent findings have previously been observed in a meta-analysis on glycaemic control in adolescent with T1D after 24-hour movement behaviours, with a reduction in HbA1c found across 76 studies (Patience et al., 2023). Potential mechanisms for the improvement of plasma glucose concentrations following a single bout of exercise in T1D include increased insulin sensitivity,

enhanced glucose uptake, and improved insulin-independent glucose transport (Bird and Hawley, 2017). The findings highlight the importance of acute aerobic exercise interventions, demonstrating that even brief bouts of PA can effectively improve glucose control. This finding supports the implementation of short, targeted bouts of exercise, such as the three-minute walking interruptions discussed in Chapter 6, as practical and immediate strategies for managing blood glucose concentrations.

7.1.3 Activities of Daily Living and Glucose Control

The aim of Chapter 5 was to measure PA (GENEActiv) and SB (ActivPAL) over a 14-day period using objective measures, alongside a CGM, to evaluate the impact of daily activities on glucose control in adults with T1D. Data showed that participants engaged more in low-intensity PA (260.25 minutes per day; ~4 hours) compared to moderate-intensity PA (92.22 minutes per day; ~2 hours) and vigorous-intensity PA (2.50 minutes per day) during the study period. While participants spent an average of 705.97 minutes per day (~12 hours) in SBs according to the GENEActiv device, the ActivPAL device indicated an average of 548.14 minutes per day (~9 hours). This indicates that despite engaging in various intensities of PA throughout the day, participants still spent a significant amount of time sedentary. Given the negative health effects of sedentary time, it is therefore important to interrupt prolonged sitting time with frequent bouts of low-intensity PA in this population.

When assessing whether daily activities of low-, moderate-, and vigorous-intensity PA (GENEActiv) predict glucose control, it was found that each minute of moderate-intensity PA was associated with an increase in mean blood glucose concentrations by 0.001 mmol/L and a 0.01% in hyperglycaemia (> 13.9 mmol/l). Conversely, each minute of vigorous-intensity PA was associated with a

decrease in mean blood glucose concentrations by 0.001 mmol/L and a 0.31% reduction in hyperglycaemia (> 13.9 mmol/l). Additionally, TIR decreased by 0.10% during moderate-intensity PA but increased by 2.92% during vigorous-intensity PA. However, hypoglycaemia was not significantly associated with daily activities. While these findings are statistically significant, the effect sizes are relatively small, suggesting they may not be large enough to have a meaningful impact on clinical outcomes. The difference between moderate and vigorous activities may be due to physiological adaptations seen with vigorous activity, as greater metabolic changes – including increased GLUT4 translocation, enhanced insulin sensitivity, and more effective glycogen depletion and replenishment – tend to occur more prominently with vigorous activity, thus promoting glucose uptake and improving glucose control (Adams, 2013; Eckstein et al., 2023). Additionally, sustained moderate activity raises stress hormones like cortisol, increasing blood glucose concentrations (Horton and Beisel, 1994), while vigorous activity, despite an initial spike in stress hormones, leads to lower blood glucose concentrations as hormone concentrations decline post-activity and muscle continue using glucose (Marliss and Vranic, 2002).

Sedentary behaviour was also assessed using the ActivPAL device to predict glucose responses over a 14-day study period. The findings indicated that each additional minute of lying time was associated with a slight rise in blood glucose concentrations of 0.001 mmol/L, which was unlikely to be clinically significant given typical fluctuations in blood glucose. Similarly, each additional sit-to-stand transition associated with a 0.02% increase in hypoglycaemia risk, a change too small to be of clinical concern in most populations. These effect sizes suggest that, although statistically detectable, the observed associations may not have practical implications for clinical practice or patient management.

Correlation analyses were performed to assess the reliability of different sedentary time assessment measures, revealing no significant correlations between GENEActiv and ActivPAL (r = 0.22; p = 0.17), GENEActiv and the IPAQ (r = 0.14; p = 0.39), and ActivPAL and the IPAQ (r = 0.04; p = 0.82). The lack of correlation between objective measures may be due to differences in device sensitivity in detecting certain types of movement, sensor placement, and the algorithm used to interpret the data, while the lack of correlation between the objective and self-reported questionnaire is most likely due to underestimation of sedentary time using the self-reported measure. This finding suggests that despite the use of objective devices, there may still be differences in estimates of sedentary time between different brands that complicate interpretation when comparing between studies using different devices. This highlights the need for careful standardisation of data, such as the analysis of raw acceleration data using open-source packages such as GGIR that can harmonise data from different brands of devices. However, devices measured PA and sedentary time still remain more accurate and reliable data than self-reported measures, which often underestimate SBs.

The findings of Chapter 5 highlight the importance of interrupting prolonged sitting to reduce the risk of hypoglycaemia, particularly through low-intensity activities. Even simple movements can significantly impact blood glucose concentrations, suggesting that regular activity breaks can help stabilise blood glucose concentrations and mitigate the negative effects of SBs, ultimately improving overall glucose control.

7.1.4 Interrupting Sitting Approach and Glucose Control

Chapters 4 and 5 reveals that adults with T1D tend to spend a considerable amount of their day being sedentary. In Chapter 6, it was proposed that

interrupted prolonged sitting with frequent short, frequent activity breaks was therefore a logical and simple approach to improve glucose control. While evidence supporting this approach and its impact on glucose control in individuals with T2D is well-established (Dempsey et al., 2016a; Dempsey et al., 2016b), the body of evidence for T1D remains limited. Current recommendations for PA in T1D are often based on conclusions drawn from studies on T2D, despite the difference in underlying mechanisms between two conditions. T2D is characterised by IR, while T1D is an autoimmune disorder resulting in insulin deficiency, necessitating different management strategies.

Given this research gap, the aim of Chapter 6 was to assess the effects of breaking up prolonged sitting with frequent, short bouts of low-intensity PA over 48-hour period. Furthermore, we aimed to investigate whether breaking up prolonged sitting time has an effect on glucose control at different times throughout the 48-hour following the intervention using CGM. The study findings indicated that mean blood glucose concentrations were reduced by 2.27 mmol/L post-SITLESS condition and by 1.18 mmol/L during the 48-hour post-intervention period under the SITLESS condition. TIR increased by ~9% and hyperglycaemia (> 10.0 mmol/L) and reduced by 7% under the SITLESS condition. The SITLESS intervention had no significant impact on glycaemic variability, hypoglycaemia, and hyperglycaemia (> 13.9 mmol/L).

Findings from the 48-hour post-experimental period indicated several important observations concerning the time of day. The mean blood glucose concentrations did not differ significantly across all time comparisons ($p > 0.05$). Time spent within the target range of glucose increased ~14% during the morning post-SITLESS compared to the evening post-SIT ($p = 0.04$). Hyperglycaemia (> 10.0 mmol/L) reduced by 15% in the evening post-SITLESS compared to the

overnight post-SIT (p = 0.03), and by 3% in the evening post-SITLESS compared to the evening post-SIT (p = 0.007). While hyperglycaemia (> 10.0 mmol/L) increased by 11% in the evening post-SIT compared to the overnight post-SITLESS (p = 0.03). Remarkably, there were no significant difference in glycaemic variability, hyperglycaemia (> 13.9 mmol/L), and hypoglycaemia between times of day across conditions (p > 0.05).

These findings suggest that the interrupted sitting is a promising approach for improving glucose control in individuals with T1D. The significant reduction in hyperglycaemia and the increase in TIR indicate that frequent, short bouts of low-intensity PA effectively manage blood glucose concentrations without increasing the risk of hypoglycaemia. This is particularly important for individuals with T1D, who often have a fear of hypoglycaemia. The interrupted sitting provides a feasible and simple strategy to improve glucose control and overall well-being, potentially supporting better glucose management and reducing the risk of long-term complications.

7.2 Methodological Considerations and Limitations

The methodological approaches used in this thesis reflect a comprehensive effort to investigate the impact of PA and SBs on glucose control in individuals with T1D using objective tools. The secondary analysis of two RCTs in Chapter 3 provided robust framework for exploring the existing data, although the original study designs restricted the scope of new hypothesis. The systematic review and meta-analysis in Chapter 4 adhered to strict (PRISMA) criteria and captured a wide range of data through the PICOs principle, while variability in measurement and reporting of exercise intensities was careful standardisation. The observational study in Chapter 5 provided valuable real-world insights, while the randomised

crossover trial in Chapter 6 employed a gold standard RCT design which enabled within-subject comparisons to be made. Across Chapters 5 and 6, consistent sample selection and use of reliable, validated measurement tools such as CGM and objective measures of PA and sedentary time (accelerometry) ensured that data collection was accurate, supporting the overall findings of the research.

Despite the strengths of the methodological approach, several limitations were noted. A significant challenge across the studies, particularly in the systematic review and meta-analysis in Chapter 4, was the variability in methodological measurement. Differences in the units, cut-off points, and tools used to measure PA and SBs across the included studies introduced heterogeneity, which complicates the comparability of results and may affect the consistency and generalisability of the findings. Despite efforts to standardise exercise intensities according to ACSM guidelines, the variety in measurement methods posed a limitation that can influence the overall conclusions drawn from the research. Furthermore, this variability, coupled with potential technical issues like missing data from the CGM devices and occasional malfunction of activity monitors, highlights the complexities involved in accurately assessing PA and SBs, which may ultimately impact the strength of the study conclusions.

7.3 Future Research

Future investigation is essential to assess whether individuals with T1D can maintain the strategy of interrupted sitting in free-living environments over the long-term and if this approach results in a reduced risk of long-term diabetes complications and improved quality of life. Longitudinal studies and randomised controlled trials are needed to assess whether individuals with T1D can maintain adherence to interrupted sitting over time and to identify behavioural,

physiological, and external factors (i.e., work and daily routine, social and environmental support, and weather) that impact long-term success. Additionally, future research should concentrate on developing tailored interventions for glucose control, considering associations with prolonged lying time, BMI, age, and sit-to-stand transitions. This is particularly important given the increasing availability of advanced wearables and CGM systems that provide real-time lifestyle data. More research is required to determine how these technologies can be effectively integrated into personalised interventions to improve glycaemia. Furthermore, exploring potential barriers to adherence – such as motivation, accessibility, and feasibility in different lifestyle settings – will be crucial for designing practical and lasting lifestyle changes for individuals with T1D. After completing my PhD, I plan to continue working in both research and clinical practice, focusing on developing and evaluating lifestyle and health interventions to improve overall well-being and disease management in those with diabetes.

7.4 Publications and Planned Submissions

The research conducted for this thesis has resulted in several peer-reviewed journal articles. Below is a summary of the published papers and abstracts, followed by the chapters intended for future submission to academic journals.

7.4.1 Published Papers and Abstracts

Table 7.1 Summary of Published Papers and Abstracts

Chapter	Cite
Part of Chapter 1 Literature Review	**Alobaid, A.M.,** Dempsey, P.C., Francois, M., Zulyniak, M.A., Hopkins, M. and Campbell, M.D., 2023. Reducing sitting time in type 1 diabetes: considerations and implications. *Canadian Journal of Diabetes*, *47*(3), pp.300-304. https://doi.org/10.1016/j.jcjd.2023.02.003

Part of Chapter 3 Barriers to Exercise in Adults with Type 1 Diabetes and Insulin Resistance	**Alobaid, A.M.,** Zulyniak, M.A., Ajjan, R.A., Brož, J., Hopkins, M. and Campbell, M.D., 2023. Barriers to exercise in adults with type 1 diabetes and insulin resistance. Canadian journal of diabetes, 47(6), pp.503-508. https://doi.org/10.1016/j.jcjd.2023.04.016
Part of Chapter 6 Interrupting prolonged sitting with frequent short bouts of light-intensity activity in people with type 1 diabetes improves glycaemic control without increasing hypoglycaemia: The SIT-LESS randomised controlled trial	Campbell, Matthew D., **Anwar M. Alobaid**, Mark Hopkins, Paddy C. Dempsey, Sam M. Pearson, Noppadol Kietsiriroje, Rachel Churm, and Ramzi A. Ajjan. "Interrupting prolonged sitting with frequent short bouts of light-intensity activity in people with type 1 diabetes improves glycaemic control without increasing hypoglycaemia: The SIT-LESS randomised controlled trial." *Diabetes, Obesity and Metabolism* 25, no. 12 (2023): 3589-3598. https://doi.org/10.1111/dom.15254

Abstracts	**Cite**
Chapter 3	**Alobaid, A.M.,** Zulyniak, M.A., Ajjan, R.A., Brož, J., Hopkins, M. and Campbell, M.D., 2023. Barriers to exercise in adults with type 1 diabetes and insulin resistance. *Canadian journal of diabetes*, *47*(6), pp.503-508.
Chapter 6	**Alobaid, A.,** Dingena, C., Marsh, A., Coales, E.M., Dempsey, P., Francois, M., Ajjan, R. and Campbell, M., 2020. Interrupted sitting improves acute postprandial glucose control without increasing risk of hypoglycaemia in people with type 1 diabetes [Conference abstract]. *Diabetologia*, 63(1), pp.1-485.
	Campbell, M., Dingena, C., Marsh, A., Coales, E.M., O'Mahoney, L.L., Dempsey, P., Francois, M., Ajjan, R. and **Alobaid, A.**, 2020. Interrupted sitting improves 24-hour glucose control in people with type 1 diabetes [Conference abstract]. *Diabetologia,* 63(1), pp.1-485.

7.4.2 Planned Submissions

The following chapters of the thesis are intended for future publication:

- **Chapter 4** – Quantifying Physical Activity and Sedentary Time in Individuals with Type 1 Diabetes and Their Effects on Glucose Control: A Systematic Review and Meta-Analysis.
    - Intended Journal: Diabetes Research and Clinical Practice.

- **Chapter 5** – Characterising the Impact of Daily Activities on Glucose Control in Adults with Type 1 Diabetes: An Observational Study.
    - Intended Journal: Canadian Journal of Diabetes.

7.5 Conclusions and Overall Implications

This thesis highlights the complexities involved in managing T1D, particularly the differing barriers to exercise faced by those with and without IR. The research further reveals the critical impact of PA intensity and patterns on glucose control, as well as the potential benefits of interventions such as interrupted sitting. These findings suggest that personalised approaches are necessary for optimising glucose management, reducing the risk of diabetes-related complications, and enhancing overall quality of life in individuals with T1D.

The overall implications of this thesis emphasise the importance of developing tailored, evidence-based strategies for managing T1D. The research advocates for integrating personalised interventions that address the distinct challenges associated with IR, physical inactivity, and SB into clinical practice and public health guidelines. Additionally, this thesis emphasises the need for further research to explore the long-term effectiveness of the interrupted sitting intervention in real-word settings and its potential to reduce complications and enhance quality of life.

By promoting practical strategies (i.e., interrupted sitting) and technological tools (i.e., CGMs), this research supports efforts to improve health outcomes for individuals with T1D. These findings can be translated into real-world applications by incorporating movement-based interventions into diabetes self-management programmes, workplace wellness efforts, and structured exercise plans tailored to individuals with T1D. Healthcare professionals can also use these insights to provide more precise guidance on PA intensity and patterns, ensuring that exercise recommendations align with individual metabolic responses. Additionally, community health programmes and healthcare providers can use this research to create simple, effective ways to encourage more movement in daily routines, especially for those at risk of sitting too much.

7.6 Impact and Adaption during the COVID-19 Pandemic

7.6.1 Impact of the COVID-19 Pandemic on the Research Programme

The COVID-19 pandemic significantly disrupted the original research plans, particularly delaying the start of the human clinical trial in individuals with T1D by ~18 months (1st experimental study (interrupted sitting study), Chapter 6). Originally scheduled to begin in June 2020, the study was postponed due to university closures, research facilities shutdowns, and restrictions imposed by the Leeds NHS Trust, which did not allow non-essential clinical research in hospitals. Additionally, national lockdowns and institutional policies prevented relocation of the study to alternative sites.

When recruitment finally began in May 2022, ongoing COVID-19 precautions made it difficult to recruit participants, resulting in a small sample size of eight participants from the Leeds site. To address this, we integrated data from Sunderland, ensuring consistency in procedures under the supervision of Dr.

Matthew Campbell. The delays in this study also impacted the timeline for the 2nd experimental study (Activities of daily living, Chapter 5), which required ethics approval and began in September 2023, ending in February 2024.

7.6.2 Steps Taken to Mitigate Disruptions

To minimise the impact of these delays, several adjustments were made:

- Weekly online meetings with my supervisor were held while I was in Kuwait to maintain progress and adapt research plans as necessary.
- The study protocol for the 1st experimental study was developed and successfully registered with the International Standard Randomised Controlled Trial Number (ISRCTN), ensuring that the trial could begin as soon as conditions allowed.
- A narrative review (Chapter 1) was prepared drafted during the period.
- The protocol for a systematic review and meta-analysis (Chapter 4) was developed, including the formulation of a search strategy.
- Presented posters at the European Association for the Study of Diabetes (EASD) 56th Annual Meeting (2020) (held online), with the following titles:
    - *Interrupted Sitting Improves 24-Hour Glucose Control in People with Type 1 Diabetes.*
    - *Interrupted Sitting Improves Acute Postprandial Glucose Control without Increasing Risk of Hypoglycaemia in People with Type 1 Diabetes.*

These strategic adaptations allow the research to continue progressing, despite the external disruptions.

7.6.3 Changes in Research Direction and Adjustments to the Plan

Since the timeline for human trials was uncertain, we decided to shift focus towards other research components that could be conducted remotely. Instead of waiting for the clinical trial to begin, we prioritised the literature-review and secondary data analysis components of the thesis, keeping the research productive and ensuring a smoother transition when the trial could begin.

7.6.4 Successful Adaptations and Outcomes (What went well)

The ability to restructure the research timeline and focus on literature review, systematic review (search strategy), and secondary data analysis ensured continued academic progress. Regular online supervision meetings provided essential guidance and allowed for real-time problem-solving. Registering the clinical trial during the delay period helped speed up ethical approval processes once the trial was able to commence.

7.6.5 Challenges and Limitations

The 18-month delay in starting the clinical trial had a significant impact on the project timeline, creating a compressed schedule for subsequent studies. Recruitment challenges in the post-pandemic period resulted in a small sample size, requiring the integration of data from an additional site to strengthen findings. The inability to relocate the study due to government and university restrictions limited research flexibility.

7.6.6 Lessons Learned and Future Improvements

Future projects should incorporate flexible contingency plans, such as shifting activity studies before the interrupted sitting, using remote recruitment, or designing hybrid approaches (e.g., virtual patient participation where possible).

7.6.7 Research Achievements and Academic Progress

Despite the significant disruptions caused by the COVID-19 pandemic, the research programme adapted through strategic planning, focusing on reviews, study protocol, and ethical approval while awaiting the clinical trials. Despite these challenges, I completed all studies, published three papers (a narrative review, a study on barrier to exercise, and an interrupted sitting study), wrote this PhD thesis, and will continue working on daily activities and a systematic review and meta-analysis. Moving forward, adopting flexible data collection methods and proactive strategies will ensure adaptability to future disruptions.

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Appendix A: Supplementary materials for Chapter 4

Table A.1: Questions per Domain for Risk of Bias 2 (RoB2)

A.1.1 Randomised Controlled Trials

Domains	Sub-questions
Domain 1a: Randomisation process	**1a.1** Was the allocation sequence random? **1a.2** Was the allocation sequence concealed until clusters were enrolled and assigned to interventions? **1a.3** Did baseline differences between intervention groups suggest a problem with the randomization process?
Domain 1b: Timing of identification or recruitment of participants	**1b.1** Were all the individual participants identified and recruited (if appropriate) before randomization of clusters? **1b.2** If N/PN/NI to **1b.1:** Is it likely that selection of individual participants was affected by knowledge of the intervention assigned to the cluster? **1b.3** Were there baseline imbalances that suggest differential identification or recruitment of individual participants between intervention groups?
Domain 2: Deviations from intended interventions	**2.1a** Were participants aware that they were in a trial? **2.1b** If Y/PY/NI to **2.1a:** Were participants aware of their assigned intervention during the trial? **2.2** Were carers and people delivering the interventions aware of participants' assigned intervention during the trial? **2.3** If Y/PY/NI to **2.1b or 2.2:** Were there deviations from the intended intervention that arose because of the trial context? **2.4** If Y/PY to **2.3:** Were these deviations likely to have affected the outcome? **2.5.** If Y/PY/NI to **2.4:** Were these deviations from intended intervention balanced between groups? **2.6** Was an appropriate analysis used to estimate the effect of assignment to intervention? **2.7** If N/PN/NI to **2.6:** Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?

Domain 3: Missing outcome data	**3.1a** Were data for this outcome available for all clusters that recruited participants? **3.1b** Were data for this outcome available for all, or nearly all, participants within clusters? **3.2** If N/PN/NI to **3.1a or 3.1b:** Is there evidence that the result was not biased by missing data? **3.3** If N/PN to **3.2:** Could missingness in the outcome depend on its true value? **3.4** If Y/PY/NI to **3.3:** Is it likely that missingness in the outcome depended on its true value?
Domain 4: Measurement of the outcome	**4.1** Was the method of measuring the outcome inappropriate? **4.2** Could measurement or ascertainment of the outcome have differed between intervention groups? **4.3a** If N/PN/NI to **4.1** and **4.2:** Were outcome assessors aware that a trial was taking place? **4.3b** If Y/PY/NI to **4.3a**: Were outcome assessors aware of the intervention received by study participants? **4.4** If Y/PY/NI to **4.3b:** Could assessment of the outcome have been influenced by knowledge of intervention received? **4.5** If Y/PY/NI to **4.4:** Is it likely that assessment of the outcome was influenced by knowledge of intervention received?
Domain 5: Selection of the reported results	**5.1** Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis? Is the numerical result being assessed likely to have been selected, on the basis of the results, from…**5.2** ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? **5.3** ... multiple eligible analyses of the data?
Note- Y: Yes; PY: Probably yes; PN: Probably no; N: No; NI: No information. The risk of bias questions derived from the Cochrane RoB2 tool (Sterne et al., 2019).	

A.1.2 Randomised Controlled Trials with a Crossover Design

Domains	Sub-questions
Domain 1: Randomisation process	**1.1** Was the allocation sequence random?
	1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?
	1.3 Did baseline differences between intervention groups at the start of the first period suggest a problem with the randomisation process?
Domain S: Bias arising from period and carryover effects	**S.1** Was the number of participants allocated to each of the two sequences equal or nearly equal?
	S.2 If N/PN/NI to **S.1:** Were period effects accounted for in the analysis?
	S.3 Was there sufficient time for any carryover effects to have disappeared before outcome assessment in the second period?
Domain 2: Deviations from intended interventions	**2.1** Were participants aware of their assigned intervention during each period of the trial?
	2.2 Were carers and people delivering the interventions aware of participants' assigned intervention during each period of the trial?
	2.3 If Y/PY/NI to **2.1 or 2.2:** Were there deviations from the intended intervention that arose because of the trial context?
	2.4 If Y/PY to **2.3:** Were these deviations likely to have affected the outcome?
	2.5 If Y/PY/NI to **2.4:** Were these deviations from intended intervention balanced between groups?
	2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?
	2.7 If N/PN/NI to **2.6:** Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomised?
Domain 3: Missing outcome data	**3.1** Were data for this outcome available for all, or nearly all, participants randomised?
	3.2 If N/PN/NI to **3.1:** Is there evidence that the result was not biased by missing outcome data?
	3.3 If N/PN to **3.2:** Could missingness in the outcome depend on its true value?

	3.4 If Y/PY/NI to **3.3:** Is it likely that missingness in the outcome depended on its true value?
Domain 4: Measurement of the outcome	**4.1** Was the method of measuring the outcome inappropriate? **4.2** Could measurement or ascertainment of the outcome have differed between intervention within each sequence? **4.3** If N/PN/NI to **4.1 and 4.2:** Were outcome assessors aware of the intervention received by study participants? **4.4** If Y/PY/NI to **4.3:** Could assessment of the outcome have been influenced by knowledge of intervention received? **4.5** If Y/PY/NI to **4.4:** Is it likely that assessment of the outcome was influenced by knowledge of intervention received?
Domain 5: Selection of the reported results	**5.1** Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalised before unblinded outcome data were available for analysis? Is the numerical result being assessed likely to have been selected, on the basis of the results, from… **5.2** ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain? **5.3** ... multiple eligible analyses of the data? **5.4** Is a result based on data from both periods sought, but unavailable on the basis of carryover having been identified?
Note- Y: Yes; PY: Probably yes; PN: Probably no; N: No; NI: No information. The risk of bias questions derived from the Cochrane RoB2 tool (Sterne et al., 2019).	

Table A.2: Questions per Domain for Risk of Bias In Non-randomised Studies – of Interventions (ROBINS-I)

A.2.1 Non-Randomised Studies

Domains	Sub-questions
Domain 1: Bias due to confounding	**1.1** Is there potential for confounding of the effect of intervention in this study? If N/PN to **1.1:** the study can be considered to be at low risk of bias due to confounding and no further signalling questions need be considered. [If Y/PY to **1.1:** determine whether there is a need to assess time-varying confounding]: **1.2** Was the analysis based on splitting participants' follow-up time according to intervention received? **1.3** Were intervention discontinuations or switches likely to be related to factors that are prognostic for outcome?
	Questions relating to baseline confounding only **1.4** Did the authors use an appropriate analysis method that controlled for all the important confounding domains? **1.5** If Y/PY to **1.4:** Were confounding domains that were controlled for measured validly and reliably by the variables available in this study? **1.6** Did the authors control for any post-intervention variables that could have been affected by the intervention?
	Questions relating to baseline and time-varying confounding **1.7** Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? **1.8** If Y/PY to **1.7**: Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?
Domain 2: Selection of participants into the study	**2.1** Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? If N/PN to **2.1:** go to **2.4** **2.2** If Y/PY to **2.1:** Were the post-intervention variables that influenced selection likely to be associated with intervention?
	2.3 If Y/PY to **2.2:** Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome?

	2.4 Do start of follow-up and start of intervention coincide for most participants? **2.5** If Y/PY to **2.2 and 2.3**, or N/PN to **2.4:** Were adjustment techniques used that are likely to correct for the presence of selection biases?
Domain 3: Classification of interventions	**3.1** Were intervention groups clearly defined? **3.2** Was the information used to define intervention groups recorded at the start of the intervention? **3.3** Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?
Domain 4: Deviations from intended interventions	If your aim for this study is to assess the effect of assignment to intervention, answer questions **4.1 and 4.2** **4.1** Were there deviations from the intended intervention beyond what would be expected in usual practice? **4.2** If Y/PY to **4.1:** Were these deviations from intended intervention unbalanced between groups and likely to have affected the outcome? If your aim for this study is to assess the effect of starting and adhering to intervention, answer questions **4.3 to 4.6** **4.3** Were important co-interventions balanced across intervention groups? **4.4** Was the intervention implemented successfully for most participants? **4.5** Did study participants adhere to the assigned intervention regimen? **4.5** If N/PN to **4.3, 4.4 or 4.5:** Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?
Domain 5: Missing data	**5.1** Were outcome data available for all, or nearly all, participants? **5.2** Were participants excluded due to missing data on intervention status? **5.3** Were participants excluded due to missing data on other variables needed for the analysis? **5.4** If PN/N to **5.1**, or Y/PY to **5.2 or 5.3:** Are the proportion of participants and reasons for missing data similar across interventions? **5.5** If PN/N to **5.1**, or Y/PY to **5.2 or 5.3:** Is there evidence that results were robust to the presence of missing data?
Domain 6:	**6.1** Could the outcome measure have been influenced by knowledge of the intervention received?

Measurement of outcomes	**6.2** Were outcome assessors aware of the intervention received by study participants? **5.3** Were the methods of outcome assessment comparable across intervention groups? **5.4** Were any systematic errors in measurement of the outcome related to intervention received?
Domain 7: Selection of the reported result	**7.1** Is the reported effect estimate likely to be selected, on the basis of the results, from ... multiple outcome measurements within the outcome domain? **7.2** ... multiple analyses of the intervention-outcome relationship? **7.3** ... different subgroups?

Note - Y: Yes; PY: Probably yes; PN: Probably no; N: No; NI: No information. The questions for risk of bias were derived from the Cochrane ROBINS-I (Sterne et al., 2016).

Table A.3: Questions per Domain for Newcastle-Ottawa Scale (NOS)

A.3.1 Cohort Studies

Domains	Sub-questions
Domain 1: Selection (Max 4*)	**1.1** Representativeness of the exposed cohort **a.** Truly representative of the average ___ (describe) in the community. * **b.** Somewhat representative of the average ___ in the community. * **c.** Selected group of users eg nurses, volunteers. **d.** No description of the derivation of the cohort. **1.2** Selection of the non-exposed cohort **a.** Drawn from the same community as the exposed cohort.* **b.** Drawn from a different source. **c.** No description of the derivation of the non-exposed cohort. **1.3** Ascertainment of exposure **a.** Secure record (eg surgical records).* **b.** Structured interview. * **c.** Written self-report. **d.** No description **1.4** Demonstration that outcome of interest was not present at start of study **a.** Yes. * **b.** No.
Domain 2: Comparability (Max 2 **)	**2.1** Comparability of cohorts on the basis of the design or analysis. **a.** Study controls for ____ (select the most important factor).* **b.** Study controls for any additional factor. * (this criteria could be modified to indicate specific control for a second important factor).

Domain 3: Outcome (Max 3*)	**3.1** Ascertainment of outcome **a.** Independent blind assessment. * **b.** Record linkage. * **c**. Self report. **d.** No description **3.2** Was follow-up long enough for outcomes to occur **a.** Yes (select an adequate follow up period for outcome of interest). * **b.** No. **3.3** Adequacy of follow up of cohorts **a.** Complete follow up – all subjects accounted for. * **b.** Subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost). * **c.** Follow up rate < ____% (select an adequate %) and no description of those lost. **d.** No statement

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure categories. A maximum of two stars can be given for Comparability. The questions for risk of bias were derived from the NOS (Wells et al., 2021).

A.3.2 Case Control Studies

Domains	Sub-questions
Domain 1: Selection (Max 4*)	**1.1** Is the case definition adequate? **a.** Yes, with independent validation. * **b.** Yes, eg record linkage or based on self-reports. **c.** No description. **1.2** Representativeness of the cases **a.** Consecutive or obviously representative series of cases. * **b.** Potential for selection biases or not stated. **1.3** Selection of Controls **a.** Community controls. * **b.** Hospital controls. **c.** No description. **1.4** Definition of Controls **a.** No history of disease (endpoint). * **b.** No description of source
Domain 2: Comparability (Max 2*)	**2.1** Comparability of cases and controls on the basis of the design or analysis. **a.** Study controls for __ (Select the most important factor). * **b.** Study controls for any additional factor. * (this criteria could be modified to indicate specific control for a second important factor).
Domain 3: Exposure (Max 3*)	**3.1** Ascertainment of exposure **a.** Secure record (e.g., surgical records). * **b.** Structured interview where blind to case/control status. * **c.** Interview not blinded to case/control status. **d.** Written self-report or medical record only. **e.** No description. **3.2** Same method of asertainment for cases and controls **a.** Yes. * **b.** No. **3.3** Non-Response rate **a.** Same rate for both groups. * **b.** Non respondents described. **c.** Rate different and no designation.

Note: A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories. A maximum of two stars can be given for comparability. The questions for risk of bias were derived from the NOS (Wells et al., 2021).

A.3.3 Cross Sectional Studies

Domains	Sub-questions
Domain 1: Selection (Max 5*)	**1.1** Representativeness of the sample **a.** Truly representative of the average in the target population. * (all subjects or random sampling) **b.** Somewhat representative of the average in the target group. * (non-random sampling) **c.** Selected group of users/convenience sample. **d.** No description of the derivation of the included subjects. **1.2** Sample size **a.** Justified and satisfactory (including sample size calculation). * **b.** Not justified. **c.** No information provided **1.3** Non-respondents **a.** Justified and satisfactory (including sample size calculation). * **b.** Not justified. **c.** No information provided **1.4** Ascertainment of the exposure (risk factor) **a.** Vaccine records/vaccine registry/clinic registers/hospital records only. ** **b.** Parental or personal recall and vaccine/hospital records. * **c.** Parental/personal recall only.
Domain 2: Comparability (Max 2*)	**2.1** Comparability of subjects in different outcome groups on the basis of design or analysis. Confounding factors controlled. **a.** Data/ results adjusted for relevant predictors/risk factors/confounders e.g. age, sex, time since vaccination, etc. ** **b.** Data/results not adjusted for all relevant confounders/risk factors/information not provided.
Domain 3: Outcome (Max 3*)	**3.1** Assessment of outcome **a.** Independent blin assessment using objective validated laboratory methods. ** **b.** Unblinded assessment using objective validated laboratory methods. ** **c.** Used non-standard or non-validated laboratory methods with gold standard. * **d.** No description/non-standard laboratory methods used.

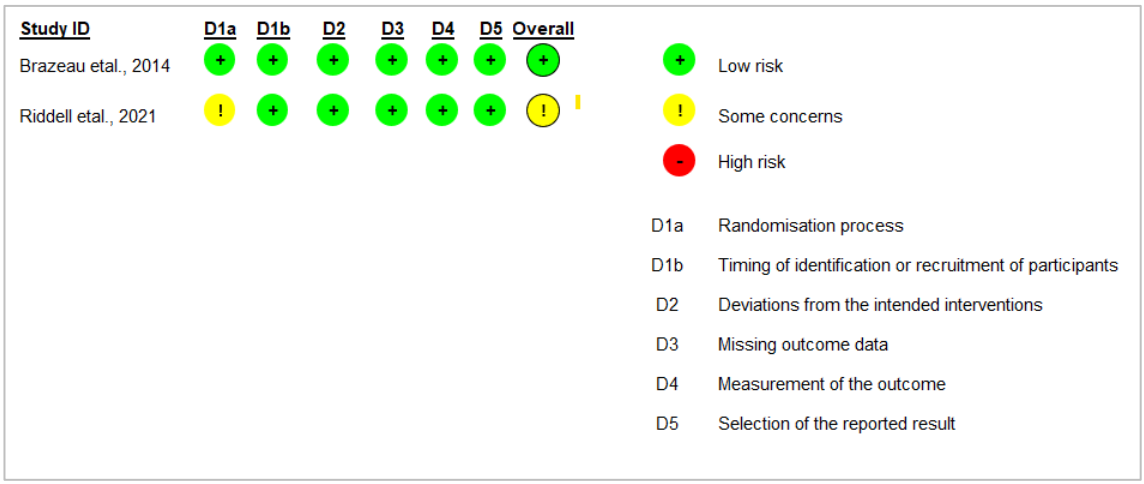
3.2 Statistical test

a. Statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and probability level (p value). *

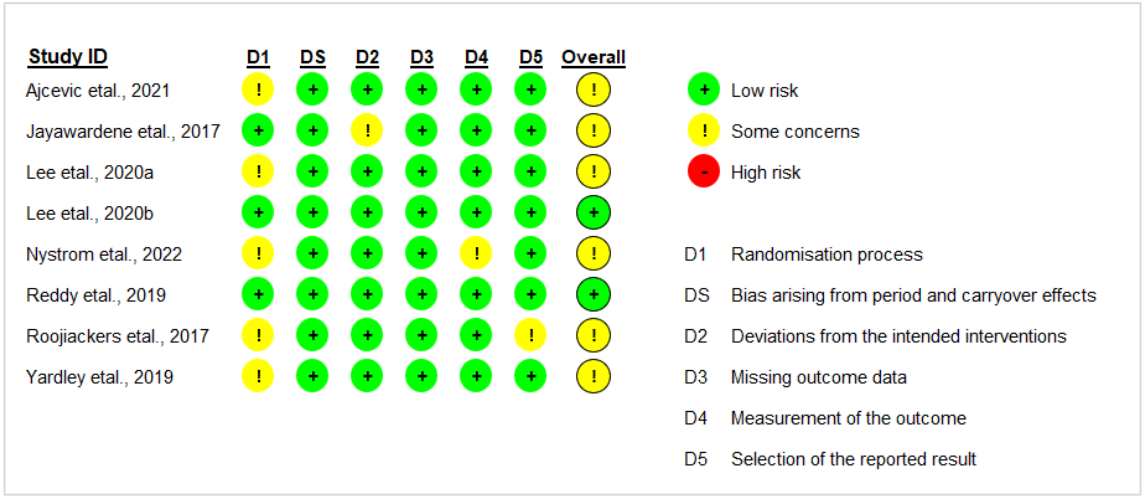
b. Statistical test not appropriate, not described or incomplete.

Note: A study can be awarded a maximum of one star for each numbered item within the selection and exposure categories. A maximum of two stars can be given for comparability. The quality of the included cross-sectional studies was assessed using an adapted version of the NOS modified for cross-sectional studies, based on criteria from previous systematic review (Herzog et al., 2013).

Table A.4: Risk of Bias (RoB2) Assessment

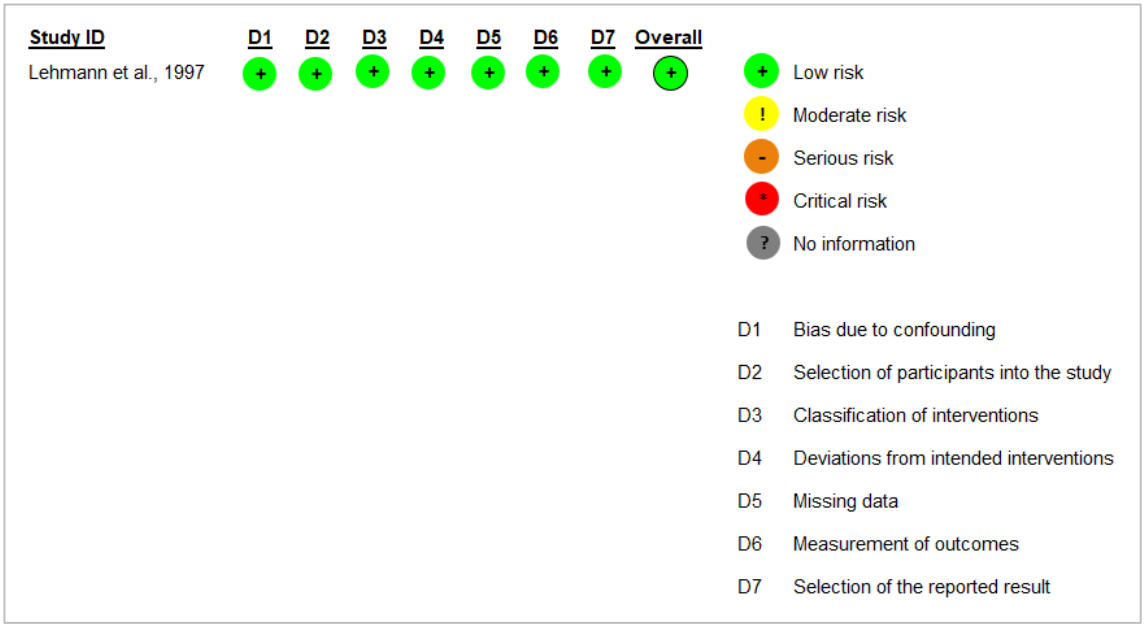


A.4.1 Risk of Bias Assessment for Randomised Controlled Trials



A.4.2 Risk of Bias Assessment for Randomised Controlled Trials with a Crossover Design

Table A.5 Risk of Bias Assessment for Non-randomized Studies - of Interventions (ROBINS-I) assessment



A.5.1 Risk of Bias for Non-Randomised studies

Table A.6 Risk of Bias Assessment for Observational Studies using Newcastle-Ottawa Scale (NOS)

A.6.1 Cohort Studies

Studies	Selection				Comparability	Outcome			Total score	Study quality
	1 (*)	2 (*)	3 (*)	4 (*)	1 (max **)	1 (*)	2 (*)	3 (*)		
(Turner et al., 2024)	*	*	*	*	**	*	*	*	9 (*********)	High
(Richardson et al., 2023)	*	*	*	*	**	*	*	*	9 (*********)	High
(Turčinović et al., 2023)	*	*	*	*	**	-	*	*	8 (********)	High
(De Ridder et al., 2022)	*	*	*	*	**	*	*	*	9 (*********)	High
(Flotynska et al., 2022)	*	*	*	*	**	-	*	*	8 (********)	High
(Soulimane et al., 2022)	*	*	*	*	**	*	*	*	9 (*********)	High
(Golka et al., 2021)	*	-	*	*	**	*	*	*	8 (********)	High
(Notkin et al., 2021)	*	-	*	*	*	*	*	*	7 (*******)	High
(Adelborg et al., 2020)	*	-	*	*	**	*	*	*	8 (********)	High
(Tikkanen-Dolenc et al., 2020)	*	*	*	*	**	*	*	*	9 (*********)	High
(Van Mark et al., 2019)	*	-	*	*	**	*	*	*	8 (********)	High
(Keshawarz et al., 2018)	*	*	*	*	**	*	*	*	9 (*********)	High
(Tikkanen-Dolenc et al., 2017)	*	*	*	*	**	*	*	*	9 (*********)	High
(Farabi et al., 2015)	*	-	*	*	*	*	*	*	7 (*******)	High
(Martínez-Ramonde et al., 2014)	*	-	*	*	**	*	*	*	8 (********)	High

Risk of bias domains: Selection: (1. Representativeness of the exposed cohort, 2. Selection of the non-exposed cohort, 3. Ascertainment of exposure, 4. Demonstration that outcome of interest was not present at start of study); Comparability: (1. Comparability of cohorts on the basis of the design or analysis); Outcome: (1. Assessment of outcome, 2. Was follow-up long enough for outcomes to occur, 3. Adequacy of follow up of cohorts). **Note:** Define scoring categorised (High risk: 0 – 3 stars; Moderate risk: 4 – 6 stars; Low risk: 7 – 9 stars).

A.6.2 Case Control Studies

Study	Selection				Comparability	Exposure			Total score	Risk of Bias
	1 (*)	2 (*)	3 (*)	4 (*)	1 (max **)	1 (*)	2 (*)	3 (*)		
(Chantelau and Wirth, 1992)	*	*	*	*	**	*	*	*	9 (*********)	Low risk

Risk of bias domains: selection: (1. Is the case definition adequate?, 2. Representativeness of the cases, 3. Selection of Controls, 4. Definition of Controls); comparability: (1. Comparability of cases and controls on the basis of the design or analysis); and outcome: (1. Assessment of exposure, 2. Same method of ascertainment for cases and controls, 3. Non-Response rate). **Notes:** Define scoring categorised (a. High risk: 0 – 3 stars; b. Moderate risk: 4 – 6 stars; c. Low risk: 7 – 9 stars).

A.6.3 Cross Sectional Studies

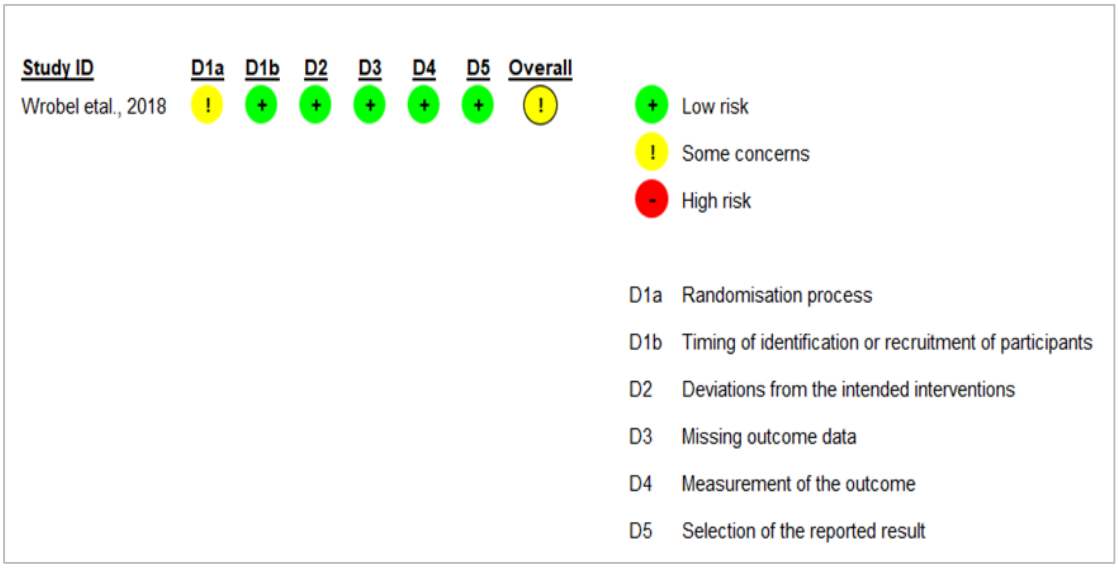
Studies	Selection				Comparability (Max 2*)	Outcome		Total score	Risk of Bias
	1 (*)	2 (*)	3 (*)	4 (**)	1(**)	1 (**)	2 (*)		
(Kowal et al., 2024)	*	-	-	*	**	**	*	7 (*******)	Low
(Murillo et al., 2024)	-	-	-	*	**	**	*	6 (******)	Moderate
(Brugnara et al., 2023)	*	-	-	*	**	**	*	7 (*******)	Low
(Çelik et al., 2023)	*	*	*	*	**	**	*	9 (*********)	Low
(Zaccaria et al., 2023)	*	-	-	*	**	**	*	7 (*******)	Low
(Jabbour et al., 2022)	*	-	*	*	**	**	*	8 (********)	Low
(Tan et al., 2022)	*	*	-	**	**	**	*	9 (*********)	Low
(Melin et al., 2021)	*	-	-	*	**	**	*	7 (*******)	Low
(Assaloni et al., 2020)	*	*	-	*	-	*	*	5 (*****)	Moderate
(Honda et al., 2020)	*	-	-	**	**	**	*	8 (********)	Low
(Koca et al., 2019)	*	-	*	*	**	**	*	8 (********)	Low
(Sadarangani et al., 2019)	*	-	-	*	**	**	*	7 (*******)	Low
(Stotl et al., 2019)	-	-	-	*	**	**	*	6 (******)	Moderate
(Duda-Sobczak et al., 2018)	*	-	*	*	**	**	*	8 (********)	Low
(Matson et al., 2018)	*	*	*	*	**	**	*	9 (*********)	Low
(Zielińska et al., 2018)	*	-	-	-	**	*	*	5 (*****)	Moderate
(Cigrovski Berkovic et al., 2017)	*	-	-	-	**	**	*	6 (******)	Moderate
(Moser et al., 2017)	*	*	-	**	**	**	*	9 (*********)	Low
(McCarthy et al., 2016)	*	-	-	**	**	**	*	8 (********)	Low
(Bohn et al., 2015)	*	*	*	*	**	**	*	9 (*********)	Low

(Tagougui et al., 2015)	*	-	-	**	**	**	*	8 (********)	Low
(Melin et al., 2014)	*	-	*	*	**	**	*	8 (********)	Low
(Valletta et al., 2014)	-	-	*	*	**	**	*	7 (*******)	Low
(Melin et al., 2013)	*	-	*	*	**	**	*	8 (********)	Low
(Brazeau et al., 2012b)	*	-	-	*	**	**	*	7 (*******)	Low
(Waden et al., 2007)	*	-	-	*	**	**	*	7 (*******)	Low

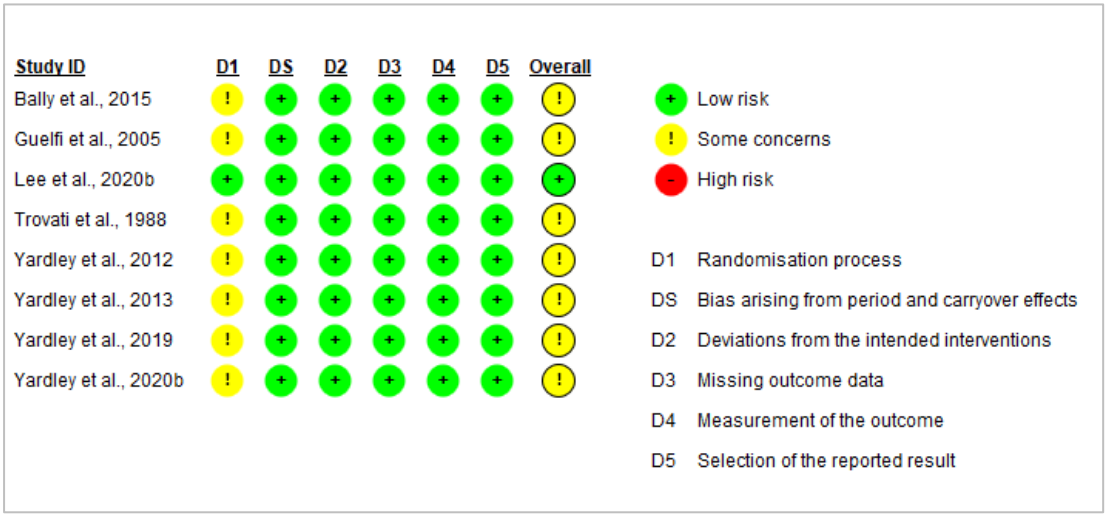
Risk of bias domains: Selection (1. Representativeness of the sample, 2. Sample size, 3. Non-respondents, 4. Ascertainment of the exposure (risk factor); Comparability: (1. Comparability of subjects in different outcome groups on the basis of design or analysis. Confounding factors controlled); and Outcome: (1. Assessment of outcome, 2. Statistical test).

Notes: Define scoring categorised (a. High risk: 0 – 3 stars; b. Moderate risk: 4 – 6 stars; c. Low risk: 7 – 10 stars).

Table A.7 Risk of Bias Assessment (Part B – Meta-Analysis)

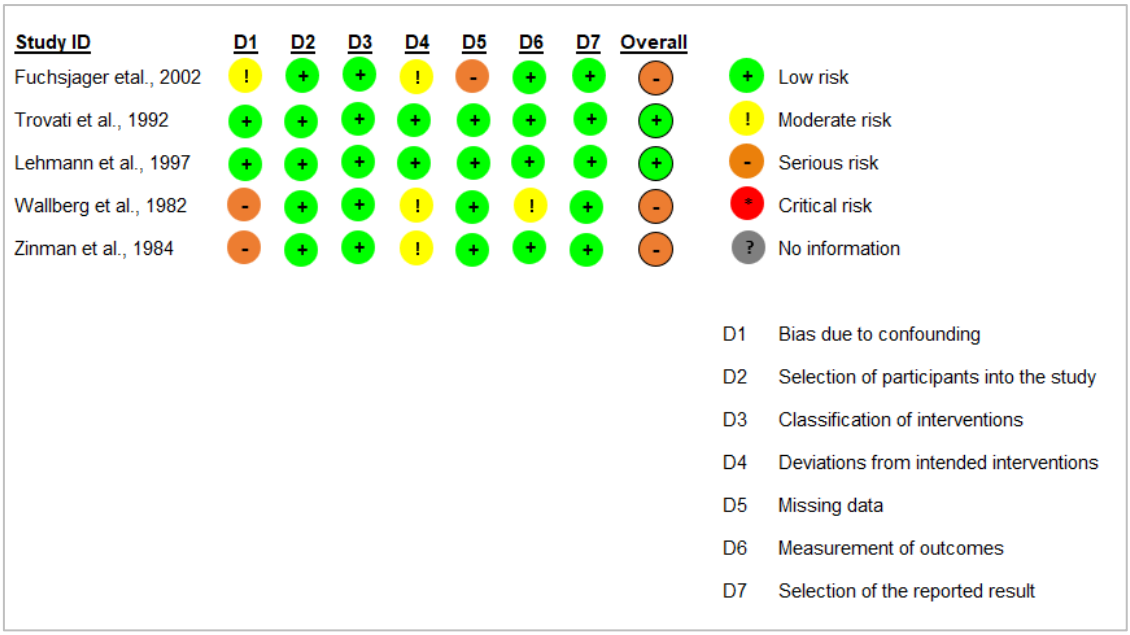


A.7.1 Risk of Bias Assessment for Randomised Controlled Trials



A.7.2 Risk of Bias Assessment for Randomised Controlled Trials with a Crossover Design

Table A.8 Risk of Bias Assessment for Non-randomized Studies - of Interventions (Part B – Meta-Analysis)



A.8.1 Risk of Bias for Non-Randomised Studies

Appendix B: Supplementary Materials for Chapter 5

Table B.1: Consent Form

I have read the participant information sheet and have received enough information about the study so that I understand what is required from me if I decide to participate	
I have had the opportunity to ask questions and discuss this study, and have had all questions answered satisfactorily	
I understand that I am free to withdraw from the study at any time without having to give a reason	
I understand that any information, including personal details, that I provide will be confidential, stored securely, and accessed only by the research team	
I understand and consent to any information to be included in published documents and stored in an open data repository, with my identity protected by using coded names/numbers	
I consent to my contact details being retained by the research team for the purpose of inviting me to participate in future research studies (only endorse this statement if you agree)	
I understand the data obtained using wearable devices (including my own CGM if applicable) will be accessed and downloaded by the research team	
I understand that I will be asked to provide data concerning my last HbA1c level from my last NHS clinical visit if I am unable to attend the laboratory preliminary visit	
I understand that anonymised data from this study can be used in other, future research studies	
I would like to receive a summary of the study results via email	
I agree to take part in this study	

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Participant	Date	Signature

Thank you for agreeing to take part in this study. This form will be stored by the research team; you will receive a copy.

Table B.2: Participant Information Sheet

Study Title: How do everyday activities effect glucose concentrations in people with type 1 diabetes?

We invite you to take part in a research study

We would really appreciate your participation in this study, but before you decide to take part, please read the following information. If you have any questions about the research or what will be expected from you if you do take part, please ask a member of the research team for clarification.

Contents

Study information

Why are we doing this research and why have I been asked to take part?

Understanding how different everyday activities impact blood glucose concentrations is important for managing T1D. In people with diabetes, good glucose control around PA has been shown to reduce the risk of developing long-term diabetes complications. However, managing glucose control around different types of activities can be very challenging; this is because different types of activities can result in different glucose responses in different people. Research has revealed that different people respond differently to physical activities, even when the same type of PA is performed. However, there is currently no research investigating what factors influence these differences in glucose responses in people with T1D.

This **study aims** to provide more information on two important aspects of T1D management:

1. Establish whether and how glucose responses differ between people with T1D when performing different types of everyday activity.

2. Determine whether these differences can be explained by certain personal characteristics.

Who is doing the study?

The study is being carried out by researchers from the School of Food Science at the University of Leeds. It is being conducted under the supervision of the Chief Investigator Dr Mark Hopkins, and the research will form the basis of a PhD project for Mrs Anwar Alobaid (who will be responsible for collecting the data if you participate).

What will I have to do if I take part?

A study timeline which summaries each main step of the study is presented on page 3. The study involves attending a single 90-minute laboratory visit and wearing two small devices for a total of 14-day. This means the total duration of your involvement in the study will be two weeks. If you already wear a CGM device as part of your current diabetes care and you are unable to attend the University of Leeds for your initial visit (due to your location for example), a remote option may be possible where we will perform a telephone/online meeting and send devices via the post. It is important to note that none of the devices or activities you will perform as part of this study should replace your normal diabetes care- this should continue as normal.

If you wish to participate in this study, we will firstly assess your eligibility against set criteria. This will involve asking you some questions about your lifestyle, age, and whether you have any medical issues or are currently receiving treatment or medication. We will arrange for you to attend our laboratory to ask you these questions and your answers will be recorded by a member of the research team; you are not obliged to answer these questions, however if you choose not to disclose information we may be unable to allow you to participate in the research. After confirming your eligibility and intention to participate, we will ask you sign an 'informed consent form'. This will confirm that you have read this information sheet and received enough information about the study including answers to any questions you may have and that you consent to participating. In addition, by signing this form, you will also be confirming that you understand how the data collected from you during the study will be stored, managed, and used.

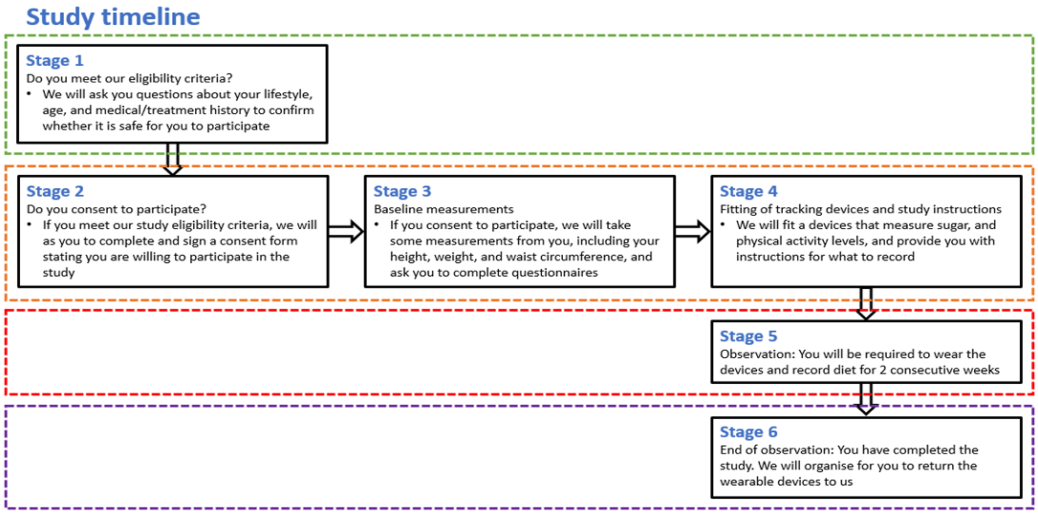
After you have consented to participating in the study, we will take some measurements of your body including your body mass, height, waist circumference, body composition, and blood pressure; please note that we may need to remove any loose-fitting clothes and your shoes to obtain accurate measures. We will also ask you to complete a series of questionnaires that will ask questions about your lifestyle and diabetes management.

During this visit, we will fit two small devices to your arm and one on the middle of your thigh. One device will measure blood glucose concentrations continuously (a CGM device). This involves the insertion of a thin sensor (0.4 mm thick) just beneath the skin (5 mm deep) which is then held in place with a sticky waterproof dressing. The procedure is simple, quick, and painless, and is used routinely in both clinical research and also diabetes care. If you already use a CGM device as part of your diabetes management, you can continue to use this as normal instead but we will request that you share the information collected from this device. The CGM device we will fit will not show you your blood glucose concentrations, and you should not use this as part of your routine diabetes care. We will also fit a small pedometer-like device to your wrist (looks like a wrist-worm

watch) which will measure your PA levels. The thigh-worn device is a small (23.5 mm wide, 43 mm long and 5 mm thick) and will be attached to the middle of your thigh using transparent waterproof film dressing (you can bath and swim with this applied as normal). Both devices are designed to be worn for long-periods of time, but should you feel any dis-comfort you can remove the device at any time. Again, you will not be able to see these data collected by this device. You will wear the CGM and pedometer-like devices for the duration of your involvement in the study, both of which are waterproof and can be worn when showering/bathing; we will also provide you with additional waterproof dressings when you require them. This initial visit should last no longer than 1 hour 30 minutes. You will be required to wear both devices for a total of 14-day. For three days of the 14-day (two week and one weekend day of your choosing), we will ask you to record your diet using an online dietary assessment tool via your phone or the internet. Separate instructions will be given to ensure you are comfortable with recording your diet.

If you currently wear a CGM device and are unable to attend an in-person laboratory visit, we can offer an online preliminary visit. You will initially be sent electronic versions of the participant information sheet, consent form, medical history and PA questionnaires, and a secure personalised link to upload these completed documents. Once these have been completed and checked via a researcher, a telephone or online (Microsoft Teams/Zoom) meeting will be arranged with a researcher who will explain the study and its requirements, and confirm eligibility based on the completed documents. During this meeting, a researcher will also ask you to self-report your body mass, height and most recent HbA1c value (if known). Body composition, blood pressure, waist circumference, and waist-hip-ratio will not be collected in individuals attending the remote visit. We will then send the pedometer-like devices to you in the post (with instructions to fit them) and inform you of the specific days during which we want you to wear the device. We will also ask you to continue to use your CGM device as normal, but we will request that you share the information collected from this device (we will provide you with a secure link to upload these data).

After the 14-day of wearing the devices, we will ask you to return the devices to us either in person or by post using a prepaid envelope that the research team will give you.



Do I have to take part and what happens if I no longer want to participate in the study?
Taking part in this study is completely voluntary. If you wish to withdraw from the study, you can do so, at any time and without prejudice by informing a member of the research team. All identifiable data will be destroyed, but we may use the data collected up to your withdrawal. If you choose to withdraw during the study, you will no longer be able to take part in any other aspects of this research project. However, this does not mean that you cannot volunteer for future studies.

What will happen to the information and data collected from me?
The University of Leeds is the sponsor for this study, and therefore the use of 'we' refers to researchers at the University of Leeds. 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. All of the information and data collected from you will be treated with the strictest of confidence. Only members of the research team will have access to your data and your personal information and data will not be discussed outside of the research team. We may share anonymised data with our research collaborators, and this data may be used in future research.

Your contact details, for the purposes of coordinating the attendance of laboratory visits, will be stored in the University, on university computer systems, under password protection. Your contact details will be destroyed immediately after the study, unless you give consent for us to retain these details for the purposes of inviting you to participate in future studies.

The data handling procedures followed in this study are in accordance with the Data Protection Act 2018. Any information you give, or data collected will be retained for a maximum of five years.

We will ask you whether we can retain your contact details and be contacted in the future about other research studies. Whether you agree to this or not will not impact your ability to participant in this study.

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.

You can find out more about how we use your information at:

- www.hra.nhs.uk/information-about-patients/
- Our leaflet available from: www.hra.nhs.uk/patientdataandresearch;
- https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/09/HRA-transparency-wording.pdf;
- https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/02/Research-Privacy-Notice.pdf
- By asking one of the research team
- By sending an email to the University of Leeds's Data Protection Office at: dpo@leeds.ac.uk, or

- By ringing us on 0113 343 3660.

What happens if new information about the research becomes available during the study?
Sometimes during research, new things are found out which may result in unforeseen physiological changes. If we notice you developing any unwanted responses to any of the study procedures that we have not already controlled for, we may have to stop you performing the study procedures and either reschedule the tests or withdraw you from the study.

What happens when the research project stops?
Results generated from this study will be presented with the intention to publish in scientific journals and presented at scientific conferences. All results will be presented as grouped data and any individual data presented will not be identifiable to you. You will have access to your own individual results after the completion of the study or may be informed during the study if we have discovered something that may be of interest to you or relevant to your health.

The results of the study may be published and/or stored in an archive so that the data can be accessed by other researchers. Use of the data will comply with the Research Councils UK's recommendations.

Who is organising and funding the research?
The School of Food Science and Nutrition are organising and funding this study.

Who has reviewed the study?
This study has been reviewed rigorously to ensure that your involvement is safe and as comfortable as possible. The study has been looked at by an independent group of people (Research Ethics Committee), to protect your interests.

This study has received full ethical approval by HRA Authority Research Ethics Committee (IRAS number: 327163).

What are the possible benefits of taking part in this study?
You will receive a £25 Amazon voucher for your participation. By participating in this study, you will be contributing to internationally leading research helping to understand the impact everyday activities on blood glucose concentrations in people with T1D. We cannot promise that the study will definitely help you, but your results, and the results from other participants may help to provide a better understanding of how different activities can impact blood glucose concentrations. We will share with you any information that may be of interest to you or relevant to your health.

What are the possible risks or disadvantages of taking part in this study?
We will ask you complete an initial screening telephone interview to establish whether the study procedures pose any risk to your health.
We will invite you to participate in the study only if you satisfy all of the study safety eligibility criteria. As we are using commercially available wearable devices, we do not anticipate any adverse effects to wearing the devices that we give you.

Although we will do our best to ensure that study visits take place on convenient dates and times, we do require that you attend the laboratory on a morning between Monday and Friday. It may be that you incur some financial shortfall through taking part in the study (for example, loss of

earnings); we can compensate you for minor travel expenses to and from the University (up to £20). You should consider whether this may have an impact on your ability to participate as no further compensation can be offered.

What happens if there is a problem or something goes wrong?
This study has been reviewed rigorously to ensure that your involvement is safe and as comfortable as possible. The Chief Investigator (Dr Mark Hopkins) will be available during the conduct of the study procedures who will oversee your health and safety.

Should something go wrong during the study, and you are harmed due to someone's negligence, you may have grounds to take legal action for compensation against the University of Leeds, but you may have to pay your legal costs.

Who should I contact if I want to make a complaint?
If you are unhappy with any of the treatment provided to you during the study you may in the first instance, contact the Chief Investigator, Dr. Mark Hopkins. If you wish to make an independent complaint you should contact the Sponsors Representative at the University of Leeds using the details provided below.

For Complaints:
governance-ethics@leeds.ac.uk
Research Ethics & Governance
The Secretariat
University of Leeds
LS2 9JT
Tel: 0113 343 1642

If you agree to take part, would like more information, or have any questions or concerns about the study please contact:
Dr Mark Hopkins
School of Food Science and Nutrition
University of Leeds
Email: m.hopkinds@leeds.ac.uk
Phone: (0) 113 343 6990

Table B.3: Medical Screening Questionnaire

Participant code:	**Yes**	**No**
A diagnosis of T1D for a minimum of 5 years?		
Currently treated on a stable insulin regimen for a minimum of six months? *[consisting of continuous subcutaneous insulin infusion (CSII) therapy or multiple daily injections (MDI) of a combination of rapid-acting and long-acting insulin]*		
Familiar and currently using the carbohydrate-counting method for determining mealtime insulin dose		
Not currently pregnant		
Free from overt diabetes complications [*including end stage renal failure requiring dialysis]*		
Free from hypoglycaemia unawareness *[assessed through a combination of the Clarke and Gold methods]*		
No recent (less than six month) history of diabetic ketoacidosis (DKA)		
No history of medical or psychiatric conditions likely to interfere with the study		
Able to understand written English and provide written informed consent		
Eligible to participate? *All answers must be Yes to be eligible.*		

Researcher: _____ Signed: _____ Date: _____

Table B.4: International Physical Activity Questionnaire (IPAQ-LF)

We are interested in finding out about the kinds of physical activities that people do as part of their everyday lives. The questions will ask you about the time you spent being physically active in the last seven days. Please answer each question even if you do not consider yourself to be an active person. Please think about the activities you do at work, as part of your house and yard work, to get from place to place, and in your spare time for recreation, exercise or sport.

Think about all the vigorous and moderate activities that you did in the last seven days. Vigorous physical activities refer to activities that take hard physical effort and make you breathe much harder than normal. Moderate activities refer to activities that take moderate physical effort and make you breathe somewhat harder than normal.

PART 1: JOB-RELATED PHYSICAL ACTIVITY

The first section is about your work. This includes paid jobs, farming, volunteer work, course work, and any other unpaid work that you did outside your home. Do not include unpaid work you might do around your home, like housework, yard work, general maintenance, and caring for your family. These are asked in Part 3.

1. Do you currently have a job or do any unpaid work outside your home?

☐ Yes

☐ No → **Skip to PART 2: TRANSPORTATION**

The next questions are about all the PA you did in the last seven days as part of your paid or unpaid work. This does not include traveling to and from work.

2. During the last seven days, on how many days did you do vigorous physical activities like heavy lifting, digging, heavy construction, or climbing upstairs **as part of your work?** Think about only those physical activities that you did for at least 10 minutes at a time.

_____ **days per week**

☐ No vigorous job-related PA → **Skip to question 4**

3. How much time did you usually spend on one of those days doing **vigorous** physical activities as part of your work?

_____ **hours per day**

_____ **minutes per day**

4. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last seven days**, on how many days did you do moderate physical activities like carrying light loads **as part of your work**? Please do not include walking.

_____ **days per week**

☐ No moderate job-related PA → **Skip to question 6**

5. How much time did you usually spend on one of those days doing **moderate** physical activities as part of your work?

_____ **hours per day**

_____ **minutes per day**

6. During the **last seven days**, on how many days did you **walk** for at least 10 minutes at a time **as part of your work**? Please do not count any walking you did to travel to or from work.

_____ **days per week**

☐ No job-related walking → **Skip to PART 2: transportation**

7. How much time did you usually spend on one of those days **walking** as part of your work?

_____ **hours per day**

_____ **minutes per day**

PART 2: TRANSPORTATION PHYSICAL ACTIVITY

These questions are about how you traveled from place to place, including to places like work, stores, movies, and so on.

8. During the last seven days, on how many days did you **travel in a motor vehicle** in a train, bus, can, tram, or other kind of motor vehicle?

_____ **days per week**

☐ No traveling in a motor vehicle → **Skip to question 10**

9. How much time did you usually spend on one of those days **traveling** in a train, bus, car, tram, or other kind of motor vehicle?

_____ **hours per day**

_____ **minutes per day**

10. During the **last seven days**, on how many days did you **bicycle** for at least 10 minutes at a time to go from **place to place**?

_____ **days per week**

☐ No bicycling from place to place → **Skip to question 12**

11. How much time did you usually spend on one of those days to **bicycle** from place to place?

_____ **hours per day**

_____ **minutes per day**

12. During the **last seven days**, on how many days did you **walk** for at least 10 minutes at a time to go **from place to place**?

_____ **days per week**

☐ No walking from place to place → **Skip to PART 3: housework, house maintenance, and caring for family.**

13. How much time did you usually spend on one of those days **walking** from place to place?

_____ **hours per day**

_____ **minutes per day**

PART 3: HOUSEWORK, HOUSE MAINTENANCE, AND CARING FOR FAMILY

This section is about some of the physical activities you might have done in the last seven days in and around your home, like housework, gardening, yard work, general maintenance work, and caring for your family.

14. Think about only those physical activities that you did for at least 10 minutes at a time. During the last seven days, on how many days did you do **vigorous** physical activities like heavy lifting, chopping wood, shoveling snow, or digging **in the garden or yard**?

_____ **days per week**

☐ No vigorous activity in garden or yard → **Skip to question 16**

15. How much time did you usually spend on one of those days doing **vigorous** physical activities in the garden or yard?

_____ **hours per day**

_____ **minutes per day**

16. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last seven days**, on how many days did you do **moderate** activities like carrying light loads, sweeping, washing windows, and raking **in the garden or yard**?

_____ **days per week**

☐ No moderate activity in garden or yard → **Skip to question 18**

17. How much time did you usually spend on one of those days doing **moderate** physical activities in the garden or yard?

_____ **hours per day**

_____ **minutes per day**

18. Once again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last seven days**, on how many days did you do moderate activities like carrying light loads, washing windows, scrubbing floors and sweeping **inside your home**?

_____ **days per week**

☐ No moderate activity inside home →**Skip to PART 4: recreation, sport, and leisure-time PA.**

19. How much time did you usually spend on one of those days doing **moderate** physical activities inside your home?

_____ **hours per day**

_____ **minutes per day**

PART 4: RECREATION, SPORT AND LEISURE-TIME PA

This section is about all the physical activities that you did in the last seven days solely for recreation, sport, exercise or leisure. Please do not include any activities you have already mentioned.

20. Not counting any walking you have already mentioned, during the **last seven days**, on how many days did you **walk** for at least 10 minutes at a time **in your leisure time**?

_____ **days per week**

☐ No walking in leisure time → **Skip to question 22**

21. How much time did you usually spend on one of those days **walking** in your leisure time?

_____ **hours per day**

_____ **minutes per day**

22. Think about only those physical activities that you did for at least 10 minutes at a time. During the **last seven days**, on how many days did you do **vigorous** physical activities like aerobic, running, fast bicycling, or fast swimming **in your leisure time**?

_____ **days per week**

☐ No vigorous activity in leisure time → **Skip to question 24**

23. How much time did you usually spend on one of those days doing **vigorous** physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

24. Again, think about only those physical activities that you did for at least 10 minutes at a time. During the **last seven days**, on how many days did you do **moderate** physical activities like bicycling at a regular pace, swimming at a regular pace, and double tennis **in your leisure time**?

_____ **days per week**

☐ No moderate activity in leisure time → **Skip to PART 5: time spent sitting**

25. How much time did you usually spend on one of those days doing moderate physical activities in your leisure time?

_____ **hours per day**

_____ **minutes per day**

PART 5: TIME SPENT SITTING

The last questions are about the time you spend sitting while at work, at home, while doing course work and during leisure time. This may include time spent sitting at a desk, visiting friends, reading or sitting or lying down to watch television. Do not include any time spent sitting in a motor vehicle that you have already told me about.

26. During the **last seven days**, how much time did you usually spend **sitting** on a **weekday**?

_____ **hours per day**

_____ **minutes per day**

27. During the **last seven days**, how much time did you usually spend **sitting** on a **weekend day**?

_____ **hours per day**

_____ **minutes per day**

Table B.5: Barrier to Physical Activity in Type 1 Diabetes Scale

Instructions: Please make a mark on each line in response to whether you feel each statement is barrier to PA.
1. The loss of control over your diabetes Extremely unlikely — Extremely likely
2. The risk of hypoglycaemia Extremely unlikely — Extremely likely
3. The fear of being tired Extremely unlikely — Extremely likely
4. The fear of hurting yourself Extremely unlikely — Extremely likely
5. The fear of suffering a heart attack Extremely unlikely — Extremely likely
6. A low fitness level Extremely unlikely — Extremely likely
7. The fact that you have diabetes Extremely unlikely — Extremely likely
8. The risk of hyperglycaemia Extremely unlikely — Extremely likely
9. Your actual physical health status excluding your diabetes Extremely unlikely — Extremely likely
10. Weather conditions Extremely unlikely — Extremely likely
11. The location of a gym Extremely unlikely — Extremely likely

Appendix C: Supplementary Materials for Chapter 5

Table C.1: Consent Form

I have read the participant information sheet and have received enough information about the study so that I understand what is required from me if I decide to participate	
I have had the opportunity to ask questions and discuss this study, and have had all questions answered satisfactorily	
I understand that I am free to withdraw from the study at any time without having to give a reason	
I understand that any information, including personal details, that I provide will be confidential, stored securely, and accessed only by the research team	
I understand and consent to any information to be included in published documents and stored in an open data repository, with my identity protected by the use of pseudonyms.	
I consent to my contact details being retained by the research team for the purpose of inviting me to participate in future research studies (only endorse this statement if you agree)	
I understand that anonymised data from this study can be used in other, future research studies	
I agree to take part in this study	

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of Participant	Date	Signature

Thank you for agreeing to take part in this study. This form will be stored by the research team; you will receive a copy.

Table C.2: Participants Information Sheet

We invite you to take part in a research study

We would really appreciate your participation in this study, but before you decide to take part, please read the following information. If you have any questions about the research or what will be expected from you if you do take part, please ask a member of the research team for clarification.

Contents

Information Sheet

Why are we doing this research and why have I been asked to take part?
Sitting for long periods of time is detrimental to our health. In people with diabetes, sitting for prolonged periods of time has shown to contribute to worsening blood glucose concentrations (blood glucose) and an increase in the risk of diabetes complications. Because of this, all individuals, including those with diabetes, are recommended to break-up the time they spend sitting, with regular, short, low-intensity ‘activity breaks’ such as walking. Research has shown that activity breaks can improve blood glucose concentrations and reduce risk factors for diabetes complications in people with type 2 diabetes (T2D). However, there is currently no research investigating how activity breaks impact glucose control, nor whether benefits seen in people with T2D translate to people with type 1 diabetes (T1D).

This study aims to answer two questions:

Does breaking-up prolonged sitting time with short frequent light-intensity bouts of walking improve:

1. Glucose concentrations over 48-hour in people with T1D?
2. Risk factors associated with diabetes complications in people with T1D?

Who is doing the study?
The study is being carried out by researchers from the University of Leeds. It is being conducted under the supervision of the Chief Investigator Dr Matthew Campbell. Other members of the research team include Professor Ramzi Ajjan, Mrs Anwar Alobaid, and Dr Sam Pearson.

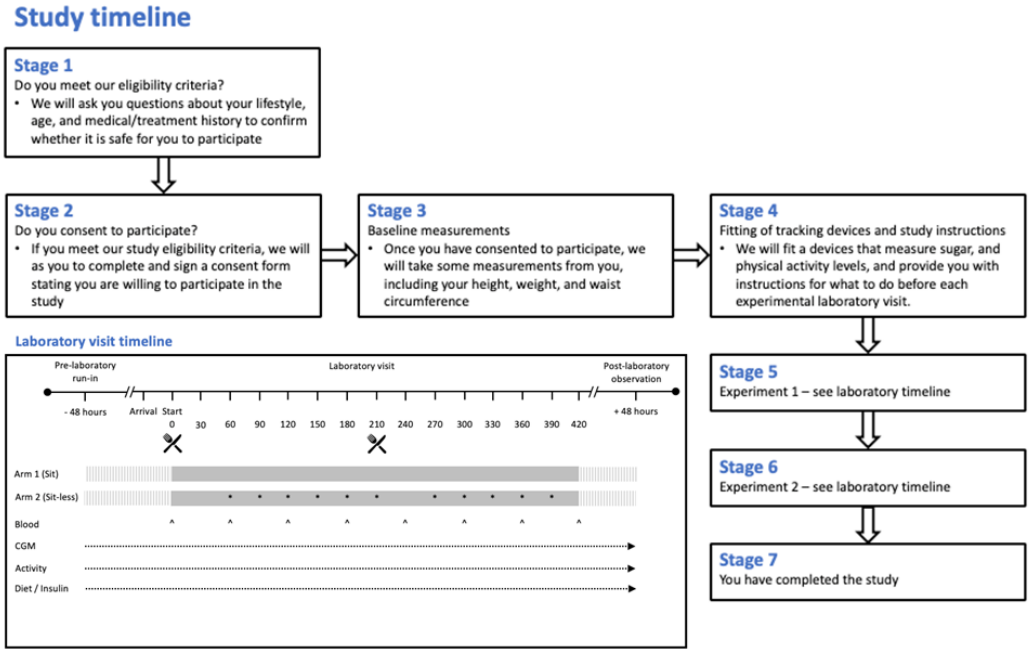
What will I have to do if I take part?

A study timeline which summaries each main step of the study is presented on the next page. If you wish to participate in this study, we will firstly assess your eligibility against set criteria. This will involve asking you some questions about your lifestyle, age, and whether you have any medical issues or are currently receiving treatment or medication. We will arrange for you to attend our laboratory to ask you these questions and your answers will be recorded by a member of the research team; you are not obliged to answer these questions, however if you choose not to disclose information we may be unable to allow you to participate in the research. After confirming your eligibility and intention to participate, we will ask you sign an 'informed consent form'. This will confirm that you have read this information sheet and received enough information about the study including answers to any questions you may have and that you consent to participating. In addition, by signing this form, you will also be confirming that you understand how the data collected from you during the study will stored, managed, and used; you are not obliged to answer these questions, however if you choose not to, we will be unable to allow you to participate in the research.

After you have consented to participating in the study, we will take some measurements of your body including your weight, height and waist circumference; please note that we may need to remove any loose-fitting clothes and your shoes to obtain accurate measures. During this visit, we will also fit two small devices to your arm. One device will measure glucose concentrations continuously (a CGM device). This involves the insertion of a thin sensor (0.4 mm thick) just beneath the skin (5 mm deep) which is then held in place with a sticky waterproof dressing. The procedure is simple, quick, and painless, and is used routinely in both clinical research and also diabetes care. If you already use a CGM device as part of your diabetes management, you can continue to use this as normal, however you will also be required to the wear the CGM device that we will give you for the duration of the study. We will also fit a small pedometer-like device to your arm which will measure your PA levels. You will wear the CGM and pedometer-like devices for the duration of your involvement in the study. In addition, we will give you a diary to keep a log of your diet, PA, and insulin regimen and supply you with prepared meals to be eaten at specific times at home, replacing your usual meals. This initial visit should last no longer than one hour. During this visit, we will arrange with you two further laboratory visits each lasting approximately 7-hour; although we will try and accommodate these visits as to minimise disruption to your schedule, all visits will be required to be made between the working week (Monday to Friday) and commencing on a morning-time (between 08:00 and 09:00 am), with each visit separated by at least seven days.

During the course of 48-hour prior to your second visit to the laboratory, we will ask you to record your diet and PA patterns by logging what you eat into the diary provided to you by the research team. You will be required to list individual food items eaten during this time and describe items in as much detail as possible (i.e. the size of the portion, time of eating, cooking methods), retaining packaging and nutritional information where possible. During this time, you will be required to abstain from drinking alcohol, caffeinated drinks and foods, as well as strenuous PA. You will be required to eat one of the meals provided to you by the research team, which will serve as your evening, and last, meal of that day. This meal will be comprised of a vegetarian lasagna dish with a

flatbread. You will be required to follow the cooking instructions on the packaging of these foods and note down the time at which you eat them. After you have eaten this meal, we will ask you not to eat or drink anything else other than water for the remainder of the night (unless you experience low blood glucose concentrations); you may drink as much water as you wish. We will ask you to replicate eating patterns (the type, amount and timing of food) and PA before each visit to the laboratory using the dietary recording sheets you previously completed on your first visit. If you experience low blood glucose concentrations during this time you should treat this using your usually methods (i.e. eating glucose tablets, or drinking sugary drinks), however we will be need to re-arrange your visit to the laboratory as having low glucose concentrations may interfere with our study measures and compromise your safety during testing.



On the morning of each visit, a researcher will call you to ensure that you well enough to attend the laboratory and have not experienced hypoglycaemia during the night. During each visit to the laboratory, you will be required to arrive in a fasted state; i.e. having not consumed anything other than water after your evening meal and having skipped breakfast. It is vital that you abstain from eating after your evening meal until we provide you with food in the laboratory as this can interfere with our measures. However, it is ok if you need to take some glucose tablets to prevent low blood glucose concentrations.

Once you have arrived at the laboratory, we will take some measurements such as your height and body mass, and blood pressure. After these measures have been taken, we will give you a meal to eat. The meal will be a breakfast-based dish; you will be able to drink water freely during the meal and throughout your time in the laboratory. We will ask you to consume the meal within a 20-minute period, which for most people is fairly easy. You will then be required to sit in a comfortable lounge chair for the remaining 7-hour (except for toilet breaks). Half-way through, (at 3.5 hours) we will provide you with a lunch meal to be taken in the lab. You will then be free to leave to the laboratory. Each of the two visits will be identical in procedures (i.e. timing), however, on one occasion we will ask you break-up the time spent sitting by performing short, light-

intensity bouts of walking at regular intervals (Sit-Less), and on the other you will simply remain seated (SIT) (See Laboratory timeline). Each bout of walking will be at a slow/easy pace and will last for 3-minute each. You will perform 11 bouts of walking in total during the visit.

Once you have the laboratory, we will ask you to eat two meals provided to you by the research team: one as your evening meal, and one as your breakfast. You may eat other things between these meals, but the foods and drinks consumed should be replicated across each visit. For 48-hour after each laboratory visit, you will be required to record your diet, and abstain from caffeine, alcohol and strenuous exercise. On your last visit, we will continue to measure glucose concentrations (using CGM) and PA for 48-hour afterwards using the devices. After this time, you will have completed the study and can remove the devices. A member of the research team will arrange to collect the devices from you.

Do I have to take part and what happens if I no longer want to participate in the study?

Taking part in this study is completely voluntary. If you wish to withdraw from the study, you can do so, at any time and without prejudice by informing a member of the research team. All identifiable data will be destroyed, but we may use the data collected up to your withdrawal. If you to choose to withdraw during the study, you will no longer be able to take part in any other aspects of this research project. However, this does not mean that you cannot volunteer for future studies.

What will happen to the information and data collected from me?

The University of Leeds is the sponsor for this study, and therefore the use of 'we' refers to researchers at the University of Leeds. If you have been approached in-clinic, your usual care team may need to use information from you and your medical records for this research project. This information will include your name and initials, NHS number, contact details, and relevant medical information. This will be accessed by a member of your care team only. Your care team will use this information and 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. If you have not been approached in-clinic we will not access your medical records. All of the information and data collected from you will be treated with the strictest of confidence. Only members of the research team will have access to your data and your personal information and data will not be discussed outside of the research team.

Your contact details, for the purposes of coordinating the attendance of laboratory visits, will be stored in the University, on university computer systems, under password protection. Your contact details will be destroyed immediately after the study, unless you give consent for us to retain these details for the purposes of inviting you to participate in future studies.

The data handling procedures followed in this study are in accordance with the Data Protection Act 2018. Any information you give, or data collected will be retained for a maximum of five years.

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.
You can find out more about how we use your information at:

- www.hra.nhs.uk/information-about-patients/
- Our leaflet available from: www.hra.nhs.uk/patientdataandresearch;
- https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/09/HRA-transparency-wording.pdf;
- https://dataprotection.leeds.ac.uk/wp-content/uploads/sites/48/2019/02/Research-Privacy-Notice.pdf
- By asking one of the research team
- By sending an email to the University of Leeds's Data Protection Office at: dpo@leeds.ac.uk , or
- By ringing us on 0113 343 3660.

What happens if new information about the research becomes available during the study?
Sometimes during research, new things are found out, which may result in unforeseen physiological changes. If we notice you developing any unwanted responses to any of the study procedures that we have not already controlled for, we may have to stop you performing the study procedures and either reschedule the tests or withdraw you from the study.

What happens when the research project stops?
Results generated from this study will be presented with the intention to publish in scientific journals, presented at scientific conferences, and written up as a PhD thesis. All results will be presented as grouped data and any individual data presented will not be identifiable to you. You will have access to your own individual results after the completion of the study or may be informed during the study if we have discovered something that may be of interest to you or relevant to your health.

The results of the study may be published and/or stored in an archive so that the data can be accessed by other researchers. Use of the data will comply with the Research Councils UK's recommendations.

Who is organizing and funding the research?
The University of Leeds is organizing this research. The research has been funded by Diabetes UK.

Who has reviewed the study?
This study has been reviewed rigorously to ensure that your involvement is safe and as comfortable as possible. The study has been looked at by an independent group of people (Research Ethics Committee), to protect your interests.

This study has received full ethical approval by the London – Surrey Authority Research Ethics Committee (number: 20/LO/0650).

What are the possible benefits of taking part in this study?
By participating in this study you will be contributing to internationally leading research on the understanding of the impact of PA on glucose concentrations and diabetes complication risk in people with T1D. We cannot promise that the study will definitely help you, but your results, and the results from other

participants may help to provide a better understanding of how breaking-up long periods of time spent sitting can impact blood glucose concentrations and the risk of developing diabetes complications. We will share with you any information that may be of interest to you or relevant to your health.

What are possible risks or disadvantages of taking part in this study?
We will ask you complete an initial screening telephone interview to establish whether the study procedures pose any risk to your health. However, as with all research, there are always some potential risks you should be aware of.
Performing light PA carries a risk of hypoglycaemia and hyperglycaemia. Although this can cause unpleasant symptoms, you will be monitored by the research team closely and treated accordingly to ensure your safety is not compromised. In addition, members of the research team will remain contactable should you experience swings in blood glucose after you have left the laboratory.

We will invite you to participate in the study only if you satisfy all of the study safety eligibility criteria. As we are using commercially available food products and preparing food items in our controlled nutritional kitchen, we do not anticipate any adverse effects to eating the foods we will give you.
Although we will do our best to ensure that study visits take place on convenient dates and times, we do require that you attend the laboratory on a morning between Monday and Friday. It may be that you incur some financial shortfall through taking part in the study (for example, loss of earnings). Minor travel expenses incurred from taking part in this study will be covered. In addition, you will receive a £100 gift voucher as compensation for your time.

What happens if there is a problem or something goes wrong?
This study has been reviewed rigorously to ensure that your involvement is safe and as comfortable as possible. The Chief Investigator (Dr Matthew Campbell) will be available during the conduct of the study procedures who will oversee your health and safety.

Should something go wrong during the study, and you are harmed due to someone's negligence, you may have grounds to take legal action for compensation against the University of Leeds, but you may have to pay your legal costs.

Who should I contact if I want to make a complaint?
If you are unhappy with any of the treatment provided to you during the study you may in the first instance contact the Chief Investigator, Dr. Matthew Campbell. If you wish to make an independent complaint you should contact the University secretariat using the details provided on the next page.

For Complaints:
Research Ethics & Governance
The Secretariat,
Room 9.29, Level 9, Worsley Building,
Clarendon Way,
University of Leeds
LS2 9NL
Tel: 0113 343 1642

If you agree to take part, would like more information, or have any questions or concerns about the study please contact:

Dr Matthew Campbell
Faculty of Medicine
University of Leeds
Leeds,
LS2 9JT
Email: m.d.campbell@leeds.ac.uk

Table C.3: Medical Screening Questionnaire

Participant code:	**Yes**	**No**
A diagnosis of T1D for a minimum of five years?		
Currently treated on a stable insulin regimen for a minimum of six months? *[consisting of continuous subcutaneous insulin infusion (CSII) therapy or multiple daily injections (MDI) of a combination of rapid-acting and long-acting insulin]*		
Familiar and currently using the carbohydrate-counting method for determining mealtime insulin dose		
Not currently pregnant		
Free from overt diabetes complications end stage renal failure requiring dialysis		
Free from hypoglycaemia unawareness *[assessed through a combination of the Clarke and Gold methods]*		
No recent (less than six months) history of diabetic ketoacidosis (DKA)		
Free from medical conditions relating to a haematological disorder, gut mobility or digestion		
No history of anorexia, bulimia, or any other disordered eating		
No history of deep vein thrombosis		
No history of heart attack or stroke within previous six months		
No history of malignancy, or other medical or psychiatric conditions likely to interfere with the study including severe functional limitations that contraindicate prolonged episodes of sitting (i.e. back pain) or short frequent bouts of light-intensity walking (i.e. mobility issues)		
No dietary allergies or intolerances likely to interfere with the study		
Able to understand written English and provide written informed consent		
Not currently diagnosed with any blood borne infectious diseases (i.e., hepatitis, HIV)		
Eligible to participate? *All answers must be Yes to be eligible.*		