MOVEMENT BEHAVIOURS AND CARDIOVASCULAR RISK FACTORS IN INDIVIDUALS LIVING WITH TYPE 1 DIABETES

by

Nana Wu

B.Sc., Shandong Sport University, 2012

M.Sc., Shanghai University of Sport, 2015

A THESIS SUBMITTED IN PARTIAL FULFILLMENT OF

THE REQUIREMENTS FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

in

THE FACULTY OF GRADUATE AND POSTDOCTORAL STUDIES

(Kinesiology)

THE UNIVERSITY OF BRITISH COLUMBIA

(Vancouver)

October 2021

The following individuals certify that they have read, and recommend to the Faculty of Graduate and Postdoctoral Studies for acceptance, a dissertation entitled:

Movement behaviours and cardiovascular risk factors in individuals living with type 1 diabetes

submitted by	Nana Wu	in partial fulfillment of the requirements for
the degree of	Doctor of Philosophy	
in	Kinesiology	

Examining Committee:

Dr. Darren E.R. Warburton, School of Kinesiology, The University of British Columbia
Supervisor

Dr. Veronica Jamnik, School of Kinesiology and Health Science, York University
Supervisory Committee Member

Dr. Mary Jung, School of Health and Exercise Science, The University of British Columbia Okanagan
University Examiner

Dr. Alex Scott, Department of Physical Therapy, The University of British Columbia
University Examiner

Additional Supervisory Committee Members:

Dr. Michael S. Koehle, School of Kinesiology, The University of British Columbia
Supervisory Committee Member

Abstract

Type 1 diabetes (T1D) is associated with an increased risk of cardiovascular disease (CVD). Research has shown that movement behaviours (physical activity, sedentary behaviour (SB), and sleep) are related to cardiovascular health; and physical activity plays an important role in the prevention of CVD and the improvement of overall health and wellbeing in individuals with T1D.

The purpose of this dissertation was to evaluate cardiovascular responses to long-term exercise (Chapter 2), and acute high intensity interval (HIIE) versus moderate intensity continuous exercise (MICE) in individuals with T1D (Chapter 3); to assess movement behaviours and CVD risk factors in adolescents living with T1D, in comparison with their peers without T1D (Chapter 4); to examine the relationships between movement behaviours and CVD risk factors (Chapter 4 & 5); to investigate the combined effect of time spent in physical activity, SB and sleep which together can be considered to constitute a composite on CVD risk factors within a compositional data analysis (Chapter 6). In Chapters 2 and 3, we conducted two systematic reviews and meta-analyses. In Chapters 4, 5 and 6, 48 adolescents living with T1D and 19 of their peers living without T1D were studied, movement behaviours and CVD risk factors were assessed.

We found that exercise training increased aerobic fitness and reduced glycated hemoglobin, daily insulin dosage and total cholesterol (Chapter 2) and HIIE may be safer than MICE for individuals with T1D, as it carries a lower risk of early-onset hypoglycemia without causing a higher occurrence of hyperglycemia and nocturnal hypoglycemia (Chapter 3); adolescents living with T1D presented early signs of CVD risk and demonstrated lower physical activity levels and aerobic fitness compared to their peers without T1D (Chapters 4); all participants slept less than the recommended 8 hours per night (Chapters 5) and increased sleep and decreased LIPA have negative consequences in cardiovascular health in adolescents living with T1D, (Chapters 6).

Movement behaviours including regular physical activity, reducing SB, and obtaining adequate sleep play important roles in the prevention of CVD in adolescents living with T1D, optimizing these behaviours may lead to improvement of cardiovascular health in these individuals.

Lay Summary

Movement behaviours (sleep, sedentary behaviour, and physical activity) are an important and integral component of effective management of T1D. The purpose of this research was to investigate the relationship of movement behaviours and cardiovascular disease (CVD) risk factors (high blood pressure, elevated blood sugar, total cholesterol levels, and obesity) in individuals with T1D. We found higher blood total cholesterol levels, lower physical activity levels and aerobic fitness in adolescents living with T1D than their peers without T1D. The risk factors of CVD in T1D can be reduced by increasing physical activity levels, reducing sedentary behaviours, and obtaining enough sleep. This project made contributions to a theoretical understanding of movement behaviours for diabetes management as they impact cardiovascular health and provided valuable information to health professionals as evidence for management of T1D. More importantly, this project facilitated the process of creating evidence-based guidelines for individuals with T1D on optimizing daily movement behaviours.

Preface

The research ideas, approach and designing of the project were initiated by me. I wrote the ethics, conducted and coordinated the recruitment of participants and data collection. All data analyses, statistical analysis, and writing of this thesis were conducted by me. All studies in the project were made possible by my supervisor Dr. Darren Warburton who trusted me and provided the encouragement with all its responsibility to pursue my research goals. My committee including Dr. Veronica Jamnik and Dr. Michael Koehle all provided exceptional support, guidance and valued feedback throughout the investigations. Pro. Yongfeng Li provided exceptional support to the process of data collection in Shandong Province, China. All research conducted in China was under the direction of Dr. Li.

Chapter 2 A version of Chapter 2 has been published. Nana Wu, Shannon SD Bredin, Yanfei Guan, Kyra Dickinson, David D. Kim, Zongyu Chua, Kai Kaufman, and Darren ER Warburton. "Cardiovascular health benefits of exercise training in persons living with type 1 diabetes: a systematic review and meta-analysis." *Journal of clinical medicine* 8, no. 2 (2019): 253. I conceptualized the study design, performed the literature search, study selection, data extraction, and meta-analysis, wrote the complete manuscript, and made all necessary edits after the peer review process. Guan, Yanfei, Dickinson, Kyra, Kim, David, Chua, Zongyu, Kaufman Kai., contributed study selection and data extraction and acted as second reviewers during the systematic review process.

Chapter 3 A version of Chapter 3 has been prepared for publication. I conceptualized the study design, performed the literature search, meta-analysis and wrote the complete manuscript with support from Drs. Shannon Bredin, Veronica Jamnik, Michael Koehle, and Darren Warburton.

Yanfei Guan, Kyra Dickson, Qinxian Jiang, Delon Chan, and Jackly Ku contributed to study selection and data extraction.

Chapter 4 A version of Chapter 4 has been published. Nana Wu, Shannon Bredin, Veronica Jamnik, Michael Koehle, Yanfei Guan, Erin M. Shellington, Yongfeng Li, Jun Li, and Darren ER Warburton. "Association between physical activity level and cardiovascular risk factors in adolescents living with type 1 diabetes mellitus: a cross-sectional study." *Cardiovascular Diabetology* 20, no. 1 (2021): 1-11. I conceptualized the study design, data collection, data analysis, wrote of the manuscript and made all necessary edits after the peer review process. Dr. Shannon Bredin contributed to the methodology. Dr. Veronica Jamnik, Dr. Michael Koehle, Dr. Erin Shellington, and Dr. Darren Warburton contributed to critical review and editing of the manuscript. Yanfei Guan contributed to data collection, statistical analysis and reviewing the manuscript. Profs Yongfeng Li and Jun Li contributed to coordinating the study implementation.

Chapter 5 A version of Chapter 5 has been prepared for publication. This manuscript is in the final stages of preparation, which are expected for publication in this year. I conceptualized the study design, data collection, data analysis, and wrote of the manuscript with support from Drs. Veronica Jamnik, Michael Koehle and Darren Warburton. Yanfei Guan contributed to data collection. Prof Yongfeng Li contributed to coordinating the study implementation.

Chapter 6 A version of Chapter 6 has been prepared for publication. This manuscript is in the final stages of preparation, which are expected for publication in this year. I conceptualized the study design, data collection, data analysis, and wrote of the manuscript support from Drs. Veronica Jamnik, Michael Koehle and Darren Warburton. Yanfei Guan contributed to data collection. Prof Yongfeng Li contributed to coordinating the study implementation.

The project protocol entitled "Association between Physical Activity Level and Cardiovascular Risk Factors in Adolescents Living with Type 1 Diabetes and Healthy Controls: A Cross-sectional Study" in Chapters 4, 5, and 6 received approval from, and was executed in exact accordance with, the ethical guidelines set forth by the Clinical Research Ethics Board of Shandong Sport University and the University of British Columbia (H18-03355) and in compliance with the Declaration of Helsinki for research involving human participants. The experimental procedures and risks were explained to participants both verbally and in writing, and written informed consent and assent were obtained from parents and children prior to study participation.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

ADA: American Diabetes Association

aIMT: aortic intimal medial thicken

BMI: Body mass index

CGM: Continuous Glucose Monitoring

CPM: counts-per-minute

CI: confidence interval

cIMT: carotid intima media thickness

CSII: continuous subcutaneous insulin infusion

CVD: cardiovascular disease

DCCT: Diabetes Control and Complications Trial

DXA: dual energy X-ray absorptiometry

EDIC: Epidemiology of Diabetes Interventions and Complications

FMD: flow-mediated dilation

HbA1c: glycosylated hemoglobin

HDL-C: high-density lipoprotein cholesterol

HIIE: high-intensity interval exercise

ISPAD: International Society for Pediatric and Adolescent Diabetes

LDL-C: low-density lipoprotein cholesterol

LIPA: light intensity physical activity

MD: mean difference

MDI: multiple daily injection

METs: metabolic equivalents

MICE: moderate-intensity continuous exercise

MVPA: moderate to vigorous intensity physical activity

RCTs: randomized controlled trials

RR: Risk Ratio

SB: sedentary behaviour

SD: standard deviation

SMBG: self-monitoring of blood glucose

T1D: type 1 diabetes

VO_2R: oxygen uptake reserve

VO_2max/VO_2peak: maximum/peak oxygen consumption ($mL \cdot kg^{-1} \cdot min^{-1}$)

WHO: World Health Organization

Acknowledgements

This thesis would not have been possible without the support and inspiration of several wonderful people— it is with much gratitude I extend my appreciation to all of them for their part of this journey and making this thesis possible. First, I would like to sincerely thank my supervisor, Dr. Darren E.R. Warburton for his guidance. He has inspired me to become an independent researcher. Thank you for introducing me to the world of T1D, and providing your untiring support, encouragement, and confidence in me. I have been given the unique opportunity to help children and adolescents living with T1D not only to be more physically active, but also improve their diabetes management, and overall quality of life. This has been extremely rewarding.

I would like to express my profound gratitude to my committee members, Dr. Veronica Jamnik and Dr. Michael Koehle who have generously offered their time, energy, expertise, guidance, feedback, and insight toward improving my work along the way. I am immensely grateful to Dr. Jamnik and Dr. Koehle for always quickly answering my e-mail queries, and even dedicated time on weekends to help. The completion of this thesis could not have been possible without the expertise and support from them. I also express my deep appreciation to Dr. Shannon Bredin for advice and support.

Professors Yongfeng Li and Jun Li deserve a very special word of gratitude. I am enormously grateful for their help during the data collection at the Shandong Sport University. I also acknowledge the important role of all the nurses for participants recruitment.

I was fortunate in receiving the China Scholarship Council (CSC) scholarship during my doctoral studies, and I am forever grateful for this financial support throughout my academic career. I would also like to express my thanks to members of the Cardiovascular Physiology &

Rehabilitation Laboratory for your friendship, support and always being so willing to lend helping hands.

I would be remiss to not acknowledge the participating families who volunteered time and energy to participate in this project. I know it is not easy to stand up and accept the risks, but you were very brave, and I am very proud of each one of you! Thank you for your trust and sharing your life stories with me. The connections we have made throughout this project have enriched my life, and I look forward to continuing our relationships. Working with all of you was the most fun and enjoyable part of this degree.

Many thanks to faculty members and staff at the University of British Columbia with whom I interacted and who made this research journey enjoyable, despite the more trying times.

My deepest and sincerest gratitude to my family for their continuous and unparalleled love, support, and encouragement. I am especially grateful to my parents, who have always supported and encouraged me in all my pursuits and inspired me to follow my dreams no matter what. I always knew that they believed in me and wanted the best for me. Thank you for teaching me that my job in life was to be happy, to learn, and to explore passions, challenges, and new directions. I am forever indebted to my parents for their pivotal role in my life and numerous untold sacrifices for me, and my siblings. I am grateful to my younger sisters (Limeng, Ruiwei) and brother (Mingpeng) for always being there listening, encouraging, and supporting me through this journey. I am very grateful to Yanfei (Ricky) for encouragement, support and giving me a helping hand.

I extend my immense gratitude to my best friend Kyra and my Canadian family. Thank you for offering me a home away from home, when I am far away from China, especially during COVID. Thank you for listening and sharing in my joy and frustrations along the way, and for putting a smile on my face.

Dedication

Dedicated to the memory of my mother, Chunyu Qin (1963-2017), who always believed in my ability to be successful in academia. Your belief in me has made this journey possible.

Chapter 1: Introduction

1.1 Executive Summary

1.1.1 Type 1 diabetes

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by insufficient production of insulin as the consequence of the destruction of the insulin-producing β-cells of the islets of Langerhans of the pancreas (1). Type 2 diabetes is due to a progressive insulin secretory defect on the background of insulin resistance (2). Of all individuals with diabetes, approximately 10% have T1D (3). According to the latest edition of the Diabetes Atlas, more than 1.1 million children and adolescents worldwide were living with T1D in 2019 (4). Furthermore, there are around 128,900 children who are expected to develop T1D each year (4).

According to the American Diabetes Association (ADA) 2018 Classification and Diagnosis of Diabetes, T1D is diagnosed based on either fasting (fasting is defined as no caloric intake for at least 8 h) plasma glucose more than 126 $mg \cdot dL^{-1}$ (7.0 $mmol \cdot L^{-1}$), or the 2-h plasma glucose value more than 200 $mg \cdot dL^{-1}$ (11.1$mmol \cdot L^{-1}$) during a 75-g oral glucose tolerance test, or glycated hemoglobin (HbA1c) being more than 6.5% (48 $mmol \cdot moL^{-1}$) (5). The cure for T1D is not available to date, therefore, individuals with T1D require exogenous insulin either via multiple daily injections (MDI) or continuous subcutaneous insulin infusion (CSII) using an insulin pump. These treatment strategies are used in combination with blood glucose monitoring including self-monitored blood glucose (SMBG) with or without continuous glucose monitoring (CGM) (6).

Type 1 diabetes is associated with a high risk for microvascular and macrovascular complications, and is also related to cardiovascular risk factors, including hypertension, hyperglycemia, dyslipidemia, and insulin resistance (7). Diabetic nephropathy accounts for the increased cardiovascular morbidity and mortality among individuals with diabetes. Cardiovascular

disease (CVD) is the most frequent cause of premature death and disability among this patient group (7).

1.1.2 Cardiovascular risk factors in T1D

1.1.2.1 Hyper/Hypoglycemia

Glycemic control is the clinical cornerstone of CVD prevention in T1D. Hyperglycemia is associated with adverse cardiovascular outcomes such as increased carotid intimal medial thickness (cIMT), and impaired diastolic velocities in T1D youth (8). The SEARCH CVD study reported a relationship between worsening glycemic control and increased arterial stiffness in youth with T1D (9). Furthermore, the Diabetes Control and Complications Trial (DCCT) /Epidemiology of Diabetes Interventions and Complications (EDIC) study found that achieving an HbA1c of < 7% reduced the incidence of microvascular complications of T1D when comparing intensive versus standard glycemic control during a 6.5-year period. After an average follow-up of 17 years, the intensive glycemic-control therapy was associated with a 57% reduction in major cardiovascular disease outcomes even with deterioration in glucose control (10).

Hypoglycemia (low blood glucose) is when blood glucose level falls below 70 $mg \cdot dL^{-1}$ (4 $mmol \cdot L^{-1}$) and individuals may feel shaky, sleepy, irritable, hungry, diaphoretic, weak, lightheaded, or notice tingling or numbness in the lips, tongue, or cheeks (11). Pena et al. demonstrated that hypoglycemia during continuous glucose monitoring relates to impaired vascular endothelial function in children with T1D (12). The ADA recommends that individuals with diabetes should aim to have HbA1c values less than 7% to lower the risk of developing diabetes-related complications (13).

1.1.2.2 Obesity

Obesity is an important risk factor for CVD in people with diabetes. In the SEARCH for diabetes in youth study, the prevalence of obesity in youth with T1D (aged 3-19 years) was higher compared to their peers without diabetes (22.1% vs. 16.1%) (14). Moreover, studies have shown that individuals with T1D who received supra-physiological insulin doses had increased weight gain and higher total cholesterol and LDL-C, central obesity, insulin resistance, blood pressure, more coronary artery calcifications, and higher cIMT during follow-up. This underlies the role of obesity in promoting CVD in individuals with T1D (8). The SEARCH CVD study also found that a waist circumference greater than the 90^{th} percentile was independently associated with higher arterial stiffness at baseline and five-year follow-up, and BMI z-score was a significant predictor of cIMT in youth with T1D after a five-year follow-up (9). These findings highlight the need for close monitoring of weight and early interventions to prevent obesity in youth living with T1D.

1.1.2.3 Dyslipidemia

Dyslipidemia is a crucial risk factor for CVD in people with diabetes. There is a high prevalence of dyslipidemia in youth living with T1D (9). Lipid levels in T1D youth are associated with cardiac and vascular abnormalities, suggesting direct effects of lipids on cardiovascular function including abnormal plethysmography responses, endothelial dysfunction, cIMT, and aIMT all correlated independently with LDL-C (8). The ADA recommends that target LDL-C levels for adults with diabetes are <100 mg·dL^{-1} (2.60 mmol·L^{-1}); HDL-C levels are >40 mg·dL^{-1} (1.02 mmol·L^{-1}); and triglyceride levels are <150 mg·dL^{-1} (1.7 mmol·L^{-1}) (15). Lifestyle intervention with weight loss, increased physical activity, reductions of carbohydrate intake, and

reduction of alcohol consumption are recommended to reduce the risk of dyslipidemia, pancreatitis and cardiovascular diseases for patients with hypertriglyceridemia (15).

1.1.2.4 Hypertension

Hypertension is a major risk factor for CVD. The prevalence of elevated blood pressure in youth with T1D is 6%. Lee et al. reported that higher daytime blood pressure was associated with increased cIMT among Korean adolescents aged 12-19 years living with T1D (16). In addition, the SEARCH CVD study illustrated that hypertension in youth living with T1D at baseline was associated with 7% worsening of arterial stiffness and elevated cIMT over a five-year period (9). The ADA recommends that target blood pressure should be $\leqslant 90^{th}$ percentile for age, sex, and height (17).

1.1.3 Movement behaviours

1.1.3.1 Physical activity

Regular physical activity and exercise can decrease the future cardiovascular risk of T1D through improving blood pressure, lipid profiles, body mass, and inflammation (8). Our meta-analysis of exercise training intervention studies in individuals with T1D demonstrated significant benefits of exercise on HbA1c, BMI, triglycerides and total cholesterol, and found that exercise training had greater beneficial effects when it involved a combination of aerobic exercise and resistance training with a higher frequency ($\geqslant$ 3 times/ week) , and/or a longer duration ($\geqslant$ 12 weeks) (18). Similar results reported by Macmillan et al.'s meta-analysis and systematic review in youth with T1D (19). The International Society for Pediatric and Adolescent Diabetes (ISPAD) recommends that children and adolescents should participate in at least 60 min of physical activity per day (20). However, many youth with T1D do not achieve the recommended levels of physical

activity for optimal health benefits due to concerns over hypoglycemic episodes (21). Exercise-induced hypoglycemia, loss of diabetes control, and low fitness are major concerns for many parents and youth with T1D (22). Youth with T1D also demonstrate that insulin resistance, impaired functional fitness and cardiovascular dysfunction, and impaired functional fitness are associated with CVD (23). Moreover, poor cardiorespiratory fitness is closely linked to CVD mortality (24). Therefore, it is very important to clarify the role of regular physical activity in the management of T1D.

1.1.3.2 Sedentary behaviour

Prolonged sedentary behavior may damage vascular function due to increased production of reactive oxygen species, decreased blood flow, and the presence of a proinflammatory state that generates endothelial dysfunction and increases cardiovascular disease risk (25). Reduced sedentary behaviour is associated with improved cardiovascular function. Long periods of sedentary behaviour was also associated with cardiovascular risk factors, such as increased arterial pressure and body mass index, dyslipidemia, insulin resistance, and decreased cardiorespiratory fitness (26). Results of an observational study of children and adolescents (aged 4-18 years) demonstrated associations between increased time spent in sedentary activities and decreased levels of physical activity and related cardiovascular risk factors (27). In addition, Michaliszyn et al. reported that more sedentary behaviour was associated with lower fitness and fat free mass and increased total cholesterol, low-density lipoprotein cholesterol (LDL-C), and triglycerides in adolescents with T1D (28). Therefore, interventions should be developed which minimize sedentary behaviour and promote physical activity in individuals living with T1D.

1.1.3.3 Sleep

Sleep is an important health behaviour for youth as it is associated with appropriate growth and development. Recently, the association between sleep and diabetes has received increasing attention. In 2017, the ADA's Standards of Medical Care in Diabetes identified sleep as an important consideration for clinicians and introduced recommendations to include "the assessment of sleep patterns and duration as part of the comprehensive medical evaluation based on emerging evidence suggesting a relationship between sleep quality and glycemic control" (29).

A meta-analysis of 22 cross-sectional studies of sleep characteristics in persons living with T1D found that children and adolescents obtained significantly less sleep than youth without diabetes, adults reported poorer sleep quality than adults living without T1D, and shorter self-reported sleep duration and poorer self-reported sleep quality were associated with increased HbA1c, with a mean difference in HbA1c of 0.19% (good sleep quality vs. poor sleep quality) and 0.24% (≤ 6 h vs. > 6 h), respectively (30). On the other hand, Hazen et al. found that parents' perceptions that their adolescents living with T1D slept more than peers living without T1D significantly related to higher glucose levels and poorer self-reported diabetes management (31). Collectively, these findings suggest that too little or too much sleep may have a negative impact on diabetes management.

1.1.4 Exercise-induced hypoglycemia in youth with T1D

Regular exercise participation is advocated in the management of T1D and offers ample health benefits including improved cardiorespiratory fitness, improved vascular health, decreased insulin requirements, improved endothelial function, reduced cardiovascular disease risks, and better self-rated quality of life (18). Particularly in adolescents, exercise is important contributor to

mental health and social development (32). Furthermore, regular exercise participation can reduce the risk of diabetes complications and mortality in individuals with T1D (33; 34). Unfortunately, exercise can also increase the risk of hypoglycemia in individuals with T1D, both during exercise (35) and for up to 15 h of recovery (36). Hypoglycemia is defined as a fall in blood glucose below the normal physiological levels and the commonest acute complication of T1D. It is difficult to use a single quantitative definition of hypoglycemia for all individuals and situations. In clinical and research settings, a glucose value ≤ 3.9 mmol·L^{-1} (70 mg·dL^{-1}) has been determined by the ADA to be generally applicable and in need of treatment in diabetes (37).

Exercise-induced hypoglycemia is determined by an increased glucose uptake and by the inability to endogenously decrease circulating insulin levels in response to exercise, an exercise-induced increase in insulin sensitivity and the potential acceleration of insulin absorption from the site of administration (38). In addition, the response of counterregulatory hormones to exercise may be blunted by antecedent exercise or hypoglycemia, and in some cases is permanently reduced in individuals with autonomic neuropathy (38).

The fear of hypoglycemia appears to be a main barrier for participation in exercise in T1D. Studies has found that children and adolescents with T1D and their parents often avoid engaging in exercise training due to a fear of hypoglycemia (39; 40). Therefore, strategies with regard to promoting safe participation in exercise for youth with T1D and protecting them against exercise-induced hypoglycemia are of critical importance. The 2018 ISPAD guidelines provide many helpful recommendations for managing hypoglycemia during and after exercise in children and adolescents with T1D (41). These guidelines include insulin reduction before, during and after

exercise, carbohydrate consumption before and/or after exercise, and the inclusion of intermittent, repeated bouts of high intensity sprints during aerobic exercise sessions.

1.1.4.1 Acute moderate intensity continuous exercise and glucose control in youth with T1D

Youth with T1D may need individualized recommendations based on the type of exercise (aerobic exercise or high-intensity interval exercise), timing (morning vs. afternoon), and duration of exercise the individual is participating in, with specific adjustments based on their treatment regimen. Aerobic exercise generally involves continuous, repeated movements of large muscle groups (e.g. walking, jogging, cycling, and swimming) for at least 10 min at a time (42).

Aerobic exercise performed at moderate intensity (40%-60% VO_2 max) may cause a rapid increase in glucose uptake into skeletal muscle. Energy for this type of exercise is provided predominantly by the aerobic oxidation of both carbohydrates and fats (38). In individuals without T1D, insulin release from pancreatic β-cells decreases and glucagon secretion increases during this intensity of exercise to make sure that fatty acids and glucose are released form storage to fuel exercising muscles in order to maintain glucose homeostasis during and for a short while following exercise (43). However, for individuals with T1D, the destruction of the insulin-producing β-cells leads to the requirements for exogenous insulin. The circulating insulin levels cannot be regulated endogenously and depend on the quantity and timing of insulin taken. It is reported that insulin levels are higher in individuals with T1D than individuals without T1D during aerobic exercise at moderate intensity (44), which would limit glucose production by liver while stimulating glucose uptake by muscle, adipose and liver cells for storage. As a result, hypoglycemia is a common

occurrence with aerobic exercise (moderate-intensity) unless insulin dosages are reduced or additional carbohydrates are supplemented before, during, or after exercise.

1.1.4.2 Acute high intensity exercise and glucose control in youth with T1D

High-intensity interval exercise consists of short periods of high intensity (> 85% maximum oxygen consumption (VO_2max)) exercise, usually lasting less than one minute, alternating with short periods of rest or light- to moderate-intensity recovery (42). Aerobic exercise performed at high intensity (> 80% VO_2max) may cause a rapid and sustained increase in counter-regulatory hormones (epinephrine, norepinephrine, growth hormone, glucagon, and cortisol) and this type of exercise is predominantly fueled by creatine phosphate and anaerobic glycolysis and cannot be maintained for a long duration (38). Studies show that increases in counter-regulatory hormones (such as epinephrine/norepinephrine) may stimulate glucose release by liver and result in an increase in blood glucose, which may cause hyperglycemia (45; 46). A series of studies explored adding a simple all-out 10-s sprint as a primer to elevate blood glucose either before (47) or after (48; 49) a 20 to 30-min bout of aerobic exercise. Bussau et al. (47) found that inclusion of a maximal 10-s sprint before 20 min of aerobic exercise (cycling at 40% VO_2max) prevented blood glucose declines in the 45 min after exercise recovery compared to an exercise session without a brief sprint and protected exercise-induced hypoglycemia in individuals with T1D. A similar protective effect was also observed when a10-s sprints was performed during a 20-min aerobic exercise at moderate intensity and the effect lasted 2 h after exercise (48). Furthermore, Fahey et al. (50) found blood glucose increase from a 10-s sprint in individuals with T1D resulting from a decline in rate of glucose uptake rather than from a disproportionate rise in glucose appearance.

Collectively, these acute studies suggest that incorporating a bout of short sprint may prevent hypoglycemia during or immediately after exercise.

1.1.4.3 Acute high intensity interval exercise and hypoglycemic excursions in youth with T1D

Recently, adding repeated bouts of high intensity exercise to aerobic exercise sessions has consequently become a topic of interest in diabetes research as it may attenuate the risk of exercise-induced hypoglycemia. In adults, many studies of individuals with T1D have examined the potential role of adding repeated bouts of high intensity interval exercise sessions to prevent the aerobic exercise induced hypoglycemia (51-53), while the following studies have also reported that the same phenomenon is true in children and adolescents with T1D.

Sills and Cerny (54) studied high-intensity interval exercise consisting of one minute at 100% of VO_2 max cycling followed by one minute of rest for 30 min compared to 30 min of aerobic cycling at 50% of VO_2max in adolescent boys (aged 10-16 years) with T1D and age-matched male controls. The authors observed that 30 min following the onset of exercise the blood glucose levels were significantly different between the continuous and interval exercise interventions in adolescents with T1D. The decrease in blood glucose was 99 mg % during aerobic exercise and 88 mg% during intermittent exercise in adolescents with T1D (50).

Similarly, Adolfsson et al. (44) performed a crossover study of hormonal responses to interval exercise (6 × 3 min bursts at 70% of VO_2max following with 1.5 min of low-intensity cycling) compared to aerobic exercise (60 min at 40% of VO_2max) in 12 adolescents (6 boys and 6 girls) with well-controlled T1D and 12 controls matched for age, sex and level of physical activity. Glucose levels decreased over time during each intervention in both groups (diabetes

group and healthy controls) and decreased more during the aerobic exercise (diabetes: -4.1 ± 5.0 mmol·L^{-1}; controls: -0.1 ± 0.4 mmol·L^{-1}; p = 0.03) than the interval exercise (diabetes: -2.7 ± 4.8 mmol·L^{-1}; controls: +0.1 ± 1.3 mmol·L^{-1}; p = 0.08) and there were no hypoglycemic episodes during and after both exercise protocols. The authors suggested that an increase in insulin concentration suppresses glucagon secretion and the increasing circulation levels of growth hormones and catecholamines induced by high-intensity interval exercise may result in decreasing glucose uptake which may contribute to the lesser decline of blood glucose compared to aerobic exercise.

Thus, for children and adolescents with T1D, the blood glucose drop is smaller during repeated bouts of high intensity interval exercise sessions compared to aerobic exercise based on study founding above. However, further investigations about the effect of this high-intensity interval exercise on exercise-induced hypoglycemia in children and adolescents need to be performed to fully understand the effect of high-intensity interval exercise in children and adolescents with T1D. In addition, randomized controlled trial studies (RCTs) need to be conducted to determine if the long-term intervention of this type of exercise would prevent hypoglycemia.

1.1.4.4 Long-term exercise training and hypoglycemic excursions in youth with T1D

Previous studies showed that active adults with T1D do not have a higher incidence of hypoglycemia compared to the less active or sedentary individuals with T1D. Brazeau et al. (55) found that the most active adults with T1D did not report more frequent hypoglycemia than the less active individuals with T1D possibly because active individuals with low barriers for physical activity also display the best knowledge of approaches to prevent exercise induced glucose fluctuations. Furthermore, Bohn et al. (56) analyzed 18,028 adults with T1D between18 to 80 years

of age in Germany and Austria, and reported that severe hypoglycemia (assistance required) did not differ among different physical activity level groups (PA0, inactive; PA1, one to two times per week; PA2, more than two times per week). They concluded that being physically active is associated with reduced cardiovascular risk and better glycemic control without an increase in severe hypoglycemia, and physical activity should be promoted in individuals with T1D.

The same phenomenon is likely to be true for children and adolescents. Herbst et al. (57) conducted a study including a cohort of 19,143 individuals with T1D (aged 3-20 years) in Germany and Austria and showed that regular physical activity participation was associated with lower HbA1c without increasing the risk of severe hypoglycemia. A lager cohort of adolescents with T1D involving 21 pediatric diabetes departments from 19 countries in Europe, Japan, Australia, and North America also reported that regular physical activity participation was not associated with frequency of hypoglycemia (58).

In addition, most long-term aerobic exercise intervention studies demonstrate that exercise training can be undertaken by adolescents and children with T1D without significant severe hypoglycemia (59-65). Landt et al. (62) reported no increase in frequency of hypoglycemia in both the intervention and control group. Campaigne et al. (60) reported only one out nine children experienced hypoglycemia, which occurred during a training session (three times a week for 12 weeks). Rowland et al. (64) conducted a crossover study and reported that mild and infrequent hypoglycemia occured in six out of 12 children during both the control and exercise period. Maggio et al. (63) reported no hypoglycemia during the training sessions. Salem et al. (65) found no difference in hypoglycemia rates between the control and intervention arms.

Conversely, D'hooge et al. (61) reported frequent hypoglycemic episodes both during and 12 h after 70 min of aerobic exercise and strength training twice a week for 12 weeks in the intervention group . In the study by Aouadi et al. (59) performed 60 min of aerobic exercise two and four times for four weeks and reported that all participants experiencing moderate hypoglycemic events completed the study. Thus, more research is needed for assessing the effect of real-life physical activity participation on glucose levels to better understand the relationship between physical activity levels and hypoglycemia.

Collectively, active children and adolescents with T1D do not have a higher incidence of hypoglycemia compared to the less active or sedentary individuals with T1D. The cross-sectional studies above did not find associations between physical activity levels and frequency of severe hypoglycemia. Furthermore, most long-term exercise intervention studies in adolescents and children with T1D did not find significant increases of severe hypoglycemic events in exercise training group compared to non-exercise group. Therefore, most of exercise training studies revealed a relatively low incidence of exercise-related adverse events. Most children and adolescents with T1D may tolerate the exercise training well.

1.1.5 Glycemic management strategies for exercise in youth with T1D

1.1.5.1 Insulin adjustments

In addition to the research evidence regarding potential exercise interventions that attenuate or prevent hypoglycemia during and following exercise, Tables 1.1 and 1.2 summarize various insulin adjustment and extra carbohydrate consumed strategies that individuals on insulin pump or MDI may want to consider before and post exercise for both short duration and more prolonged physical activities, these strategies is recommended by the ISPAD (20).

Table 1.1 Insulin adjustment strategies before, during and after for hypoglycemia prevention in children and adolescents with T1D

	Insulin adjustments before exercise				**Insulin adjustments at the meal after exercise**	
	Moderate intensity continuous exercise		**High-intensity interval exercise**		**Moderate intensity continuous exercise**	**High-intensity interval exercise**
	< 30 min	**> 30 min**	**< 30 min**	**> 30 min**		
Basal insulin rate (BRR)reduction (CSII)	50% BRR, set 60-90 min pre-exercise or Pump suspension at exercise onset	50-80% BRR, set 60-90 min pre-exercise or Pump suspension at exercise onset	Pump suspension at exercise onset	50% BRR, set 60-90 min pre-exercise	20% BRR overnight lasting 6 h	20% BRR overnight lasting 6 h
Basal insulin reduction (multiple daily injections)	basal insulin dose reduction (of ~10%) if exercise occurs less than every 3 days (camp) or if the frequency of exercise is high throughout the day; might also be useful if individuals are on twice daily intermediate insulin		Basal insulin dose reduction not advised	Basal insulin dose reduction not advised	Basal insulin dose reduction not advised	Basal insulin dose reduction not advised
Bolus insulin	25% reduction @ ~25% VO_2max 50% reduction @ ~50% VO_2max 75%reduction @ 70-75% VO_2max	50% reduction @ ~25% VO_2max 75%reduction @ ~50% VO_2max	25% reduction	50% reduction	25-50% reduction	25-50% reduction

Table 1.2 Summary of suggested carbohydrate intake before, during and after exercise for hypoglycemia prevention in children and adolescents with T1D

	Meal (Low fat whole grain low glycemic index carbohydrate**) three to four h before exercise**	**Immediately before exercise (**high glycemic index)	**During exercise**				**Immediately post exercise**	**Meal** (Low fat whole grain glycemic index carbohydrate) **one to two h post-exercise**
			< 30 min	**30-60 min**	**60-150 min**	**> 150 mins**		
Carbohydrate	A minimum of 1 g carbohydrate per kg bodyweight according to exercise intensity and type	If blood glucose concentration is less than 5 mmol·L^{-1} (<90 mg·dL^{-1}), ingest 10-20 g snack	If blood glucose concentration is less than 5 mmol·L^{-1} (< 90 mg·dL^{-1}), ingest 10-15 g carbohydrate	10-15 g per 30 min for aerobic of carbohydrate adjusted according to insulin on board and blood glucose levels. High intensity: no carbohydrate required during exercise unless blood glucose concentration measured during the activity is less than 5 mmol·L^{-1} (<90 mg·dL^{-1}); if so, ingest 10-20 g carbohydrate; replace carbohydrate needs after exercise	30-60 g carbohydrate per h to prevent hypoglycemia and enhance performance	Follow sports nutrition guidelines (60-90 g·h^{-1}) with appropriate insulin adjustment for glycemic management	If meal to be eaten within an hour not needed unless indicated by BGL. If meal >1-hour post-exercise 10-15 g snack, for example, fruit, low fat cereal bar, 150-200 mL milk	1.0-1.2 g carbohydrate per kg bodyweight For exercise activity before sleep consume additional bedtime snack

Individuals with T1D who use an insulin pump may choose to decrease, or sometimes completely stop their basal insulin infusion at any time before, during and post exercise. It is recommended that for children and adolescents basal insulin reduction be set approximately 90 min before the onset of exercise to allow insulin levels to drop sufficiently in the circulation before exercise starts, lasting until the end of exercise (66; 67). In contrast, for individuals on MDI, basal insulin adjustments can only be made when long-acting insulin is administered, often in the early morning or before bedtime. If individuals on MDI are unable to reduce the long-acting component they can compensate by ingesting an appropriate amount of carbohydrates.

The insulin adjustment should be based on the intensity, duration and timing of exercise. For prolonged aerobic exercise (>30 min), the Diabetes Research in Children Network (DirecNet) Study Group involving 49 children and adolescents (aged 8-17 years) with T1D reported a decreased frequency of hypoglycemia when basal insulin was discontinued compared with continued normal basal insulin delivery (16% vs. 43%; $p = 0.003$) during four 15-min intervals on the treadmill at a target heart rate of 140 bpm (interspersed with three 5-min rest breaks over 75 min), but the risk of post-exercise (45 min after the completion of exercise) hyperglycemia and risk of ketosis was increased (68). In contrast, a pediatric study (n = 10) investigated a 40-45-min aerobic exercise session (submaximal cycling (~60% of VO_2max)) with basal insulin reduction of 50% compared with suspended basal insulin during exercise showing similar hypoglycemia episodes and the drop in glycemia during between groups (69). Moreover, six of ten children developed hypoglycemia during sleep even with the removal of the insulin pump during exercise.

For adolescents with TID, Taplin et al. (70) found that a reduction in basal insulin by ~20% from 9:00 pm. to 3:00 am. following four 15-min intervals on the treadmill at 55% of VO_2max (interspersed with three 5-min rest) aerobic exercise in the afternoon attenuated nocturnal hypoglycemia. However, it is important to note that responses varied among the individuals, with

2 of 16 individuals still having blood glucose readings of 80 mg·dL^{-1} (4.4 mmol·L^{-1}), while 12 of 16 had hyperglycemia (≥ 250 mg·dL^{-1}) during the night following basal insulin reductions.

A more recent study by Miller et al. (71) was conducted on 256 children and adolescents aged 7 to 15 years (55% were on pumps) attending a week-long summer camp. They reduced all children's basal insulin by 10%. Sixty percent of them had at least one episode of hypoglycemia during the first day. Overall insulin doses did not decrease further during the camp; however, the number of hypoglycemic episodes decreased. There was a difference between pumps and injections with children using injections requiring approximately an extra 8% insulin reduction. The authors stated that consideration of these factors may be wise before recommending the scale of insulin reduction.

In addition to manipulating basal insulin delivery, another strategy to reduce the risk of exercise-induced hypoglycemia during and after exercise is to reduce exercise premeal bolus insulin. Bolus adjustments require planning in advance and are needed when aerobic exercise is performed more than 30 min within 1-3 h after a meal. The bolus reduction should also be based on the intensity and duration of exercise (Table 1.1). Very limited studies have been performed in youth with T1D. In adults, one crossover study examined reductions in bolus insulin (following either 100, 50, or 25% of usual insulin dose) given at breakfast 90 min prior to exercise. Then they performed exercise at 25% VO_2max for 60 min, 50% VO_2max for 30 min and 60 min, and 75% VO_2max for 30 min. One hundred percentage of pre-meal usual insulin doses were associated with increased hypoglycemia. Greater reductions of insulin doses were associated with a lower incidence of exercise-induced hypoglycemia (35). Furthermore, Campbell et al. (72) found a 75% reduction in pre-exercise food bolus and a 50% reduction in post-exercise insulin bolus resulting

in protection against hypoglycemia during, and for 8 h after exercise without basal insulin adjustments. Thus, adjustments of both pre- and post-exercise meal boluses are also effective to avoid the exercise-related hypoglycemia.

1.1.5.2 Carbohydrate consumption

A standard meal containing carbohydrates, protein and fat about 3-4 h prior to exercise is recommended (66). Carbohydrate supplementation is another important strategy to consider in the avoidance of hypoglycemia. Carbohydrate feeding should also be based on the intensity, duration and timing of exercise. Perrone et al. (73) studied whether ingestion of a drink containing sufficient carbohydrates (8% or 10% carbohydrate) can help avoid exercise-induced hypoglycemia in T1D adolescents. The authors asked participants to cycle at 55-60% VO_2max for 60 min, consuming either an 8% or a 10% carbohydrate solution before the exercise. They found blood glucose concentrations were lower following the consumption of the 8% solution with four individuals experiencing severe hypoglycemia, with blood glucose concentrations dropping to ~1.8 $mmol \cdot L^{-1}$ in the hour post-exercise, whereas concentrations remained stable under the 10% carbohydrate solution condition (73).

Riddell and Milliken conducted a study at a diabetes camp assessing the use of a simple snacking strategy before exercise based on sensor glucose readings (74), they found that the consumption of 16 g of carbohydrates failed to prevent hypoglycemia in nearly 40% of cases when glucose was < 90 $mg \cdot dL^{-1}$ (5 $mmol \cdot L^{-1}$) before exercise (74). In addition, it has been suggested that those living with T1D may benefit from consumption of 1-1.5 g of carbohydrate per kilogram of body mass per hour of activity, especially if the activity is occurring during peak insulin action (41). Dube et al. (75) examined the effect of a postprandial exercise supplement (30 g of

carbohydrates, e.g. Sandwich or a glass of milk) and intensity of exercise (moderate and high intensity) strategies on blood glucose and suggested that moderate-intensity exercise with a 30-g pre-exercise glucose beverage or interspersed with intermittent high-intensity sprints may be safe strategies to prevent hypoglycemia in glargine/glulisine users with T1D. Dube et al. (76) suggested that taking carbohydrate supplement before unplanned exercise is the best strategy to prevent exercise-induced hypoglycemia in an adolescent population and a protein supplement strategy may also have some benefits in limiting the rate of hypoglycemia during and immediately after exercise.

Soon et al. (77) examined whether pre-exercise ingestion of carbohydrates can help maintain stable glycemia during aerobic exercise results in exercise hyperglycemia if combined with repeated sprints in individuals with T1D. The authors concluded that adding repeated sprints is not significantly detrimental to glycemic management in overnight fasted individuals with T1D when carbohydrates are ingested prior to aerobic exercise.

Combination of reduction of insulin doses with ingestion of carbohydrates is also an alternative strategy for reducing the incidence of hypoglycemia. A study conducted by West et al. (78) investigated whether the combination of a 75% reduction in rapid-insulin and ingestion of 75 g of carbohydrates 30, 60, 90 or 120 min before a 45-min running exercise (70% VO_2max) could assure that blood glucose levels stayed within target ranges. They found that no hypoglycemia occurred when carbohydrate was ingested 30 min before exercise compared with increasing frequency when carbohydrate was ingested 120 min before exercise. Therefore, the combination of a low glycemic index carbohydrate, administered 30 min, before exercise and reduced pre-exercise insulin dose may abolish the risk of hypoglycemia associated with prolonged aerobic exercise in T1D.

1.1.5.3 Blood glucose monitoring

In addition to strategies mentioned above, frequent glucose monitoring, antecedent hypoglycemia, and timing of exercise (morning versus afternoon) are important factors that need to be considered in the maintenance of euglycemia during and following exercise. Blood glucose monitoring should be performed at least twice before exercise to assess if the direction of blood glucose levels is increasing or decreasing before starting of the exercise (79). Before starting of the exercise, the ISPAD recommends that a patient's blood glucose should be greater than 90 $mg \cdot dL^{-1}$ (5 $mmol \cdot L^{-1}$). If initial blood glucose levels are low, the individual should avoid physical activity at that time and consume sufficient carbohydrates to achieve euglycemia (41). It is also advised (though it may not be practical) that self-monitoring of blood glucose should be performed every 30 min during exercise and for 24 hours afterwards to monitor late-onset hypoglycemia (41).

1.1.5.4 Antecedent hypoglycemia

Exercise and physical activity should be avoided if there is significant hypoglycemia in the days before exercise. Galassetti and Riddell (80) stated that hypoglycemia in the 24 to 48 h prior to exercise in T1D can blunt counterregulatory hormone responses during moderate intensity aerobic exercise, and, thus, increase further the risk of hypoglycemia. The authors documented that the glucagon, epinephrine, and other counterregulatory responses to exercise in individuals with T1D (n=16) were comparable to those of healthy controls after a few days without any hypoglycemic episodes. However, the glucagon response to exercise was completely suppressed, and the epinephrine response as well as endogenous glucose production and lipolysis were reduced by ~50% when those individuals were exposed to 4-h of hypoglycemia at ~50 $mg \cdot dL^{-1}$ and they exercised the following day (81).

In Galassetti et al. (82) 's subsequent study the depth of prior hypoglycemia was varied (at 70, 60, and 50 $mg \cdot dL^{-1}$), resulting in proportional levels of suppression of the subsequent glucagon response to exercise (40%, 60%, and 95% suppression, respectively), indicating the presence of a clear dose-dependent response. As the prior hypoglycemia was induced on the day before the exercise (which occurred the next morning), this blunting effect was shown to persist for many hours. While no longer-term data are available on this effect, Tran and Galassetti (83) stated that counterregulatory responses will return to normal levels over time and there should be no more continued blunting stimuli. Thus, physical activity should be avoided if individuals with T1D have severe hypoglycemia in 24 to 48 h prior to exercise.

1.1.5.5 Timing of exercise

Timing exercise earlier in the day may be an adequate strategy to avoid nocturnal hypoglycemia. Morning activity before breakfast and bolus insulin administration reduce the risk of hypoglycemia as circulating insulin levels are typically low. Gomez et al. (84) compared morning versus afternoon exercise in adults with T1D and found that there were fewer episodes of late-onset hypoglycemia when exercise was performed in the morning (5.6 vs. 10.7, events per individuals, up to 36 h post-exercise). They also suggested a benefit of glycemic control in morning exercise but not in afternoon exercise. Studies of adolescents with T1D found that aerobic exercise in the afternoon was associated with an increased risk of overnight and next-day hypoglycemia as insulin sensitivity was increased for the post-exercise 11 h (85; 86). Thus, the risk of hypoglycemia after midnight may be attenuated from morning exercise compared with afternoon exercise. In addition, individuals with T1D should avoid exercise during peak insulin action and snack before bedtime is recommended if exercise is undertaken in the afternoon (87).

1.1.5.6 Treatment of hypoglycemia

During exercise, if a child with diabetes is feeling unwell with any signs or symptoms of hypoglycemia, glucose tablets or other forms of quick-acting carbohydrate should be given as for a treatment of hypoglycemia, even if blood glucose cannot be measured to confirm hypoglycemia. The ISPAD recommends treatment with approximately 9 g of glucose for a 30-kg child (0.3 $g \cdot kg^{-1}$) and 15 g for a 50-kg child for hypoglycemia with a rise in blood glucose of approximately 3 to 4 $mmol \cdot L^{-1}$ (55-70 $mg \cdot dL^{-1}$) (41). Blood glucose levels should be retested 15 min after glucose treatment, and glucose or carbohydrate should be re-dosed if an individual continues to be hypoglycemic. Retesting the blood glucose in another 20-30 min to confirm that target glucose has been maintained and not exceeded is recommended. Traditionally, blood glucose is tested by using fingerstick capillary sampling and a handheld glucose meter (6). Continuous glucose monitoring (CGM) is being used increasingly in adults as well as children and adolescents with T1D (88) and needs repeated calibration by finger-stick capillary glucose testing and has a relatively shorter sensor life. However, the flash glucose monitor can easily measure glucose levels by scanning the sensor at any point of time without the need for repeated patient-self calibration and has a longer sensor life of 14 days (89).

Most of the literature regarding T1D has focused on aerobic exercise training which always was aligned with continuous steady state light and/or moderate intensity. However, purely aerobic exercise does not exist as exercise at all intensities involves a varying degree of interplay between aerobic and anaerobic bimetallism. Although the existing studies examining the acute effects of inclusion of short sprints indicate this may be a successful approach to preventing hypoglycemia during and up 2 h after exercise, no studies exist to date using a randomized controlled trial design

to determine the long-term benefits of this type of exercise in youth with T1D. The majority of related studies have been crossover designs and relied on small sample sizes of individuals, and generally tested very short maximal-intensity (i.e., sprint) intervals, and thus, have limited their observations to a short post-exercise window. Therefore, the translation of this knowledge into a practical or clinical setting is still very limited.

On the basis of the available data, the inclusion of intermittent bouts of high-intensity physical activity in aerobic exercise has the potential to stabilize blood glucose levels on exercise days. The research evidence contributes to general guidelines that exercise-induced hypoglycemia can be decreased or prevented by frequent glucose monitoring, adjustments to type and timing of insulin dosing, and the amount and timing of carbohydrate administration before, during and after exercise. Physical activity participation should be promoted in children and adolescents for health benefits and exercise-induced hypoglycemia management needs to be based on intensity, duration, and timing of exercise, customized, and individualized as blood glucose responses to the various forms, duration and intensities, and timing of exercise show high variability between and within individuals.

Given the findings in the current literature, further investigating the association of daily physical activity, sedentary behaviour, sleep, and cardiovascular risk factors, in adolescents living with T1D is needed. Moreover, the effects of acute and long-term effects of exercise on cardiovascular risk factors in individuals with T1D would provide a theoretical understanding of exercise for T1D as it impacts cardiovascular health outcomes, as well as provide valuable information to health professionals as evidence for the preventative and therapeutic effects of

exercise on cardiovascular risk factors in T1D, and the potential mechanisms by which exercise may improve cardiovascular health.

1.2 Purposes and Hypotheses

1) The first study consisted of a systematic review and meta-analysis of published randomized or non-randomized controlled studies on exercise training for cardiovascular disease risk factors in individuals living with T1D. It was hypothesized that exercise training would lead to significant improvements in cardiovascular risk factors (maximal aerobic power, HbA1c, lipid profiles, BMI, blood pressure, and hypoglycemia) in persons living with T1D (**Chapter 2**).
2) The second study was also a systematic review and meta-analysis evaluating the acute effects of high intensity interval exercise (HIIE) versus moderate intensity continuous exercise (MICE) on metabolic outcomes and hormonal responses in individuals living T1D. We hypothesized that in persons with T1D, HIIE may be associated with less of a decrease in glucose levels or risk of hypoglycemia compared to MICE. Furthermore, counter-regulatory hormones were hypothesized to be associated with higher glucose levels during high-intensity interval exercise (**Chapter 3**).
3) The third study was a cross-sectional study comparing the cardiovascular risk factors (maximal aerobic power, HbA1c, lipid profiles, BMI, and blood pressure) in youth with and without T1D, and exploring the role of daily physical activity on the hypothesized improved cardiovascular risk factors in adolescents in T1D. We hypothesized that the cardiovascular profile in adolescents with T1D would be proatherogenic compared with that in healthy nondiabetic youth, and that higher physical activity levels would be

associated with improved cardiovascular disease risk factors among adolescents with T1D (**Chapter 4**).

4) The fourth study compared objectively measured sleep characteristics in adolescents with T1D with peers living without T1D and investigated the associations between sleep patterns and CVD risk factors in individuals living with T1D and healthy controls. We hypothesized that sleep would be disturbed in adolescents living with T1D in comparison to adolescents without T1D, and poor sleep quality and shorter sleep duration would be associated with proatherogenic CVD risk factors (**Chapter 5**).
5) The fifth study investigated associations between time spent in any 24-h movement behaviours, relative to the other behaviours, and the CVD risk factors in adolescents with T1D. It was hypothesized that each movement behaviour, relative to the other behaviours, would be associated with the CVD risk factors (maximal aerobic power, HbA1c, lipid profiles, BMI, blood pressure, and hypoglycemia) in adolescents with T1D (**Chapter 6**).

Chapter 2: Cardiovascular Health Benefits of Exercise Training in Persons Living with Type 1 Diabetes: A Systematic Review and Meta-analysis

2.1 Introduction

Type 1 diabetes is an autoimmune disease characterized by insufficient production of insulin resulting from the destruction of the insulin-producing β-cells of the islets of Langerhans of the pancreas (90; 91). The prevalence of T1D continues to increase considerably. According to the latest edition of the Diabetes Atlas, more than 1.1 million children and adolescents worldwide were living with T1D in 2019 (92). Moreover, around 128,900 children (aged 0-19 years) are expected to develop T1D each year (93).

Type 1 diabetes is associated with high risks of microvascular and macrovascular complications, as well as other cardiovascular risk factors, including obesity, hypertension, hyperglycemia, dyslipidemia, insulin resistance, and physical inactivity (8; 94). Type 1 diabetes is also related to cardiovascular abnormalities (such as reduced myocardial function, increased carotid intima-media thickness, arterial stiffness, and endothelial dysfunction) that may increase the risk for the development of chronic heart failure (7; 95). Diabetic nephropathy is associated with higher the incidence of cardiovascular morbidity and mortality among individuals with diabetes. Additionally, cardiovascular disease is the most frequent cause of premature death and disability in T1D. In individuals aged from 8 to 43 years old with T1D, up to 5 out of 1,000 people die from cardiovascular disease each year (93; 96). Accordingly, cardiovascular risk identification and prevention is essential in such a high-risk population.

Regular exercise and physical activity participation and reduced sedentary behavior are important for cardiovascular disease risk management (97; 98). Regular exercise training offers

ample health benefits for persons living with T1D resulting in improved cardiorespiratory fitness, improved vascular health, decreased insulin requirements, improved endothelial function, reduced cardiovascular disease risks, and better self-rated quality of life (98-102). Exercise training has been shown to reduce the severity of cardiovascular risk factors, such as obesity, high blood pressure, lipid lipoprotein profile (LDL-C, HDL-C, total cholesterol, triglycerides), and systemic inflammation (103). Although RCTs examining the association between physical activity and mortality in T1D are limited, epidemiological studies suggest that regular physical activity participation reduces the risk of macrovascular disease and death (33; 34). Moreover, a systematic review and meta-analysis has shown that exercise training has an overall beneficial lowering effect on cardiovascular risk factors in type 2 diabetes mellitus (104). However, evidence for the effects of exercise training on cardiovascular risk factors in T1D is lacking. Consequently, the aim of this study is to conduct a systematic review and meta-analysis of published RCTs on exercise training for cardiovascular disease risk factors in persons living with T1D. We hypothesized that exercise training would have led to significant improvements in cardiovascular risk profile in persons living with T1D.

2.2 Methods

We adhered to the standards established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (105). This review was registered in PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/PROSPERO, identifier CRD42017060953). No study protocol was published before the initiation of the systematic review and meta-analysis.

2.2.1 Search strategy

Preliminary searches were performed to identify any existing or ongoing reviews on this topic prior to commencing this project. The systematic review was conducted to identify relevant trials by electronic searches of MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, SPORTDiscus, and Cumulative Index of Nursing and Allied Health (CINAHL) from their inceptions to December 2017 (see electronic Appendix A material Methods for a complete list of search terms). Individualized search strategies were designed for each database. Databases were also searched for ongoing trials using Current Controlled Trials (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov). The reference lists were manually screened for all relevant additional studies and reviews. No language restrictions were imposed.

2.2.2 Study selection

Studies that fit the following criteria were included in this review: RCTs, quasi-experimental trials, and crossover trials examining cardiovascular risk factors before and after exercise training. Cardiovascular risk factors of interest included aerobic fitness, glycated hemoglobin, daily insulin dosages, blood pressure, blood lipid profile (LDL-C, HDL-C, total cholesterol, triglycerides), and body mass index. Exercise training modalities of interest included aerobic, resistance, and/or combined exercise and could be supervised or unsupervised. To determine chronic adaptations, the duration of training was to be no less than four weeks. Study populations included individuals of any age or sex who had been diagnosed with T1D; the comparator was the control group for long term intervention studies. Context studies reporting at least one cardiovascular disease risk factor were also considered in this review.

We excluded case studies, reviews, and studies that included persons living with type 2 diabetes, gestational diabetes, individuals with significant diabetic complications (e.g., diabetic foot, retinopathy, severe neuropathy, uncontrolled hypertension, and diabetic keto-acidosis), cardiovascular disease, or participants on lipid-lowering therapy. Studies that failed to report cardiovascular risk factors pre- and post-exercise were excluded. Two authors (NW & YG) independently scanned titles and abstracts, and the keywords of every study identified. Both authors independently evaluated the remaining studies based on full texts, applying the eligibility criteria for included studies. Any disagreements were resolved by consensus, or by discussion with third and fourth reviewers (KD & DK). The process was overseen by a professor with expertise in systematic reviews and knowledge mobilization (SB).

2.2.3 Data extraction and quality assessment

Two authors (NW & YG) independently extracted data using a standardized form. If agreement was not reached regarding the extraction of the data, an additional investigator (DW) adjudicated the outcome. Missing data from the included studies were requested directly from the study authors. Extracted information included: authors, title of the study, year of publication, study design, study population (age, sex, diabetic duration, sample size), details of the intervention, control conditions, recruitment, and outcomes.

Using the Physiotherapy Evidence Database (PEDro) scale (106), we carried out assessments of the methodological quality of each included study according to the items addressed by the tool: selection bias, performance bias, detection bias, attrition bias, and reporting bias. An independent reviewer validated the assessment process, and any discrepancies were checked by another reviewer.

2.2.4 Data synthesis and analysis

Review Manager software (RevMan version 5.1, Cochrane Collaboration, Oxford, UK) was used to extract data from the included studies, the primary (cardiovascular risk factors) and secondary (adverse events) outcome data were reported as mean ± standard deviation (SD), median (range) or weighted mean and 95% confidence intervals (CI). Weighted mean differences (effect size, ES) of each cardiovascular risk factor between exercise groups and controls were calculated using a random effects model. We quantified and explored the statistical heterogeneity between studies using the I-squared test and chi-squared test, with 95% uncertainty intervals. Publication bias was assessed by viewing the overlap of the study CI, using funnel plot techniques. Random effects models were chosen to conduct the meta-analyses when significant heterogeneity was present. Subgroup analyses for the participants' age, exercise frequency, type of exercise, and program duration were used to explore the sources of heterogeneity. Sensitivity analyses were conducted by excluding one study at a time to examine if the results were driven by any one study. Standard error of the mean (SEM) values were converted to SD values.

2.3 Results

2.3.1 Study characteristics

After the removal of duplicates, 2,446 articles were identified in the initial electronic search. Following screening of the titles and abstracts, 80 full articles met the eligibility criteria for further examination (Fig. 2.1*)*. A total of 56 articles were excluded with the following reasons: inappropriate study design (n = 39); insufficient data for meta-analysis (n = 11); not relevant outcomes (n = 5); participants with autonomic neuropathy (n = 1). A total of 24 controlled studies published between 1984 (60) and 2017 (107) met our inclusion criteria.

Origins and settings of the included studies, characteristics of the samples, interventions, and primary outcomes assessment are summarized in Table 2.1. Multiple studies utilized different program durations and/or different frequencies of exercise training intervention - these studies were reported as two related trials. When accounting for differences, the total number of comparisons increased from 24 studies to 28 trials, each with an exercise condition and a control condition. In summary, four studies (six trials) reported diastolic and systolic blood pressure data, ten studies (ten trials) reported body mass index data, five studies (six trials) reported daily insulin dosage data, 21 studies (24 trials) reported HbA1c data, 11 studies (11 trials) reported peak/maximal oxygen consumption (VO_2peak/VO_2max) data, 12 studies (15 trials) reported total cholesterol and triglycerides data, 11 studies (14 trials) reported HDL-C, and nine studies (12 trials) reported LDL-C.

2.3.2 Quality assessment

The mean PEDro score for the 24 studies was 4.96 ± 1.71. All studies were generally of moderate quality (Table 2.1). However, due to the inherent problem of blinding which accounts for three of the 10 items on the PEDro checklist (eligibility criteria item does not contribute to total score), the PEDro scores often will be lower in exercise interventions of this nature (where it is not possible to blind participants to the treatment condition).

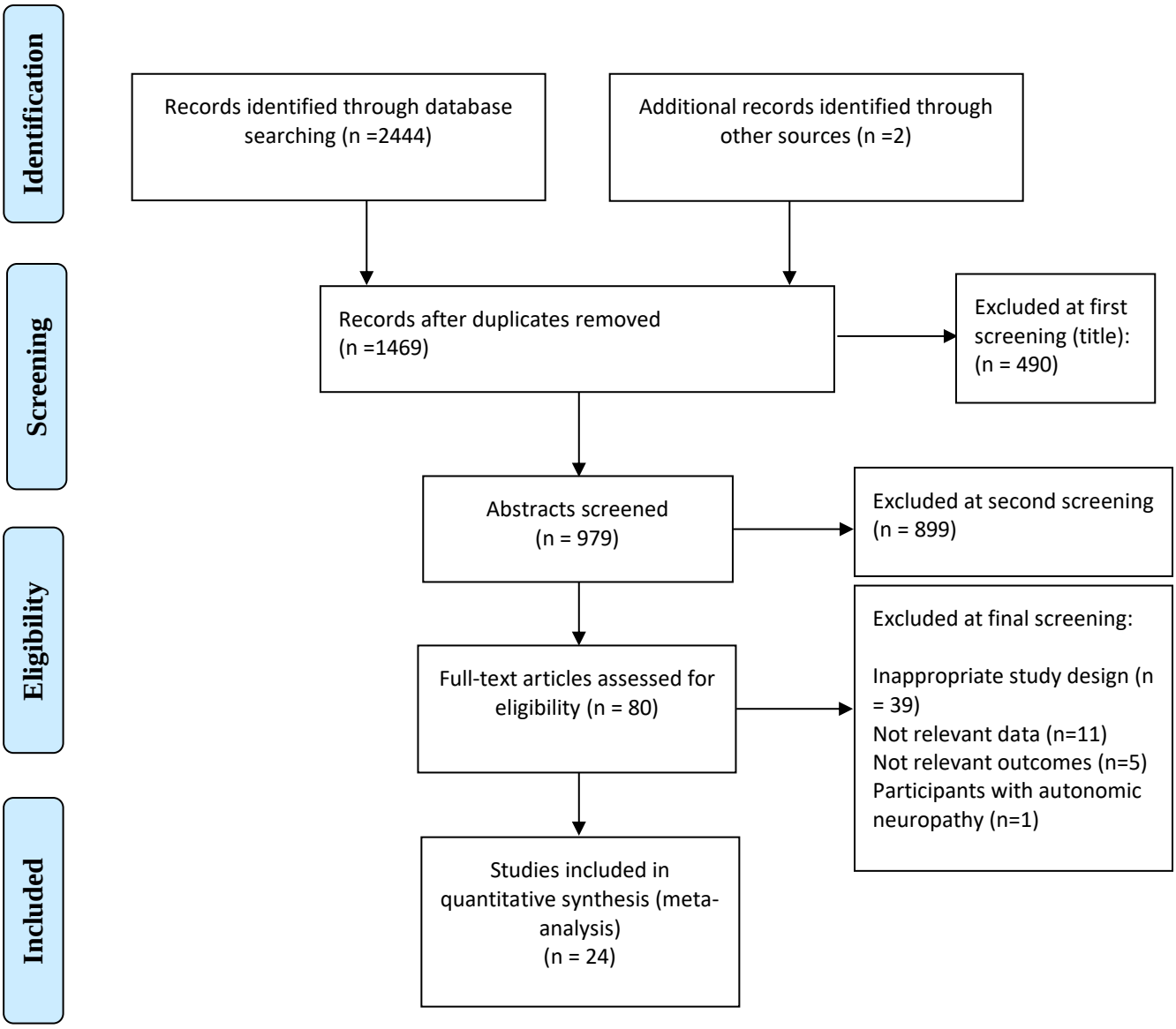

Figure 2.1 Study flow diagram in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations

Table 2.1 Characteristics of the included studies

Study, year (ref)	Participants (age, simple size, diabetes duration)			Intervention (frequency, intensity, type, session time)		Outcome measures	PEDro score
	N	Mean age ± SD/age range (years)	Duration of T1D (years)	Type of exercise (FITT)	Program duration		
Aouadi et al, 1999 [a] (108)	EG: 11 CG: 11	EG: 12.2 ± 1.5; CG: 12.9 ± 1.3	EG: 3.6 ± 0.8; CG: 3.2 ± 0.54	EG: 2x/week, 50-55% HR_{max} at weeks 1-2; 55-60% HR_{max} at weeks 3-4; 60-65% HR_{max} at weeks 5-24; 60 min; aerobic exercise CG: continue with normal PA behavior	EG: 24 weeks	BMI ↔ in all groups HDL-C↑significant in EG Triglyceride↓in EG Daily insulin dose↓in EG	6
Aouadi et al, 1999 [b] (108)	EG: 11 CG: 11	EG: 13.5 ± 0.8; CG: 12.9 ± 1.3	EG: 4.1 ± 1.3; CG: 3.2 ± 0.54	EG: 4x/week; 50-55% HR_{max} at weeks 1-2; 55-60% HR_{max} at weeks 3-4, 60-65% HR_{max} at weeks 5-24; 60 min; aerobic exercise CG: continue with normal PA behavior	EG: 24 weeks	HbA1c↓significant in EG HDL-C↑significant in EG Triglyceride↓in EG LDL-C↓in EG Daily insulin dose↓in EG	6
Brazeau et al, 2014 (109)	EG: 23 (12F;11M) CG: 25 (14F;11M)	EG: 45.1 ± 14.5; CG: 44.2 ± 12.5	EG: 20.3 ± 12.9; CG: 24.4 ± 13.6	EG: 1x/week, 60 min of various activities (endurance, resistance, flexibility); 30 min of counselling (initiate PA and introduce glycemic management) CG: given leaflet and allowed to carry out normal PA	12 weeks	Weight↓in EG BMI ↔ in both groups HbA1c ↔ in both groups VO_{2peak}↑in EG SBP ↓ in EG DBP↑in EG	7
Campaigne et al, 1984 (60)	EG: 9 CG: 10	EG: 9.0 ± 0.47 (SEM); CG: 8.5 ± 0.57 (SEM)	EG: 5.1 ± 0.95 (SEM); CG: 3.89 ± 0.70(SEM)	EG: 3x/week, HR≥160 bpm, 30 min vigorous exercise (running, movement to music etc.), supervised aerobic exercise CG: continued with normal PA behavior	12 weeks	Weight↑in both groups Fasting blood glucose levels ↔ in both groups HbA1↓significant in EG and lower than CG Daily insulin dose ↔ in both groups VO_{2peak}↑in EG,	5
Campaigne et al, 1985 (110)	EG: 9 (6F; 3M) CG: 5 (3M; 6F)	EG: 16.0 ±1 (SEM); CG: 15 ± 0.4 (SEM);	EG: 6.6 ±1.1 (SEM); CG: 6.2 ± 1.1 (SEM);	EG: 3x/week, HR >160 bpm intensity, 45 min, supervised aerobic exercise CG: continued with normal PA behavior	12 weeks	VO_{2peak}↑in EG, LDL-C↓significant in EG, HbA1 ↔ in both groups Daily insulin dosage ↔ in both groups	5

D' hooge et al, 2011 (61)	EG: 8 CG: 8	EG: 14.1 (10.1 - 16.8); CG: 13.2 (10.1 - 15.3);	EG: 5.4 (3.4 - 7.3); CG: 5.3 (2.9 - 5.9)	EG: 2x/week, aerobic training intensity 60% HRR increased to 70% HRR after 6 weeks, 75% HRR after 12 weeks; 70 min [5 min WU + 30 min strength training of upper, lower limbs, and abdominal muscles + 30 min aerobic training (10 min cycling,10 running and 10 stepping + 5 min CD)]. First 12 sessions: 2 sets of 15 reps at 20RM. Next 12 sessions: 2 sets of 12 reps at 17RM. Final 8 weeks: 3 sets of 10 reps at 12RM. 60s rest between two sets; Supervised aerobic exercise and strength training CG: normal activity	20 weeks	Daily insulin dose↓significant in EG BMI ↔ in both Muscle fatigue score, number of sit to stand, upper and lower limb strength, 6 min walking distance ↑in EG VO_{2peak} ↔ in both groups HbA1c ↔ in both groups Weight ↔ in both groups Quality of life (SF-36) ↔ in both	7
Dahl-Jorgensen et al, 1980 (111)	EG: 14 CG: 8	9-15	5	EG: 2x/week, 60 min; supervised exercise; and supplemented by a weekly home exercise experience CG: did not participate in any standardized exercise regime	20 weeks	VO_{2peak} ↔ in EG Insulin dosage ↔ HbA1c↓significant in EG	5
Durak et al, 1990 (crossover) (112)	EG: 8 CG: 8	EG: 31 ± 3.5 CG: 31 ± 3.5	EG: 12.3 ± 9.8 CG: 12.3 ± 9.8	EG: 3x/week, 6 upper-body exercises and 4 lower-body exercises (maximum 12 reps), 3-7 sets, total 40-50 sets, rest interval: 30s-2min; 60 min, heavy resistance training concentrating on the strengthening of major muscle groups CG: rest	10 weeks	HbA1c↓significant in EG Total cholesterol↓significant in EG Blood glucose levels↓significant in EG Triglyceride and LDL-C↓not significant in EG HDL-C ↔ Weight ↔ in both Strength and endurance↑in EG	2
Fuchsjager-Maryle et al 2002 (113)	EG: 18 (11F; 7M) CG: 8 (3F; 5M)	EG: 42 ± 10; CG: 33 ± 11;	EG: 20 ± 10; CG: 20 ± 10	EG: First 2 weeks: 2x/week, 60 min, stationary cycling with increasing resistance till 60-70% HR. After 2 weeks: 3x/week CG: no training intervention	16 weeks	Weight BMI Mean arterial BP VO_{2peak}↑in EG HbA1c, total cholesterol, LDL-C and HDL-C, and triglycerides ↔ in EG Daily insulin dose↓in EG	3

						Isometric muscle strength of legs and hands↑	
Gusso et al, 2017(107)	EG: 38 CG: 15	EG: 15.6 ± 1.3; CG: 15.5 ± 0.9	EG: 5.4 ± 3.4; CG: 7.5 ± 4.0	EG2: 4x/week; 3 times aerobic sessions, progressively to 85% HR_{max} at weeks 1-5; 85% HR_{max} at weeks 5-20; 40 min/session; 1x/week resistance training at weeks 1-12; 4x/week combined aerobic and resistance training at week 12-20; 60-min exercise sessions per week (including WU and CD) CG: No training intervention	20 weeks	BMI ↔ VO_{2peak}↑in EG Diastolic blood pressure (resting)↓in EG Daily insulin dosage and HbA1c in EG↔	7
Heyman et al, 2007 (114)	EG: 9 (F) CG: 7 (F)	EG: 15.9 ± 1.5; CG: 16.3 ± 1.2;	EG: 6.3 ± 4.4; CG: 8.4 ± 4.5	EG: 2x/week; 80-90% of HRR intensity (measured by monitors); one 2h supervised session and one 1h unsupervised session, combined aerobic and strength sessions in ratio of 2:1 CG: spent equal amount of time on activities that did not require physical effort	24 weeks	Daily insulin dosage ↔ in both groups PWC_{170}↑significant in EG in watts Total cholesterol, LDL-C, HDL-C, triglycerides ↔ in both groups Quality of life (DQOL) ↑ in EG	4
Huttunen et al, 1989 (115)	EG: 16 CG: 16	EG: 11.9 (8.2 - 16.9) CG: 11.9 (8.2 - 16.9)	EG: 4.7 (0.6 - 12.0); CG: 5.6 (2.0 - 13.1)	EG: 1x/week, HR >150 bpm, 60 min, aerobic exercise (jogging, running, gymnastics & various kinds of active games) CG: continue with normal PA behavior	13 weeks	VO_{2peak}↑significant in EG; HbA1c↑significant in EG	5
Laaksonen et al, 2000 (116)	EG: 20 CG: 22	EG: 32.5 ± 5.7; CG: 29.5 ± 6.3;	EG: 13.8 ± 9.2; CG: 10.8 ± 5.8	EG: 1 week, 3x/week, 50-60% VO_{2peak}, 20-30 min, gradually increased to 4-5x/week, 60-80% VO_{2peak}, 30-60 min aerobic training CG: continue with normal PA behavior	12-16 weeks	VO_{2peak} ↑ significant in EG; HbA1c, daily insulin dosage, BMI, % body fat ↔ in both groups Total cholesterol and LDL-C ↓ in EG; HDL-C ↑ in both groups; Triglycerides changes were significantly greater in EG compared with CG	4
Landt et al, 1985 (117)	EG: 9 (6F; 3M) CG: 6 (2F; 4M)	EG: 16.1 ± 0.8; CG: 15.9 ± 0.3;	EG: 6.7 ± 1.1; CG: 7.7 ± 1.5	EG: 3x/week, HR ≥ 160 bpm, 45 min (10 min WU + 25 min aerobic movement + 10 min CD) CG: continue with normal PA behavior	12 weeks	Daily insulin dose ↔ in both VO_2max↑in EG Lean body mass↑in EG Insulin-sensitivity↑in EG	4

						HbA1c↔ in both groups	
Maggio et al, 2011 (63)	EG: 15 (7F; 8M) CG: 12 (7F: 5M)	EG: 10.5 ± 2.0 CG: 10.5 ± 2.9	EG: 3.1 ± 2.7 CG: 3.4 ± 1.7	EG: 2x/week; HR ≥ 140 bpm, 90 min (10 min WU, 10 min drop jump (height of platform from 20cm for the first 3 months, to 40 cm in last 6 months. 60 min of various weight bearing activities, 10 min CD); weight bearing activities (ball games, jumping, rope skipping, and gymnastics) CG: relatively, inactive	36 weeks	BMI ↔ HbA1c ↔ Daily insulin dose ↔	8
Newton et al, 2009 (118)	EG: 38 (16F; 22M) CG: 40 (20F; 20M)	EG: 11 - 18 years CG: 11 - 18 years		EG: wore open pedometer every day and received weekly text messages CG: received usual care for 12 weeks	12 weeks	HbA1c ↔ Systolic BP ↔ Diastolic BP ↔ BMI z-score ↔ Quality of life ↔ Insulin total daily dose	7
Perry et al, 1997 [a] Crossover (119)	EG: 31 CG: 31	EG: 41.5 ± 11; CG: 41.5 ± 11	EG: 14.1 ± 11.9; CG: 14.1 ± 11.9	EG: ≥3x/week, intensity and duration were based on individual fitness level and goals (walking, cycling, running, weight training) CG: non-supervised and individualized aerobic PA	24 weeks	Weight↓significant in EG HbA1↓not significant in EG Triglycerides, total cholesterol and LDL-C ↔ in EG HDL-C↑in EG VO_2max ↑in EG BP ↔ in EG	5
Perry et al, 1997 b (119) crossover	EG: 30 CG: 30	EG: 42.8 ± 12.6; CG: 42.8 ± 12.6	EG: 16.8 ± 13; CG: 16.8 ± 13	EG: ≥ 3x/week, intensity and duration were based on individual fitness level and goals (walking, cycling, running, weight training) CG: non-supervised and individualized aerobic PA	24 weeks	HbA1↓not significant in EG BP ↔ in EG Total and LDL-C↓significant in EG Total and HDL-C ↔ in EG	5
Roberts et al, 2002 (120)	EG: 12 CG: 12	14 ± 1.2	5.0 ± 3.1	EG: 3x/week, 45 min/session, HR≥ 160 bpm, each training session included an aerobic and an anaerobic component in a ratio of 7:3. Activities included running, light training circuits, games and aerobics	12 weeks	HbA1↔ in both groups BMI ↔ in both groups Body mass ↔ in both groups	3

Rowland et al, 1985 crossover (121)	EG: 14 CG: 14	(9 - 14)	4.2 (0.5 - 9.5)	EG: 3x/week, 1h/session; 10 min stretching + 20 min alternating 5 min walking/running increased to 30 min running 60% of HRR (160 bpm) following 5 min CD, recreational swim for 15 min twice weekly	12 weeks	VO_2max↑in EG HbA1c ↔ Insulin dosage	6
Salem et al, 2010 [a] (91)	EG: 75 CG: 48	EG: 14.7 ± 2.2; CG: 15 ± 2.35	EG: 3.6 ± 1.8; CG: 4.9 ± 1.9	EG: 1x/week, 65 min/session; 1. Aerobic exercise (cycling/treadmill) Intensity: THHR 65-85% (220-age) 2. Anaerobic exercise (treadmill interval running at 85-95% HR_{max} for 1-2 min) 3. Leg extension & leg curl exercises (progressive resistive exercises, 10RM) 4. Different free strength and endurance exercises (10 min, 10 reps per set, number of sets increase gradually) 5. Flexibility exercises (5 min, stretching) 6. Neuromuscular exercises (5 min, coordination exercises, 10 reps Balance exercise regime on firm surface for 10 min, 10 reps which increased from 1 set to 3 sets after 6 sessions. Supervised exercise CG: continued with normal PA behavior	24 weeks	HbA1c↓significant in EG BMI (SDS)↓in EG Insulin dosage↓significant in EG HDL-C ↑ in EG Triglycerides, total cholesterol and LDL-C↓in EG	4
Salem et al, 2010 [b] (91)	EG: 73 CG: 48	EG: 14.5 ± 2.4; CG: 15 ± 2.35	EG: 5.5 ± 2; CG: 4.9 ± 1.9	EG: 3x/week, 65 min/session; 1. Aerobic exercise (cycling/treadmill) Intensity: 65-85% (220-age) 2. Anaerobic exercise (treadmill interval running at 85-95% HR_{max} for 1-2 min) 3. Leg extension & leg curl exercises (progressive resistive exercises, 10RM) 4. Different free strength and endurance exercises (10 min, 10 reps/set, number of sets increase gradually) 5. Flexibility exercises (5 min, stretching) 6. Neuromuscular exercises (5 min, coordination exercises, 10 reps	24 weeks	HbA1c ↓significant in EG Insulin dosage↓in EG BMI (SDS)↓in EG DBP percentile ↓in EG Insulin dosage↓in EG Triglycerides, total cholesterol and LDL-C HDL-C ↑ in EG	4

				Balance exercise regime on firm surface for 10 min, 10 reps which increased from 1 set to 3 sets after 6 sessions. Supervised exercise CG: continued with normal PA behavior			
Stratton et al, 1987 (122)	EG: 8 (4F; 4M) CG: 8	EG: 15.1 ± 1.2 CG: 15.5 ± 0.9	EG: 3.7 ± 2.1; CG: 5.5 ± 3.3	EG: 3x/week, 30-45 min of supervised highly aerobic activities (treadmill jogging, cycle ergometer) on 2/3 days; On 1/3 days, participants were allowed to choose activities such as basketball, swimming, or resistance exercise machines (mostly aerobic); diet advice given once a week CG: encouraged to exercise unsupervised and given an outline exercise program	8 weeks	Daily insulin dose↓in EG Bruce treadmill time, submaximal exercise heart rates ↑ in EG HbA1c, total cholesterol, Triglycerides, HDL-C ↔ in both groups	6
Tunar et al, 2012 (123)	EG: 17 (11F; 6M) CG: 14 (5F; 9M)	EG: 14.2 ± 2.2; CG: 14.3 ± 1.8;	EG: 5.3 ± 4.1; CG: 6 ± 4.2	EG: mat-based pilates 3x/week, 45 min/session CG: continue with normal PA behavior	12 weeks	BMI ↔ HbA1c ↔ in both groups Daily insulin dose ↔ HDL-C↑in CG LDL-C ↔ Total cholesterol ↔ Triglycerides ↔ Peak power, mean power, flexibility and vertical jump ↑	5
Wallberg-Henriksson et al, 1986 (124)	EG: 6 (F) CG: 7 (F)	EG: 36 ± 2 (SEM); CG: 35 ± 2 (SEM);	EG: 14 ± 4 (SEM); CG: 13 ± 2 (SEM);	EG: 7x/week, 20 min bicycle training (5 min low intensity WU, 15 min high intensity cycling at 60-70% VO_2max for first month, 70-80% VO_2max for 2nd and 3rd month, 75-90% VO_2max for last 2 months) CG: same as EG without exercise program	20 weeks	VO_2max↑significant in EG HbA1c ↔ in both groups Total cholesterol↓in both groups LDL-C, Total triglycerides, blood glucose, HDL-C ↔ in both groups	4
Wong et al, 2011 (125)	Home-based EG: 12 Self-directed EG: 5 CG:11	Home-based EG: 11.62 ± 2.12; Self-directed EG: 13.44 ± 2.23 CG: 12.77 ± 1.79	Home-based EG: 4.42 ± 2.58; Self-directed EG: 3.42 ± 3.48; CG: 3.82 ± 2.87	Home-based EG: 3x/week, aerobic home-based exercise delivered via VCR and/or phone from a researcher; aid compliance and a handbook to provide guidance and log exercise, session duration increased from 10-20 min at week 1 to 20-30 min at weeks 3-12 Intensity: 10-30% HRR during WU and CD and 40-60% HRR during aerobic exercises	12 weeks	HbA1c levels ↔ in home-based EG, self-directed EG and CG; Home-based EG had higher HbA1c levels than self-directed EG and CG had higher HbA1c levels than self-directed EG	6

				Self-directed EG: self-directed exercise CG: not applicable		at 9-month follow-up VO_2max ↔ in all groups	
Yki-Jarvinen et al, 1984 (126)	EG: 7 (1F; 6M) CG: 6 (2F; 4M)	EG: 26 ± 1; CG: 24 ± 1;	EG: 7 ± 1; CG: 9 ± 1	EG: 4x/week, 60 min, 150-160 bpm Treated with CSII therapy for 6 weeks first; training program using cycle ergometer for 1h (4x15 min with 5 min rest intervals); intensity at 150-160 bpm CG: CSII therapy: 6 weeks Sedentary activity: 6 weeks	6 weeks	VO_2max↑significant in EG HbA1c ↔ Daily insulin dosage↓significant in EG Triglycerides, total cholesterol HDL-C and LDL-C ↔	1

FITT, frequency, intensity, type of exercise, time duration per session; PA, physical activity;↑, increase; ↓, decrease; ↔, no changes; d, day; s, seconds; h, hour; WU, warm up; CD, cool down; HR, heart rate; THRR, Target Heart Rate Range; HR_{max}, maximal heart rate; HRR, heart rate reserve; bpm, beats per min; min, minutes; RE, resistance exercise; RM, repetition maximum;; T1D, type 1 diabetes; VO_2max & VO_2peak, maximum peak oxygen uptake; PEP, physical exercise promotion program in type 1 diabetes; CSII, continuous subcutaneous insulin infusion; F, female; M, Male; EG, exercise group; CG, control group; BMI, body mass index; SDS, Standard Deviation Score; DQOL, diabetes quality-of-life; HDL-C, high-density lipoproteins cholesterol; LDL-C, low density lipoproteins cholesterol; HbA1c, glycated hemoglobin; SBP, systolic blood pressure; DBP, diastolic blood pressure SF-36, The Short Form (36) Health Survey; [a, b] these data in one study included more than one condition.

2.3.3 Participants and exercise intervention

Sample sizes ranged from 13 to 196, with a total of 928 participants who had been diagnosed with T1D. The duration of T1D was reported in all studies ranging from 3.1 ± 1.7 to 24.4 ± 3.6 years (Table 2.1); 546 from exercise groups and 382 from control groups. Seven of the studies included adults, whereas 17 of the studies included children and adolescents.

The frequency of the exercise interventions varied between 1 and 7 times per week, with 16 of 24 studies prescribing exercise at least three times per week. Exercise intensity was reported in terms of percentage of VO_2max or VO_2peak, maximum heart rate (HR_{max}), or heart rate reserve (HRR). The intensity of aerobic exercise ranged between 50% and 90% VO_2max or VO_2peak, 50% and 95% HR_{max}, and 40% and 60% HRR. Resistance training was generally performed based on one repetition maximum values, 10 repetition maximum values, and/or as a percentage of maximal heart rate max (e.g., 85-95% HR_{max}). The range of resistance training exercise intensity was between 50% and 80% one Repetition maximum (RM) among the studies. Length of exercise sessions ranged between 20 and 120 min, and duration of exercise intervention ranged between six and 36 weeks. Exercise training included weight-bearing, weight training, jumping, and sprinting.

2.3.4 Synthesis of results and statistical analysis (meta-analysis)

2.3.4.1 Aerobic fitness

Aerobic fitness was measured in relative (to body mass) and absolute terms. Eleven studies were pooled in a meta-analysis yielding a significant effect of exercise training on relative VO_2max (effect size, ES 3.01 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI 0.94 to 6.38; $p = 0.004$) (60; 107; 109; 110; 113; 115; 117; 121; 124; 126; 127). However, significant heterogeneity among these studies was detected (I^2 = 80%, Q = 50.68, $T^2 = 7.76$, $df = 10$, $p < 0.01$).

Subgroup analyses of moderator variables (age, frequency, type of exercise, and program duration) were used to explore the sources of heterogeneity (Table 2.2). It was found that studies which focused on intervention with a higher frequency (≥ 3 times/week) had an overall treatment effect (ES 4.25 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI 3.37 to 5.52; $p < 0.001$) on VO_2max while intervention with a lower frequency (<3 times/week), which included two studies, had limited effect (Table 2.2); interventions with longer duration (> 12 weeks) had an overall treatment effect (ES 5.05 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI 3.81 to 6.29; $p < 0.001$, Table 2.2) while interventions with a shorter duration (< 12 weeks) had limited effect (Table 2.2); interventions involving aerobic exercise only had an overall treatment effect (ES 4.25 $mL \cdot kg^{-1} \cdot min^{-1}$, 95% CI 3.16 to 5.34; $p < 0.001$, Table 2.2) while interventions involving the combination of aerobic exercise and resistance training, which included two studies, had limited effect (Table 2.2). Sensitivity analysis showed minor shifts only, and these shifts did not impact the overall significance of the mean effect.

2.3.4.2 Glycemic control

The HbA1c was measured in all included studies (60; 61; 91; 107-115; 117; 119; 121-128). Twenty-one studies (24 trials) were appropriate for meta-analysis (60; 61; 91; 107-115; 117; 119; 121-123; 125-128). Statistically significant differences in the reduction of this parameter were found in five studies favoring the exercise intervention (60; 91; 108; 111; 112). In T1D individuals, there was a statistically significant decrease in mean HbA1c in exercise trials compared to control trials (ES −0.45%, 95% CI −0.73% to −0.17%; $p = 0.001$) (Table 2.2). Heterogeneity was found to be high between these studies ($I^2 = 76\%$; $Q = 97.69$, $T^2 = 0.24$, and $df = 23$).

Subgroup analyses of moderator variables (age, frequency, type of exercise, and program duration) were used to explore the sources of heterogeneity (Table 2.2). There was a statistically significant reduction in HbA1c of 0.60% (95% CI − 1.07% to − 0.14%) in children and adolescents

despite the fact that heterogeneity remained significant (I^2 = 74%; Q = 61.03, T^2 = 0.58, and df = 16), but no effect was seen in the adult studies. It was found that studies focused on interventions with a higher frequency (≥ 3 times/week) had an overall treatment effect (ES − 0.53%, 95% CI −0.88% to − 0.17%; p = 0.004) on HbA1c while interventions with a lower frequency (＜3 times/week) had lesser effect (Table 2.2); interventions with longer duration (> 12 weeks) had an overall treatment effect (ES −0.56%, 95% CI −0.95% to −0.17%; p = 0.005, Table 2.2) while interventions with shorter duration (≤ 12 weeks) had no effect (p = 0.38, Table 2.2); interventions involving aerobic exercise only had no treatment effect (p = 0.09, Table 2.2) while interventions involving the combination of aerobic exercise and resistance training had an overall treatment effect (ES −0.56%, 95% CI −1.05% to −0.08% p = 0.02, Table 2.2). Sensitivity analysis showed minimal shifts only, which did not influence the overall significance of the mean effect.

2.3.4.3 Daily insulin dosage

The weighted mean treatment effect of the six trials which measured daily insulin dosage was −0.88 $U \cdot kg^{-1}$ (95 % CI −1.27 to −0.48; p < 0.001; Table 2.2) indicating a decrease in daily insulin requirements in diabetic individuals who participated in an exercise training program (91; 111; 113; 123; 127). Heterogeneity was found to be high between these studies (I^2 = 98%; Q = 276.52, T^2 = 0.22, and df = 5).

There was a statistically significant reduction in daily insulin requirements of 1.69 $U \cdot kg^{-1} \cdot day^{-1}$ (95 % CI −2.43 to −0.95; p < 0.001; Table 2.2) in children and adolescents despite the fact that heterogeneity remained significant (I^2 = 99%; Q = 256.38, T^2 = 0.52 and df = 3), no effect was seen in adult studies with only two included studies. Sensitivity analysis showed minor shifts only, and these shifts did not affect the overall significance of the mean effect.

2.3.4.4 Lipid profiles

Serum lipids were measured in 12 studies (91; 108; 110; 112-114; 119; 122-124; 126; 127). Among these studies, total cholesterol, triglycerides, HDL-C, and LDL-C levels were measured. Fifteen trials reporting total cholesterol, triglycerides, and HDL-C, and thirteen trials reporting LDL-C were pooled for meta-analysis. The pooled effect of the exercise training intervention was a statistically significant reduction in total cholesterol of 0.38 mmol·L^{-1} (95% CI −0.71 to −0.04; p = 0.03; Table 2.2). Heterogeneity was found to be high between these studies (I^2= 89%; Q = 125.08, T^2 = 0.33, and df = 14).

Subgroup analyses of moderator variables (age, frequency, type of exercise, and program duration) were used to explore the sources of heterogeneity (Table 2.2). A greater total cholesterol reduction was seen in the seven trials of children and young adults (91; 108; 110; 114; 123), which was considered significant (ES −0.84, 95% CI −1.22 to −0.46; p＜0.01). In the eight trials of adult studies, no statistically significant effect was seen (ES −0.02, 95% CI −0.25 to 0.21; p = 0.86) (112; 113; 119; 124; 126; 127).

There were no other moderator variables found influencing the variability among studies examining total cholesterol. Sensitivity analysis revealed that a study by Salem et al. (91) in the subgroup “children and young adults” influenced the results. The removal of this study changed the “children and young adults” subgroup ES to −0.45 (95 % CI −0.70 to 0.19, p＜0.01) and overall ES to −0.15 (95 % CI −0.36 to 0 .05, p = 0.14) removing its significance.

The meta-analysis of the random-effects model revealed a small mean effect for exercise to decrease triglycerides values (ES −0.09, 95% CI −0.19 to 0.01, n=15), although this is only trended towards a significant difference (p = 0.08). There was high heterogeneity among these studies (I^2 = 83 %; Q = 82.66, df = 14, p＜ 0.01). Sensitivity analysis showed that removing a

study with the largest positive ES by Campaigne et al. (110), influenced the results. The removal of this trial changed the ES to −0.11 (95 % CI −0.21 to −0.01) and would also create a significant difference (p = 0.03).

Significant effect of exercise on HDL-C (ES −0.03, 95% CI −0.20 to 0.14; n=14; p = 0.74) or LDL-C (ES −0.03, 95% CI −0.14 to 0.09; n=12; p = 0.63) was not found. Sensitivity analysis showed minimal shifts only, which did not influence the overall significance of the mean effect.

2.3.4.5 Body mass index, blood pressure and quality of life

Exercise was not found to have a significant effect on body mass index (ES −1.00; CI −2.19 to 0.18; p = 0.10). Heterogeneity was found to be high between these studies (I^2 = 88%; Q = 74.60, T^2 = 3.03, and df = 9). Sensitivity analysis showed that a study by Roberts et al. (120) influenced the results. The removal of this trial changed the ES to −1.31 (CI −2.54 to −0.09) and also would create a significant difference (p = 0.04).

Out of five controlled intervention studies (91; 107; 109; 118; 119), three studies detected improvements with respect to systolic or diastolic blood pressure (91; 107; 109), while two studies did not (118; 119). No significant relationships were found between exercise and changes in systolic blood pressure (ES 6.10, 95% CI −0.58 to 12.78), or diastolic blood pressure (ES 0.54, 95% CI −1.29 to 2.36; p = 0.57). No significant heterogeneity among diastolic blood pressure studies was detected (I^2 = 43%; Q = 8.71, df = 5, p = 0.12). Sensitivity analysis showed minimal shifts, which did not influence the overall significance of the mean effect.

Quality of life was measured in three studies using three different survey measures (i.e., the SF-36, Diabetes-specific Quality-of-life (DSQOLS), and the EQ-5D)) (61; 114; 118). One study reported a positive effect on quality of life in the exercise group. There was insufficient data for pooling meta-analysis.

2.3.4.6 Adverse events

The frequency of hypoglycemia was reported in seven studies (61; 91; 109; 117; 121; 124; 126). One study reported frequent hypoglycemia episodes during and after exercise in the exercise group (61). One study reported an increase in hypoglycemic symptoms during the first two weeks of the exercise program, but the frequency of hypoglycemic attacks declined thereafter (126). Collectively, the incidence of adverse-exercise related events was low.

Table 2.2 Subgroup analyses of moderator variables of maximal aerobic power, HbA1c, daily insulin requirements, and total cholesterol

Outcome	Moderator variable	Subgroups	No. of trials	No. of participants	Pooled meta-analysis			Heterogeneity			Subgroup differences		
					Mean difference	95% (confidence interval)	*p* (overall effect)	I^2 (%)	Chi^2	*p*	I^2	Chi^2	*p*
Maximal Aerobic Power ($mL \cdot kg^{-1} \cdot min^{-1}$)		Total	11	303	3.01	(0.94 to 5.07)	＜0.01	80	50.68	＜0.01			
	Age groups	Children and adolescents	6	161	2.98	(0.96 to 5.00)	＜0.01	0	2.54	0.77	0.0	0.02	0.89
		Adults	5	142	3.24	(0.10 to 6.38)	0.04	91	46.08	＜0.01			
	Exercise frequency	≥ 3 times/week	9	223	4.45	(3.37 to 5.52)	＜0.01	0	6.48	0.59	97.7	44.01	＜0.01
		＜3 times/week	2	80	−0.17	(−1.01 to 0.67)	0.69	0	0.19	0.69			
	Type of exercise	Aerobic exercise	9	202	4.25	(3.16 to 5.34)	< 0.01	0	7.36	0.50	0.0	0.43	0.51
		Combined aerobic and resistance training	2	101	2.32	(−3.36 to 8.00)	0.42	85	6.68	0.01			
	Program duration	＞ 12 weeks	4	134	5.05	(3.81 to 6.29)	< 0.01	0	2.22	0.53	96.7	30.44	< 0.01
		≤ 12 weeks	7	169	0.48	(−0.37 to 1.53)	0.37	5	6.34	0.39			
HbA1c (%)		Total	24	862	−0.45	(−0.73 to −0.17)	＜0.01	76	97.69	＜0.01			
	Age groups	Children and adolescents	17	595	−0.60	(−1.07 to −0.14)	0.01	74	61.03	＜0.01	72.4	3.62	0.06
		Adults	7	267	−0.10	(−0.33 to 0.13)	0.40	54	13.06	0.04			
	Exercise frequency	≥ 3 times/week	16	561	−0.53	(−0.88 to −0.17)	＜0.01	69	47.64	＜0.01	0	0.27	0.60
		＜3 times/week	8	301	−0.34	(−0.93 to 0.24)	0.25	85	46.91	＜0.01			
	Type of exercise	Aerobic exercise	14	316	−0.39	(−0.84 to 0.06)	0.09	74	50.36	＜0.01	0	2.29	0.51

		Combined aerobic and resistance training	8	499	−0.56	(−1.05 to −0.08)	0.02	84	43.66	＜0.01			
		Resistance training	1	16	−1.10	(−2.25 to 0.05)	0.06	−	−	−			
		Pilates	1	31	−0.10	(−1.08 to 1.28)	0.87	−	−	−			
	Program duration	＞ 12 weeks	14	620	−0.56	(−0.95 to −0.17)	＜0.01	83	76.76	＜0.01	40	1.67	0.20
		≤ 12 weeks	10	242	−0.19	(−0.59 to 0.22)	0.38	27	12.35	0.19			
Daily Insulin Dosage（$U \cdot kg^{-1} \cdot day^{-1}$）		Total	6	355	−0.88	(−1.27 to −0.48)	＜0.01	98	276.52	＜0.01			
	Age groups	Children and adolescents	4	297	−1.69	(−2.43 to −0.95)	＜0.01	99	256.38	＜0.01	94.4	17.81	＜0.01
		Adults	2	58	−0.09	(−0.19 to 0.02)	0.11	56	2.25	0.13			
	Exercise frequency	≥ 3 times/week	4	210	−1.54	(−2.21 to −0.88)	＜0.01	99	270.57	＜0.01	93.1	14.44	＜0.01
		＜3 times/weeks	2	145	−0.19	(−0.40 to 0.01)	0.07	83	5.71	0.02			
	Type of exercise	Aerobic exercise	3	80	−0.09	(−0.15 to −0.03)	＜0.01	12	2.26	0.32	99.2	253.33	＜0.01
		Combined aerobic and resistance training	2	244	−0.40	(−0.60 to −0.20)	＜0.01	76	4.22	0.04			
		Pilates,	1	31	−7.7	(−8.65 to −6.75)	＜0.01	−	−	−			
	Program duration	＞ 12 weeks	5	324	−0.20	(−0.35 to −0.06)	＜0.01	89	34.82	＜0.01	99.6	234.66	＜0.01
		≤ 12 weeks	1	31	−7.70	(−8.65 to −6.75)	＜0.01	−	−	−			
Total Cholesterol（$mmol \cdot L^{-1}$）		Total	15	588	−0.38	(−0.71 to −0.04)	0.03	89	125.08	＜0.01			
	Age groups	Children and adolescents	7	343	−0.84	(−1.22 to −0.46)	＜0.01	75	24.32	＜0.01	92.4	13.08	＜0.01

	Adults	8	245	−0. 02	(−0.25	to	0.86	57	16.31	0.02			
					0.21)								
Exercise frequency	≥ 3 times/week	13	451	−0.25	(−0.54	to	0.08	80	59.51	＜0.01	71.1	3.46	0.06
					0.03)								
	＜3 times/week	2	137	−0. 96	(−1.65	to	＜0.01	81	5.21	0.02			
					−0.27)								
Type of exercise	Aerobic exercise	9	190	−0.10	(−0.37	to	0.43	66	23.75	＜0.01	62.5	5.34	0.07
					0.16)								
	Combined aerobic and resistance training	5	382	−0.71	(−1.15	to	＜0.01	84	24.67	＜0.01			
					−0.27)								
	Resistance training	1	16	−0.30	(−1.28	to	0.55	−	−	−			
					0.68)								
Program duration	＞ 12 weeks	10	498	−0.40	(−0.76	to	0.03	90	89.96	＜0.01	0.0	0.07	0.78
					−0.04)								
	≤ 12 weeks	5	90	−0.29	(−0.95	to	0.38	58	9.49	0.05			
					0.37)								

2.4 Discussion

This systematic review and meta-analysis included 24 studies examining the effects of exercise training on cardiovascular disease risk factors in persons living with T1D, indicating evidence for clinically important health benefits of exercise training compared to no exercise intervention on various cardiovascular risk factors. More specifically, the results of our meta-analysis indicate significant effects of exercise training on enhancing aerobic fitness (VO_2max) while decreasing HbA1c, daily insulin dosage, and total cholesterol. However, no significant difference was found with respect to body mass index, blood pressure, triglycerides, HDL-C, or LDL-C. Collectively, these findings reinforce the importance of routine exercise participation in T1D management to delay and/or reduce the risk of cardiovascular disease.

2.4.1 Aerobic fitness

Aerobic fitness is related inversely to cardiovascular disease risk and all-cause mortality in T1D (129). The gold standard assessment of aerobic fitness is VO_2max. Eleven studies measured VO_2max or VO_2peak revealing a significant increase of 3.01 $mL \cdot kg^{-1} \cdot min^{-1}$ in individuals living with T1D who followed a structured exercise training program. It is noted that changes in VO_2max or VO_2peak (expressed in relative terms) may be affected by the changes of body weight; however, in this systematic review exercise training improved aerobic fitness in T1D without significant changes in BMI. This finding further supports the potential for exercise training to improve cardiovascular health and risk profile independent of changes in body composition (98; 101; 102). In clinical terms, several authors have recently demonstrated the importance of similar changes in aerobic fitness for reducing the risk for premature mortality (130; 131). For instance, Martin and colleagues revealed that each metabolic equivalent (MET) (approximately 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) increase in aerobic fitness was associated with 25% reduction in all-cause mortality in cardiac

rehabilitation cohort (130). Similarly, Kokkinos and colleagues revealed that there was a 12% lower risk for premature mortality for each 1-MET increase in exercise capacity in older men (131).

Our sub-analyses showed that greater aerobic fitness improvements were generally attained from interventions that involved aerobic exercise with a higher frequency per week, and/or a longer duration. However, there was some evidence of cardiovascular beneficial changes with rather small volumes of exercise (132). Previous research demonstrated that a one-size fits all approach to exercise prescription is not ideal for persons living with T1D (98). Further research is required to establish the minimal and optimal levels of exercise training for changes in aerobic fitness. Moreover, additional research is required to determine the effects of exercise training on other determinants of health-related physical fitness (such as musculoskeletal fitness).

2.4.2 Glycemic control

Glycemic control is strongly associated with cardiovascular disease and is fundamental to diabetes management. For each percentage point increase in mean HbA1c, the risk of cardiovascular disease increases by 31% in individuals living with T1D (10). In our current systematic review, the majority of included individual studies on exercise training demonstrated no significant results on glycemic control. This is possibly due to insufficient power to detect a difference in a small sample of participants in each individual study. However, when viewed in totality, our meta-analysis of the grouped studies shows significant effects of exercise on reduction of HbA1c reinforcing the importance of exercise in the clinical diabetic management to improve glycemic control in children and youth living with T1D. Improving glycemic control may be important to decreasing cardiovascular disease and correlates with reduced cardiovascular disease related mortality in epidemiologic and longitudinal studies (10).

Our sub-analyses showed that training less than three times a week or less than 12-weeks in duration may not be enough to improve HbA1c in T1D. It also showed that exercise training has

greater beneficial effects when it involved a combination of aerobic exercise and resistance training. Salem et al. and Aouadi et al. found that increased frequency and a longer period of exercise training resulted in greater reductions of HbA1c (91; 108). Therefore, for optimal reductions in HbA1c it is recommended that combined aerobic and resistance training should be performed at least 3 times/week with at least 12 weeks in duration. Interpretation of these finding should be considered with caution as some unclear risks of bias and significant heterogeneity were present in most of the included studies, with the additional unknown confounding effect of baseline HbA1c levels, diet, hypo/hyperglycemic episodes, and insulin dose in treatment practices.

2.4.3 Daily insulin requirements

Insulin resistance appears predominant in the pathophysiology of cardiovascular disease in type 2 diabetes (133) and has recently emerged as a consistent finding among contemporary youth and adults with T1D (134). Insulin resistance is a strong risk factor for cardiovascular disease in T1D (134). Insulin dose adjustment in T1D is preferentially based on blood glucose monitoring in order to avoid hypoglycemia associated with exercise (100). The results of this meta-analysis demonstrate that a decrease of up to 0.88 $U \cdot kg^{-1} \cdot day^{-1}$ in insulin requirements in T1D was induced by exercise. It is possible that these reductions masked the glycemic improvement as measured by HbA1c (91). In T1D, there is an increased risk of hypoglycemia following exercise. Reducing the insulin requirements and increasing carbohydrate intake before exercise are suitable approaches to prevent exercise-induced hyperglycemia (100).

2.4.4 Lipid profiles

Previous studies have shown that approximately 15% of children with T1D have high LDL-C and triglycerides, in particular LDL-C, which is a well-established risk factor for cardiovascular disease (135). Results show that exercise decreases total cholesterol levels by 0.38 $mmol \cdot L^{-1}$ in T1D individuals. Decreases in total cholesterol levels are associated with decreased risk of heart

disease (136). However, we did not find statistical support for the existence of a relationship between exercise and reduced triglycerides, HDL-C and LDL-C, among individuals with T1D. Higher exercise frequency and longer duration of exercise engagement were found to be significantly associated with total cholesterol reduction. Our findings were consistent with previous reports by Salem et al. who found that frequent exercise was associated with a statistically significant decrease in the levels of total cholesterol in T1D (91). Moreover, Aouadi et al. found that increasing frequency and duration of exercise intervention was associated with lower triglycerides, LDL-C, and HDL-C improvement in T1D (108). Therefore, it is important for persons living with T1D to engage in regular exercise.

2.4.5 Body mass index, blood pressure and quality of life

Overweight and obesity are very common in children with T1D and major influences on the development of cardiovascular disease (137). No significant relationships were found in this meta-analysis between exercise training and changes in BMI. Most of the participants were lean individuals (BMI < 25 $kg \cdot m^{-2}$), and only three of the studies evaluated overweight and obese individuals (BMI > 25 $kg \cdot m^{-2}$) (109; 113; 114). It can be speculated that those individuals with higher BMI at study entry may experience a greater improvement in BMI with exercise training than leaner individuals. Further research in this field is warranted.

Hypertension is a well-established risk factor for cardiovascular disease and more prevalent in people with T1D than in the general population (138). Treatment of high blood pressure is one of the most important strategies to prevent cardiovascular disease in T1D individuals. The meta-analysis was unable to identify if exercise training contributes to a significant change in blood pressure. However, a meta-analysis of 54 randomized trials evaluated 2419 participants (aged > 18 years) and found that aerobic exercise reduces blood pressure in both hypertensive and

normotensive persons without diabetes (139). Moreover, in a randomized controlled trial of effects of exercise intensity on blood pressure in type 2 diabetic individuals, it was found that higher intensity exercise may elicit greater reductions in blood pressure than lower intensity (140). Therefore, it is likely that exercise interventions prescribing higher quantity of exercise need to be carried out to positively affect blood pressure in persons living with T1D. Further research is required to fully elucidate the effects of exercise training on blood pressure in persons living with T1D.

Previous research highlights the importance of quality of life in T1D as this outcome can often be poorer than peers without diabetes (141). The effects of exercise training on quality of life were well documented in type 2 diabetes (142), but the body of evidence for T1D is very limited. A systematic review has shown that aerobic exercise training was a safe and effective way to improve the quality of life in persons living with type 2 diabetes and participants can feel more enjoyable, motivated, and confident from professionally supervised, group-based exercise training (142). However, this has not been directly investigated in persons living with T1D. Previously, D'hooge et al. reported that exercise improves quality of life in persons living with T1D and this improvement is greatest in those with lower quality of life at baseline (61).

2.4.6 Adverse events

Recent work has reinforced the importance of exercise training for persons living with chronic medical conditions (including T1D) with the benefits of exercise consistently outweighing the risks (87; 98; 101; 102). However, in comparison to other medical conditions, leading experts have outlined the importance of carefully monitoring exercise-related risks (in particular hypoglycemia) (87). Hypoglycemia is associated with an increased risk of cardiovascular events and all-cause mortality in insulin-treated individuals with diabetes (143; 144). A retrospective analysis of a large cohort of individuals with T1D on continuous subcutaneous insulin infusion

(CSII) pointed to a higher prevalence of cardiovascular disease in those with repeated severe hypoglycemia (145). Individuals with T1D and their parents often avoid engaging in exercise training due to a fear of hypoglycemia (39). However, it should be noted that our systematic review revealed a relatively low incidence of exercise-related adverse events. The vast majority of individuals with T1D tolerated the training well and the frequency and intensity of hypoglycemic episodes reactions did not change during the exercise training program in most included studies (61; 91; 109; 117; 121; 124; 126). D'hooge et al. reported that frequent hypoglycemia episodes during and after exercise (61). Yki-Jarvinen et al. showed that the minimal increase hypoglycemia could easily have been avoided through insulin adjustment (126). Exercise-induced hypoglycemia may be a result of blunted glucagon response, reduced adrenomedullary response, and diminished clearance of injected insulin (100). In addition, some people with T1D with poor glycemic control may have low hepatic glycogen content, which may also contribute to exercise-induced hypoglycemia (146). Collectively, this research supported the belief that the benefits of exercise training far outweigh the risks in persons living with T1D (87).

2.4.7 Management options

It is important to acknowledge the recent advancements in T1D treatment strategies that may affect the findings of this systematic review. Twelve of 24 studies were published before 2000, and the remaining studies were published after 2000. Most of the studies focused on the effects of long-term exercise intervention in T1D offering limited information about the treatment therapy. Multiple daily injection therapy and CSII (e.g., insulin pumps) are effective management approaches that have been increasingly used by persons living with T1D to help maintain more normal glucose levels. Continuous subcutaneous insulin infusion has evolved significantly since its introduction in the 1970s and offers the capacity to modify basal infusion rate and to obtain an

effect in 1-2 h (87). Continuous subcutaneous insulin infusion has been in particular associated with improvements in glycemic control (147).

Blood glucose level fluctuations are challenging to manage before, during, and after exercise in T1D. Thus, glycemic management is based on frequent glucose monitoring, insulin dose adjustments, and carbohydrate intake modification before, during, and after exercise (6). From the current findings, it is not completely clear what form of glucose assessment (e.g., self-monitored vs. continuous glucose monitoring), insulin dosage modification, or carbohydrate adjustments were used for glycemic management of exercise. As such, the potential confounding effects of these treatment strategies should not be overlooked. Accordingly, further research is warranted to determine whether the incidence of adverse exercise-related events varies in individuals living with T1D according to the treatment strategy employed.

2.4.8 Hyperglycemia, dyslipidemia, and obesity

Hyperglycemia is associated with adverse cardiovascular outcomes such as vascular smooth muscle dysfunction in T1D women, increased carotid intimal medial thickness, and impaired diastolic velocities in T1D youth (8). The DCCT/EDIC study demonstrated that achieving an HbA1c of < 7% reduced the incidence of microvascular complications of T1D compared intensive versus standard glycemic control during a 6.5-year period. After an average follow-up of 17 years, the intensive glycemic-control therapy was associated with a 57% reduction in major cardiovascular disease outcomes even with deterioration in glucose control (10). The ADA recommends that individuals with diabetes should be to have HbA1c values less than 7% to lower the risk of developing diabetes-related complications (13).

Dyslipidemia is a risk factor for cardiovascular disease in people with diabetes. Lipid levels in T1D are associated with cardiac and vascular abnormalities, suggesting direct effects of lipids on cardiovascular function including abnormal plethysmography responses, endothelial

dysfunction, carotid intimal medial thickness, and aortic intimal medial thicken all correlated independently with LDL-C in T1D youth (8). The ADA recommends that target LDL-C levels for adults with diabetes are <100 $mg \cdot dL^{-1}$ (2.60 $mmol \cdot L^{-1}$); HDL-C levels are >40 $mg \cdot dL^{-1}$ (1.02 $mmol \cdot L^{-1}$); and triglyceride levels are <150 $mg \cdot dL^{-1}$ (1.7 $mmol \cdot L^{-1}$) (15). Regular physical activity, severe dietary fat restriction (<10% of calories), and pharmacological therapy is recommended to reduce the risk of dyslipidemia, pancreatitis and cardiovascular diseases (15).

Obesity is an important risk factor for cardiovascular diseases. Studies showed that T1D who received supra-physiological insulin doses had increased weight gain and higher total cholesterol and LDL-C, central obesity, insulin resistance, blood pressure, more coronary artery calcifications, and higher carotid intima-media thickness on follow-up, underlying the role of obesity in promoting cardiovascular disease in individuals with T1D (8). A study of nearly 300,000 adults of white European descent challenges the 'obesity paradox' shows that risk of cardiovascular disease, such as heart attacks, strokes and high blood pressure, increases as BMI increases beyond a BMI of 22-23 $kg \cdot m^{-2}$ (148).

2.4.9 Comparison with existing literature

The results of this meta-analysis are broadly similar to those of previous reviews. In MacMillan et al.'s meta-analysis of trials of unsupervised exercise and alternative forms of exercise (i.e. Pilates) vs sedentary behavior intervention in youth with T1D, effect sizes for HbA1c (ES -0.85%, 95% CI −1.45% to −0.25%) more strongly favored exercise (19). Quirk et al.'s meta-analysis, which included both controlled and uncontrolled (pre and post) trials of physical activity interventions in children and young people with T1D until 2014, reported standardized mean difference of exercise training on HbA1c (ES −0.52, 95% CI −0.97% to −0.07%), BMI (ES −0.41, 95% CI −0.70 to −0.12), triglycerides (ES −0.70 , 95% CI −1.25 to −0.14), and total cholesterol (ES −0.91, 95% CI −1.66 to −0.17) (149). This meta-analysis analyzed participants of all ages as

well as four additional outcome variables not included in previous meta-analyses: systolic blood pressure, diastolic blood pressure, HDL-C, and LDL-C, as well as identified trials with control groups. Tonoli et al's meta-analysis reported a significant but small HbA1c lowering effect of exercise in T1D (ES −0.27%, 95% CI −0.06 to −0.47), and subgroup analyses found that trials restricted to T1D with poorly controlled HbA1c youth had greater overall treatment effect (ES −0.66%, 95% CI −0.99 to 0.34) (150). These results suggest that exercise training could decease the HbA1c level and participants with poor glycemic control before intervention may experience a greater reduction in HbA1c with exercise training.

However, Kennedy et al.'s meta-analysis with a focus on glycemic control included randomized and non-RCTs found no changes with exercise training (151). Ostman et al's meta-analysis only included RCT found exercise training improves body mass, BMI, VO2max and LDL in adults and insulin dose, waist circumference, LDL and triglycerides in children with T1D (152). However, this meta-analysis used different inclusion criteria, it included only RCTs. Our meta-analysis included studies of quasi-experimental trials, and crossover trials that were excluded in Ostman et al's meta-analysis (107; 108; 110; 112; 118; 121; 122; 125; 126). We believe these differences accounts for the partially inconsistent conclusion. Ostman et al (152) did however agree that studies of exercise training showed improvement in cardiovascular risk factors in T1D.

2.5 Strengths and Limitations

It was a goal to minimize selection bias through a comprehensive literature search and perform a comprehensive systematic literature review. A large number of RCTs relevant to our meta-analysis were included. Subgroup analyses were conducted to assess the effects among these participants of different age groups, exercise interventions of various frequency, types of exercise, and program durations. The applicability of the results was assessed.

Whilst this meta-analysis provides useful updated information for healthcare providers and policymakers, the results should be considered with the following limitations. First, most meta-analyses had substantial to considerable heterogeneity. Our systematic subgroup analyses attempted to identify reasons for heterogeneity and reduced heterogeneity, a few subgroup analyses still showed large heterogeneity — potentially indicating that inadequate definition of subgroups such as substantial differences in intensity of interventions, gender of participants, control conditions, and/or outcome assessments. All potential explanations would reduce the confidence in the effects found in this meta-analysis. Second, several studies did not fully report outcomes of interest, and not all authors who were contacted for further information to provide missing data responded. Additionally, for many studies, the standard deviation of the post-intervention outcome was not reported, and this data was inputted using the mean correlation coefficient from the available data. Sensitivity analyses were performed using a range of correlation coefficients, which did not show any changes to the pooled effect sizes.

2.6 Future Research

Specificity of timing, frequency, duration, and intensity of exercise intervention is required to see beneficial results for cardiovascular risk factors and to provide evidence-based activity recommendations specifically designed for T1D. Growing evidence indicates that generic physical activity guidelines are likely not optimal for persons living with chronic medical conditions. In a recent systematic review of current systematic reviews, Warburton and Bredin revealed that marked health benefits are achieved in persons living with chronic medical conditions (including diabetes) with relatively minor volumes of physical activity (98). This research directly challenged current threshold-based messaging related to physical activity and health. Future research should more carefully examine the minimal and optimal dosages of physical activity for health benefits in persons living with T1D. Additional research is warranted that more closely examines the

relationships between physical activity volumes (and/or intensities) and glycemia control, insulin dosages, aerobic fitness, and quality of life. Furthermore, more studies with larger sample sizes are required to examine the relative contributions of multicomponent interventions and differential glycemic control treatment strategies.

2.7 Conclusions

Our findings support the conclusion that exercise training plays an important role in the prevention of cardiovascular disease in T1D. The meta-analysis reveals that exercise training may result in positive changes in biological cardiovascular risk factors including aerobic fitness, HbA1c, insulin dosage, and lipids in persons living with T1D. However, while these effects were not clearly distinguishable due to heterogeneity and possible bias. The optimal and minimal dosages of exercise for beneficial changes in the cardiovascular risk profile of those living with T1D remains to be determined.

Further examination of diet and hypo/hyperglycemic episodes should be executed to fully understand the benefits of exercise on persons living with T1D. The results and recommendations of this meta-analysis are of relevance for health professionals involved in the primary prevention of cardiovascular disease highlighting further the importance of exercise as a cornerstone in diabetes management and health promotion in T1D. Further research is required in order to demonstrate the full benefits of exercise training for individuals of all ages living with T1D.

Chapter 3: Metabolic and Hormonal Responses to Moderate-intensity Continuous versus High-intensity Interval Exercise in Individuals with Type 1 Diabetes: A Systematic Review and Meta-analysis

3.1 Introduction

Exercise is critical for the management of diabetes as it is associated with well-defined health benefits for persons with T1D. These health benefits include improved glycemic control (18), aerobic fitness (153), vascular health (153), endothelial function (154), and reduced insulin requirements, cardiovascular risk factors, body mass, body fat, and better self-rated quality of life (18; 152). The ACSM guidelines for exercise prescription state that individuals with T1D should engage in 150 min of exercise at 40-59% of their VO_2max or 75 min of vigorous intensity (60-89% VO_2max) exercise per week (155). Moderate-intensity continuous exercise (MICE) typically involves continuous, repeated movements of large muscle groups (e.g., jogging, cycling, and swimming) at 40-59% of maximum oxygen uptake (VO_2max) or 55-69% of maximal heart rate (HRmax) for at least 10 min at a time (156).

Unfortunately, MICE can also increase the risk of hypoglycemia in individuals with T1D, both during activity (61) and for up to 31 h post-exercise (157). Previous research has found that many individuals with T1D do not achieve the recommended levels of physical activity for optimal health benefits due to concerns over hypoglycemic episodes (21; 158). Given this concern, there has been an increased research focus on establishing exercise protocols to prevent hypoglycemia. High-intensity interval exercise (HIIE), which is defined as alternating brief intermittent bursts of high-intensity exercise interspersed with periods of rest or low-intensity exercise, is associated with less hypoglycemia (150). High-intensity interval exercise has been recommended by the ISPAD to

minimize the risk of exercise-induced hypoglycemia in individuals with T1D who have no complications (159).

Despite this, a crossover study conducted by Maran et al. find no significant difference on blood glucose changes between HIIE and MICE and HIIE was associated with higher risk for nocturnal hypoglycemia when compared with MICE in non-trained individuals with T1D (10). In contrast, Guelfi et al. found declines in glycaemia from HIIE were smaller compared with MICE and concluded that HIIE could increase blood glucose during exercise and in immediate recovery and help prevent post-exercise hypoglycemia in persons with T1D (11). There has been an increasing number of well-designed exercise trials showing inconsistent findings of blood glucose in response to HIIE versus MICE in persons with T1D (160-170). The physiological mechanisms responsible for preventing or attenuating hypoglycemic excursion was attributed to counter-regulatory hormones such as glucagon, growth hormone, catecholamines, and cortisol in order to prevent hypoglycemia. As such, a systematic review that critically evaluates the effect of HIIE versus MICE on metabolic outcomes and hormonal responses in individuals living with T1D is warranted. Findings from this review will provide updated recommendations for researchers, clinicians and front-line exercise professionals to design and develop targeted exercise interventions for effective management of T1D with exercise.

The objective of this study was to evaluate the acute effects of HIIE versus MICE on metabolic outcomes and hormonal responses in individuals with T1D in order to develop evidence-based guidelines to allow for safe physical activity and exercise participation. We hypothesized that HIIE will be associated with less of a decrease in glucose levels or risk of early-onset hypoglycemia compared with MICE in individuals with T1D. Additionally, we hypothesized that the acute response for hormones and other metabolic parameters would be different between the two exercise modes.

3.2 Methods

3.2.1 Data sources and searches

We adhered to the standards established by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (171). This review was registered in PROSPERO International Prospective Register of Systematic Reviews (https://www.crd.york.ac.uk/prospero/; Identifier CRD 42019120002). No study protocol was published previously before this initiation of the systematic review and meta-analysis.

The systematic review was conducted to identify relevant trials by electronic searches of MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Web of Science, SPORTDiscus, and CINAHL from inception to December 2019. Databases were also searched for ongoing trials using Current Controlled Trials (www.controlled-trials.com) and ClinicalTrials.gov (www.clinicaltrials.gov). We manually screened the reference lists in an effort to find relevant additional studies and reviews. The keyword searches were performed related to high-intensity interval exercise ('interval exercise' or 'interval training' or 'intermittent exercise' or 'intermittent training' or 'sprint exercise' or 'sprint training' or 'sprint interval training' or 'sprint interval exercise' or 'high intensity exercise' or 'continuous exercise' or 'moderate-intensity continuous exercise' or 'HIIE' or 'HIIT') and type 1 diabetes ('type I diabetes' or 'juvenile-onset diabetes' or 'insulin-dependent diabetes' or 'IDDM' or 'sudden-onset diabetes'). The search was restricted to include only human studies that were published in English. The search was updated in March 2021 to include any new studies on the topic.

3.2.2 Study selection

Studies that fit the following criteria were included in the review: RCTs and crossover trials that evaluated the effects of HIIE compared with MICE on metabolic and hormonal responses in individuals with T1D. The metabolic and hormonal responses of interest included: glucose, insulin,

lactate, glucagon, cortisol, growth hormone, and catecholamines. Study populations included individuals of any age or sex who were diagnosed with T1D.

The selection criteria were limited to trials that randomized participants with T1D to HIIE or to MICE. Multi-component interventions including single-hormone artificial pancreas, dual-hormone artificial pancreas (DAP), Continuous Glucose Monitoring, and nutritional intake (of which one component was HIIE) compared with MICE were included. We included any arm that met the inclusion criteria if a study included multiple arms. Context studies reporting at least one metabolic or hormonal outcome were considered in this review.

We excluded case studies, reviews, and studies that included persons living with type 2 diabetes, gestational diabetes, participants with significant diabetic complications (e.g., diabetic foot, retinopathy, severe neuropathy, uncontrolled hypertension, and diabetic keto-acidosis), or participants on lipid-lowering therapy. Two authors independently scanned titles and abstracts, and the keywords of every study identified (N.W. and Y.G.). Four authors (N.W., Q.J., D.C. and J.K.) independently evaluated the remaining studies based on full texts, applying the eligibility criteria for included studies. Any disagreements were resolved by consensus, or by discussion with additional reviewers (Y.G. and K.D.).

3.2.3 Data extraction and quality assessment

Data were extracted independently by two authors using a standardized form. If agreement was not reached regarding the extraction of the data, an additional investigator adjudicated the outcome. Missing data from the included studies were required directly from the study authors. Extracted information included: authors, title of the study, year of publication, study design, study population (age, sex, diabetic duration, sample size, VO_2max), details of the intervention (exercise type, duration, and intensity), washout period, planned nutritional intake, and/or insulin interventions, and outcomes.

Studies were assessed for risk of bias using the Cochrane Collaboration's risk of bias tool in crossover studies which assesses the following domains (172): bias from randomization process, bias from period and carryover effects, bias due to deviations from intended interventions, bias due to missing outcome data, bias from measurements of the outcome, bias from selection of reported result. Based on signaling questions, each domain is assessed as either "some concerns," "low risk," or "high risk". The overall bias of each study is considered "low risk of bias" if all domains are classified as "low risk"; "some concerns" if there is at least one domain rated as "some concern"; and "high risk of bias" if there are multiple domains rated as "some concerns" or at least one domain rated as "high risk".

3.2.4 Data synthesis and analysis

RevMan (version 5.1) was used to extract data from the included studies, the outcome data was reported as mean ± standard deviation (SD), mean ± standard error of the mean (SEM), median (range) or weighted mean and 95% confidence intervals (CI). Weighted mean differences (effect size, ES) of each cardiovascular risk factor between exercise groups and controls were calculated using a random effects model. We quantified and explored the statistical heterogeneity between studies using the I-squared test and chi-squared test, with 95% uncertainty intervals. Publication bias was assessed by viewing the overlap of the study CI using the funnel plot technique. All data were initially analyzed with a fixed effects model and random effects models were chosen to conduct the meta-analyses when significant heterogeneity was present. Sensitivity analyses were performed by excluding one study at a time to examine if the results were led by any one study. Standard error of the mean (SEM) values reported in the included studies were converted to SD values. If the outcome measures were reported in median, range, or 25^{th}-75^{th} percentiles, mean and SD values was estimated using formulas published by Wan et al. (173). If related outcome data were absent, the authors were contacted via e-mail to obtain the necessary information.

3.3 Results

3.3.1 Study characteristics

Figure 1 shows the flow of the literature. After the removal of duplicates, 1146 articles were identified in the initial electronic search. Following screening of the titles and abstracts, 41 full articles met the eligibility criteria for further examination (Figure 1). A total of 24 articles were then excluded for the following reasons: inappropriate study design (n = 15); case study (n=1); not relevant data (n = 4); and study with duplicate data sets (a project with multiple publications, n = 4). In total, 17 crossover studies published between 1985 (174) and 2021 (175) met our inclusion criteria and examined the counter-regulatory hormones or metabolites in T1D. Table 3.1 summarizes the main characteristics of the final 17 publications incorporated in this systematic review and meta-analysis. All trials were crossover design.

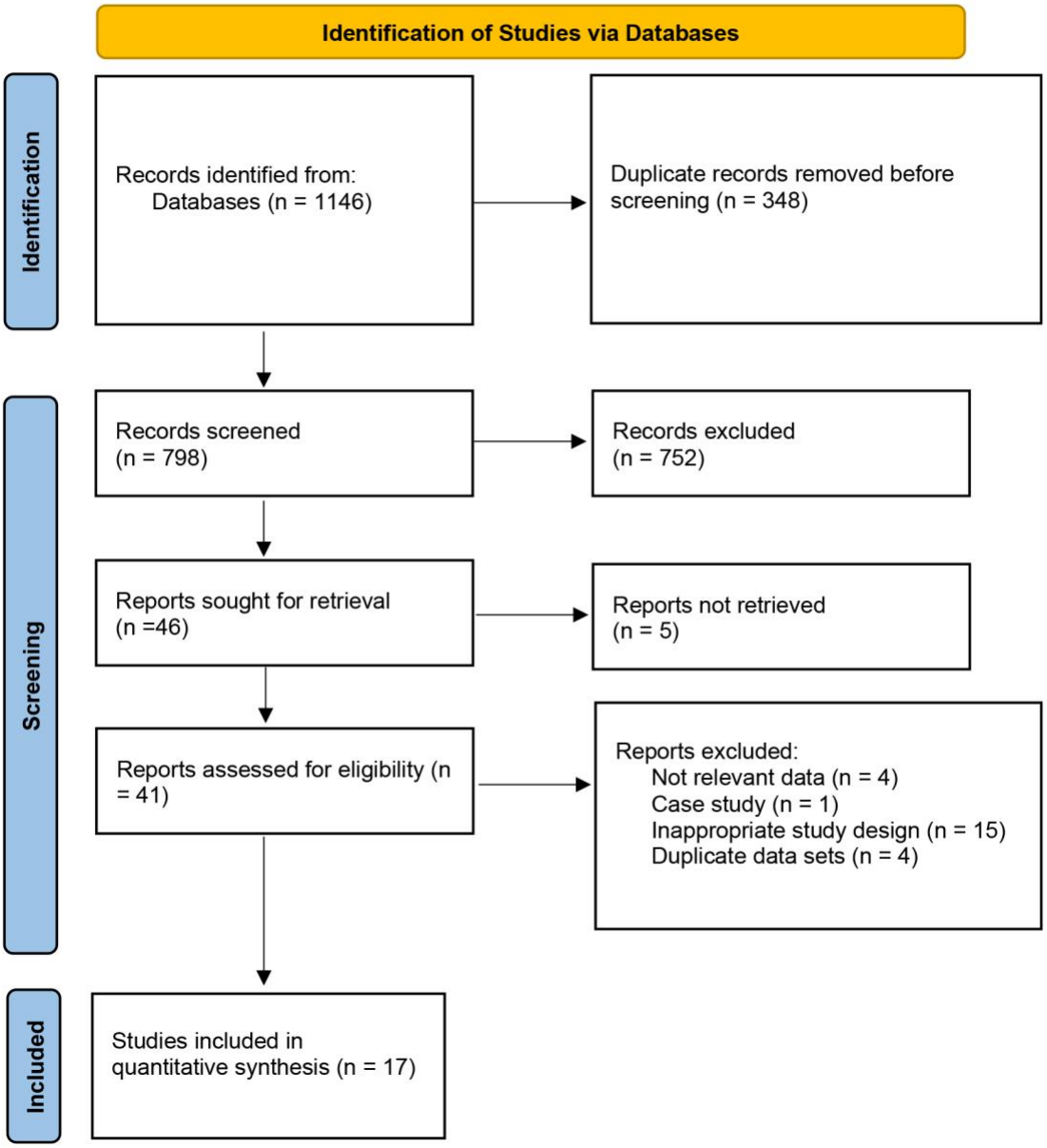

Figure 3.1 Study flow diagram with Preferred reporting Items for Systematic Reviews and Meta-analysis (PRISMA)

3.3.2 Participants and intervention characteristics

Sample sizes ranged from 7 to 17, with a total of 185 participants (105 males, 80 females) diagnosed with T1D. The duration of T1D was reported in all studies, ranging from 6.3 ± 4.4 to 25.0 ± 4.0 years (Table 3.1). Fifteen of the studies included adults, whereas two of the studies included adolescents (16.4 ± 1.5 and 17.5 ± 0.8 years old). All included studies reported the VO_2max of participants at the time of enrolment. Lee and colleagues (168) recruited participants with the lowest VO_2max values (mean: 28.2 ± 5.8 $mL \cdot kg^{-1} \cdot min^{-1}$). Moser et al. (164) recruited participants with the highest VO_2max values (52.0 ± 8.2 $mL \cdot kg^{-1} \cdot min^{-1}$).

Exercise interventions described in Table 3.1 varied widely between HIIE and MICE interventions. The total duration of HIIE ranged between 30 and 90 min per session. HIIE interventions included maximal sprint cycling (161; 176-178), cycling (161; 163; 165; 166; 169; 170; 174-177; 179; 180), game-based activities (167), treadmill walking/running (181), and circuit-based exercise (e.g., jumping jacks, squats, running on the spot, planks, push-ups) (182). The number (range 3-28), duration (range 4 s-4 min) and intensity (range from 55% VO_2max to all-out effort) of 'high-intensity' intervals, as well as duration (range 4 s-10 min) and intensity (range from complete rest to 70% HRpeak) of recovery intervals varied widely between studies. Most studies (11 out of 17) reported that the MICE and HIIE energy expenditures were matched and similar. Moderate-intensity continuous exercise ranged from 30-90 min per session and included cycling (160; 161; 163; 165; 166; 168-170; 174-180) and treadmill walking/running (167; 181; 182). The intensity of MICE was reported in terms of percentage of VO_2max or VO_2peak, peak heart rate (HRpeak), peak work rate (WRpeak), lactate threshold (LAT), anaerobic threshold (AT), or heart rate reserve (HRR). The intensity of MICE ranged between 40% and 77% VO_2max or VO_2peak, 45% and 70% HRmax, 40% and 55% HRR.

Table 3.1 Characteristics of the included studies

Study, year,	**Characteristics of the study population**						**Insulin adjustment & nutritional intake**	**Washout period**			**Exercise intervention**	
	study design	**Simple size, sex,**	**Age (years)**	**VO_2 max**	**Duration of T1D (years)**	**HbA1c (%) (mmol/mol)**	***(Before, during and post exercise)***	**No hypoglycaemia pre-trial**	**No exercise pre-trial**	**Gap between trial arms**	**HIIE**	**MICE**
Adolfsson et al.,2012[a,b]	Crossover study	12 (6M, 6F)	16.4 ± 1.5	49.8 ± 9.9	6.3 ± 4.4	7.9 (6.6 - 9.6); 63 (49-81)	**BE:** insulin adjustment + normal breakfast; **PE:** a meal	24 h	24 h	NR	5 min warm up + 6×3 min bursts @ 70% VO_2max with 1.5 min @ low-intensity cycling + 5 min slow down	60 min cycling @ 40% VO_2max
Bally et al., 2016[c]	Crossover study	12 (all M)	26.2 ± 3.9	47.9 ± 10.2	14.2 ± 6.2	7.0 ± 0.6; (53)	**BE:** standardised diet for 48 h +usual insulin regimen; **PE:** a standardized meal; **DE&PE**: Oral administration of a 10% dextrose solution for prevention of hypoglycemia if needed	48 h	48 h	2-4 weeks	90 min cycling @ 50% VO_2max with 9×10 s supramaximal sprints @120% peak work load followed by a 50 s recovery every 10 min	**9**0 min cycling @ 50% VO_2max

Campbell et al., 2015[c]	Crossover study	9 (7M, 2F)	35 ± 4	41.8 ± 1.6	25 ± 4	8.1 ± 0.2;(65)	**BE:** normal diets for 48 hours + usual insulin regimen of basal insulin+ 50% reduction of bolus insulin; **DE&PE** :20 g carbohydrate bolus for prevention of hypoglycemia if needed	NR	48 h	NR	45 min simulated games-play activity with repeated alternation of 3×20 m walking @ 55% VO_2peak, 1×20 m sprinting, 4 s recovery, 3×20 m run @ 55% VO_2peak, 3×20 m running @ 95% VO_2peak	45 min treadmill running @ ~77.0% VO_2peak
Dube et al., 2012[c]	Crossover study	11 (5M, 6F)	26.5 ± 6.6	33.4 ± 6.4	12.2 ± 5.1	7.3 ± 0.4;(56)	**BE:** normal diets and snack + usual insulin regimen; a standard meal; placebo beverage (sucaryl in 10% water solution) at 15 min; **BE, DE&PE:** dextrose infusion for prevention of hypoglycemia if needed	24 h	24 h	1 week	60 min cycling @ 50% VO_{2peak} with 28×10 s maximal sprint every 2 min	60 min cycling @ 50% VO_{2peak}

Guelfi et al., 2005[a]	Crossover study	7 (4M, 3F)	21.6 ± 4.0	39.3 ± 7.4	8.6 ± 5.0	7.4 ± 1.5; (57)	**BE:** usual insulin regimen + normal breakfast; **DE&PE:** carbohydrate supplementation in the form of oral polycose for prevention of hypoglycemia if needed	48 h	24 h	1 week	30 min cycling **@** 40% VO_2peak with 16×4 s maximal sprint every 2 min	30 min cycling @ 40% VO_2peak
Hubinger et al., 1985[c]	Crossover study	9 (4M, 5F)	20-47	NR	1-17	NR	**BE:** 1/3 reduction of morning bolus insulin and 1/3 of reduction basal insulin + breakfast	NR	NR	> 1 day	3 x 10 min cycling with 3 min rest	30 min cycling @ half maximal workload (75-125 W)
Iscoe et al., 2011[c]	Crossover study	11 (5M, 6F)	35.1 ± 3.5	42.4 ± 1.6	15.6 ± 5.6	7.8 ± 0.4; (62)	**BE:** standardized meals and snacks + usual insulin dose; **PE:** low glycaemic index beverage snack (30g carbohydrate) at a bedtime	NR	24 h	1-4 weeks	45 min cycling @ 50% WRpeak with 9×15 s @ 100% WRpeak every 5 min	45 min cycling @ 55% WRpeak

Jayawardene et al., 2017[a]	Crossover study	12 (3M, 9F)	40 ± 13	34.3 ± 8.9	24 ± 9	7.6 ± 0.7;(60)	**BE:** a light breakfast 20 g carbohydrate for prevention of hypoglycemia if needed	NR	NR	1-4 weeks	5 min warm-up cycling @ 25% VO_2max, 6×4 min cycling at mid-way between AT and VO_2max with 2 min rest (with an additional 4 min rest between third and fourth repetitions)	5 min warm-up cycling @ 25% VO_2max + 40 min cycling @ 70% AT
Lee et al., 2020[a]	Crossover study	12 (3M, 9F)	40.4 ± 9.9	28.2 ± 5.8	16.5 ± 9.8	8.0 ± 0.8;(64)	**BE:** usual insulin doses; **PE (MDI):** 25% reduction of bolus insulin at first meal after exercise + 20% reduction of basal insulin at night + 15 g of carbohydrate snack at bedtime; **PE (CSSI**): 20% reduction of basal rate of for 9 h (21:00 - 06:00)	NR	48 h	NR	5 min of warm-up cycling @ 60% HRpeak + 25 min cycling 4×4 min @ 85-95% HRpeak interspersed with 3×3 min recovery intervals @ 50-70% HRpeak + 3 min of cool-down	33 min cycling @ 60-70% HRpeak + 3 min of cool-down
Maran et al., 2010[a]	Crossover study	8 (all M)	34 ± 7	33.7 ± 6.1	14.3 ± 8	7.14 ± 0.6; (55)	**PE:** 20% reduction of evening dose	48 h	48 h	1 week	2 min warm-up + 30 min cycling @ 40% VO_2max	30 min cycling @

							of bolus insulin + usual basal insulin				with 14×5 s @ 85% VO_2max sprints every 2 min	40% VO_2max
Moser et al., 2015[a]	Crossover study	7 (all M)	24 ± 5.3	52 ± 8.2	16.9 ± 8.1	7.4 ± 0.6; (57)	**BE:** a standardized meal + 25% reduction of bolus insulin for A, 50% for B, and 75% for C; Carbohydrate supplements for prevention of hypoglycemia **PE:** usual insulin doses	48 h	NR	1 week	3 min warm-up @ 40 W before each exercise + 3 min active recovery at 40 W+3 min passive recovery (0 W) after each protocol **(A):** 30 min cycling @ 5% P_{max} from IET below LTP1 with 20 s @ peak workload every120 s	3 min warm-up @ 40 W before each exercise + 3 min active recovery at 40 W + 3 min passive recovery (0 W) after each protocol **(A):** 30 min cycling @ 5% P_{max} from IET below LTP1
											(B): 30 min cycling @ 5% P_{max} from IET above LTP1 with 20 s @ peak workload every 60 s	**(B):** 30 min cycling @ 5% P_{max} from IET above LTP1
											(C): 30 min cycling @ 5% P_{max} from IET below LTP2 with 20 s @ peak workload every 20 s	**(C):** 30 min cycling @ 5% P_{max} from IET below LTP2

Rempel et al., 2018[a,d]	Crossover study	10 (6M, 4F)	30 (25-32)	37.6 (30.5 - 41.0)	9.5 (5.3-15.8)	8.0 (7.0 ± 8.6); 64 (53 ± 70)	**BE (MDI):** 10% reduction of basal insulin + bolus insulin adjustment; **BE (CSII):** 50% reduction of basal rate for 2 hours before exercise until the end of exercise; **PE:** bedtime snack	NR	NR	48 hours	**(Condition 1):** 45 min walking @ 45-55% HRR with 6×60 s @70% HRR every 4 min	45 min walking @ 45-55% of HRR
											(Condition 2): 45 min walking @ 45-55% HRR with 6×60 s @ 80% HRR every 4 min	45 min walking @ 45-55% of HRR
											(Condition 3): 45 min walking @ 45-55% HRR with 6×60 s @ 90% HRR every 4 min	45 min walking @ 45-55% of HRR
Sarnblad et al., 2021[a]	Crossover study	8 (all M)	17.5 ± 0.8	50.8 ± 6.5	8.1 ± 4.8	7.2 ± 0.5; (55)	**BE:** a standardized breakfast; **BE (MDI):** fast-acting insulin adjustment+10 % reduction of long-acting insulin; **BE (CSII):** 50% reduction of basal insulin dosage 1hr before the start of	24 h	Same day	1 week	5 min warm-up @ 30% VO_2max + 2×4×3 min cycling @ 70% VO_2max with 90s recovery @ 30% VO_2max + 5 min cool-down @ 30% VO_2max	5 min warm-up @ 30% VO_2max + 45 min cycling @ 60% VO_2max + 5 min cool-down @ 30% VO_2max

							exercise until 105 min after exercise start.					
Scott et al., 2018[c]	Crossover study	14 (6 M; 8F)	26 ± 3	30.8 ± 2.0	8.2 ±1.4	NR	**BE:** standardized diet; **DE + PE:** additional snacks for prevention of hypoglycemia.	NR	NR	48 hours	5 min warm-up @ 50 W + 6 × 1 min cycling @ 100% VO_2max with 1min rest	5 min warm-up @ 50 W + 30 min cycling @ 65% VO_2max
Taleb et al., 2016[a]	Crossover study	17 (8M;9 F)	37.2 ± 13.6	34.2 ± 5.4	23.1 ± 11.7	8.0 ± 1.0; (64)	**BE:** a standardized diet	NR	NR	NR	**SAP:** 10 min cycling @ 45% VO_2peak warm up+ 40 min @ 50% VO_2peak with 2 min alternation @ 85% and 50% VO_2peak + 10 min cycling @ 45% VO_2peak cool down; **DAP**: Same exercise intervention	**SAP:** 60 min cycling @ 60% VO_2peak; **DAP**: Same exercise intervention
Zaharieva et al., 2017[a]	Crossover study	12 (6M; 6F)	32 ± 11	50.1 ± 13.7	16 ± 13	7.0 ± 0.9; (53)	**BE (CSII):** basal insulin suspension at the onset of exercise until the end of exercise;	NR	24 h	2 days	3 x 13 min (4 min treadmill walking + 45s marching on the spot with dumbbells + 60 s squats with front sweep + four jumping jacks + 30 s quadruped +	40 min treadmill walking @ 40-50% VO_2max

							DE+ PE: 16 g of oral dextrose for prevention of hypoglycemia if needed				two jumping jacks + four push-ups + 20 s prone forearm planks + 30 s marching on the spot with dumbbells + 60 s weighted ball lifts + four push-ups + 20 s prone forearm plank + 4 min cycling at a moderate workload)	
Zebrowska et al., 2018[a]	Crossover study	14 (7M;7 F)	26.9 ± 5.9	41.4 ± 10.5	12.1 ± 7.7	7.2 ± 0.6; (55)	**BE:** 30-50% of insulin reduction; carbohydrates for prevention of hypoglycemia if needed	NR	24 h	1 week	4×5 min cycling @ 120% LAT with 5 min rest	40 min cycling @ 50% LAT

[a.] Data are expressed as mean ± standard deviation mean ± standard deviation (SD); [b.] Data are expressed as median (range); [c.] Data are expressed as mean ± standard error of the mean; [d.] Data are expressed as median and percentiles (Q1-Q3).T1D, type 1 diabetes; HIIE, high-intensity interval exercise; MICE, moderate intensity continuous exercise; BE, before exercise; DE, during exercise; PE, post-exercise; M, male; F, female; NR, not reported; VO_2max, maximal oxygen consumption; VO_2peak, peak oxygen consumption; AT, anaerobic threshold; WR_{peak}, peak work rate; g, grammes; LTP1, power output at the first lactate turn point; LTP2, power output at the second lactate turn point; P_{max}, maximal power output; HRR, heart rate; SAP, single-hormone artificial pancreas; DAP, dual-hormone artificial pancreas; LAT, lactate threshold reserve;

3.3.3 Risk of bias

Table 3.2 shows the individual and summary Cochrane risk of bias assessments of the included trials (172). Three studies (164; 166; 169) were at high risk of an order effect as they did not report any randomization. Three studies (160; 168; 170) were classified as low risk, providing sufficient information regarding method of randomization. All other studies were classified as unclear risk because they did not provide sufficient information regarding method of randomization. Table 3.1 also contains a summary of the washout periods in each trial, specified by authors in order to avoid/minimize the presence of carry-over effects between two intervention arms. Most studies (nine out of 17) required physical exertions to be at least one week apart, with some using shorter washouts, although never less than 12 h. Most studies provided outcome data for all participants. Eight studies referred to publicly available study protocols (160; 164; 168; 175; 180-183).

The Cochrane risk-of-bias tool (Table 3.2) showed that 11 studies (64%) had some concerns, three studies (18%) had high risk of bias, and three studies (18%) had low risk of bias for randomization process. Fourteen studies (82%) had low risk of bias and three studies (18%) had some concerns for period and carryover effects. Seventeen studies (100%) had unclear risk of bias for deviations from intended interventions. Seventeen studies (100%) had low risk of bias for missing outcome data. Sixteen studies (94%) had some concerns and one study (5%) had low risk of bias for measurements of the outcome. Nine studies (53%) had some concerns and eight studies (47%) had high risk of bias for selection of the reported result. Three studies (18%) had high risk of bias and 14 studies had some concerns (82%) for overall bias. We assessed the potential for the publication bias graphically via funnel plots. Visual inspection of funnel plots suggests no asymmetry in included outcomes.

Table 3.2 Cochrane summary assessment of risk of bias for crossover trials

Author and year	Randomization process	Period and carryover effects	Deviations from intended interventions	Missing outcome data	Measurements of the outcome	Selection of reported result	Overall
Adolfsson et al., 2012	High	Low	Low	Low	SC	SC	High
Bally et al., 2016,	Low	Low	Low	Low	SC	Low	SC
Campbell et al., 2014	SC	SC	Low	Low	SC	SC	SC
Dube et al., 2012	SC	Low	Low	Low	SC	SC	SC
Guelfi et al., 2005,	SC	Low	Low	Low	SC	SC	SC
Huger et al., 1985	SC	SC	Low	Low	SC	SC	SC
Iscoe et al., 2011	SC	Low	Low	Low	Low	SC	SC
Jayawardene et al., 2017	Low	Low	Low	Low	SC	SC	SC
Lee et al., 2020	Low	Low	Low	Low	SC	Low	SC
Maran et al., 2010	SC	Low	Low	Low	SC	SC	SC
Moser et al., 2015	High	Low	Low	Low	SC	Low	High
Rempel et al., 2018	SC	Low	Low	Low	SC	Low	SC
Sarnblad et al., 2021	SC	Low	Low	Low	SC	Low	SC
Scott et al., 2018	SC	low	Low	Low	SC	Low	SC
Taleb et al., 2016,	SC	SC	Low	Low	SC	Low	SC
Zahrieva et al, 2017	SC	Low	Low	Low	SC	Low	SC
Zebrowska et al., 2018	High	Low	Low	Low	SC	SC	High

SC: Some concerns

3.3.4 Synthesis of results and statistical analysis (meta-analysis)

3.3.4.1 Glycaemia

Seven out of 17 studies (Appendix A) presented glucose values during exercise (160; 161; 165; 166; 169; 170; 176). In individuals living with T1D, the comparison between MICE and HIIE did not present a significant difference in glucose, with an overall ES of 0.43 mmol·L^{-1} (95% CI −0.02 to 0.88; $p = 0.06$) favorable to MICE. Heterogeneity was found to be low between these studies (I^2= 9%; T^2 = 7.66, and df = 7) (Figure 3.2). Sensitivity analysis revealed that a study by Taleb et al. with DAP among both exercise arms influenced the results. The removal of this trial created its significance 0.62 (95% CI 0.15 to 1.10, p = 0.01) and removed its heterogeneity (I^2 = 0%, T^2 = 2.71, and df = 6).

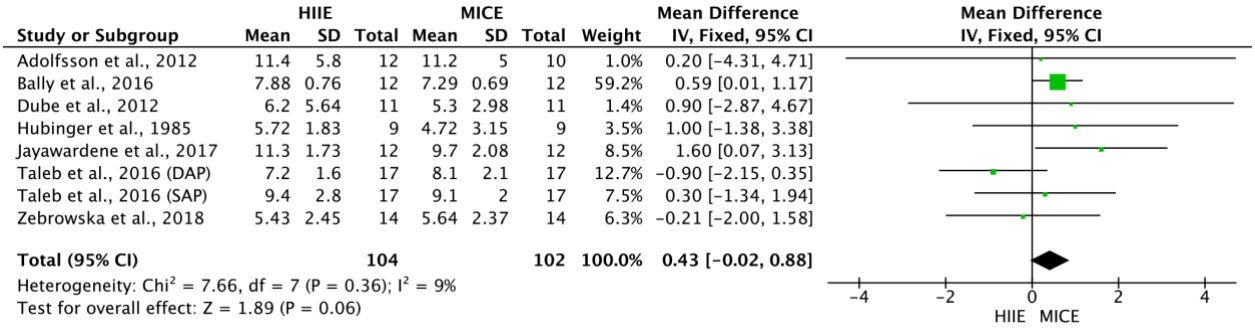

Figure 3.2 Meta-analysis of blood glucose levels during high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE); mmol·L^{-1}

Thirteen out of 17 (Appendix A) studies presented glucose data as changes from baseline glycemia to the end of exercise (161; 163-169; 175; 178; 181; 182; 184). In individuals with T1D, there was a statistically significant difference in blood glucose reduction over HIIE trials compared with MICE, with a favourable result for the MICE (ES 0.73 mmol·L^{-1}, 95% CI 0.22 to 1.24; p = 0.005) (Figure 3.3). Heterogeneity was found to be moderate between these studies (I^2 = 50%; Q

= 34.32, T^2 = 0.52, *df* = 17, and *p* = 0.008). Sensitivity analysis showed only minor shifts, and these shifts did not affect the overall significance of the mean effect.

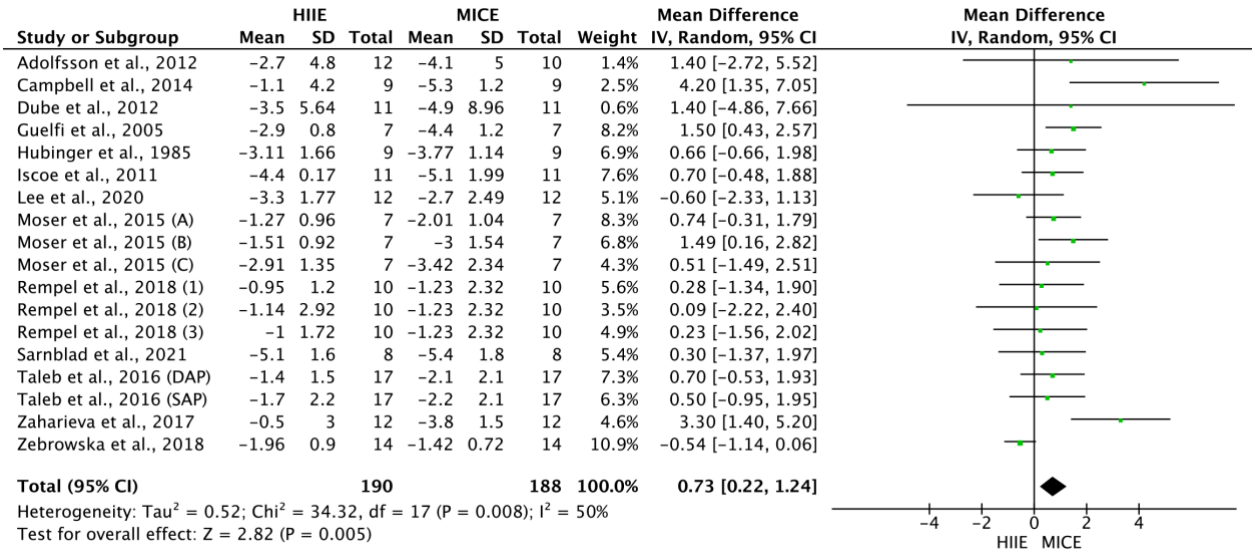

Figure 3.3 Meta-analysis of changes of blood glucose from baseline in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE); mmol·L^{-1}

Blood glucose values during early recovery post-exercise were reported in seven studies and only three studies were appropriate for meta-analysis (160; 161; 170). The comparison between MICE and HIIE did not show a significant difference in blood glucose values during early recovery post-exercise (ES 0.05 mmo^{-1}L^{-1}, 95% CI −2.68 to 2.79; *p* = 0.97) (Figure 3.4). Differences in mean nocturnal interstitial glucose following exercise were not significantly different between MICE and HIIE, with an ES of −0.92 mmol·L^{-1} (95% CI −2.10 to 0.27; *p* = 0.13) (Figure 3.5). Heterogeneity was found to be high between these studies (I^2 = 74%; *Q* = 34.59, T^2 = 2.54, *df* = 9, and *p* < 0.00001). Sensitivity analysis revealed that a study by Moser et al. with cycling at control A (Table 3.1) influenced the results. The removal of this trial created its significance (ES −1.58 mmo·L^{-1}, 95% CI −2.96 to −0.20, *p* = 0.02), despite the fact that heterogeneity remained significant (I^2 = 67%; *Q* = 24.09, T^2 = 1.82, *df* = 8, and *p* = 0.03).

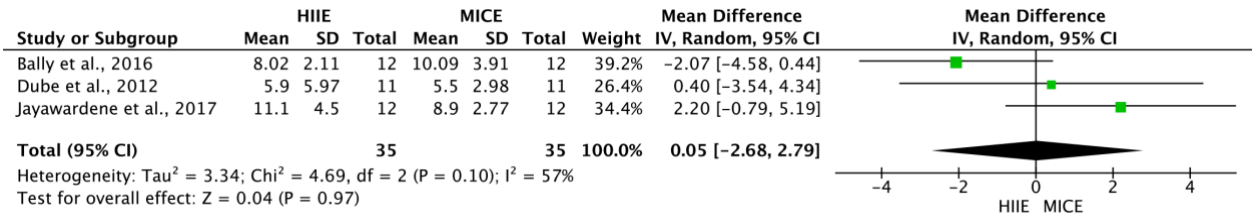

Figure 3.4 Meta-analysis of blood glucose levels in early recovery state in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE); mmol·L^{-1}

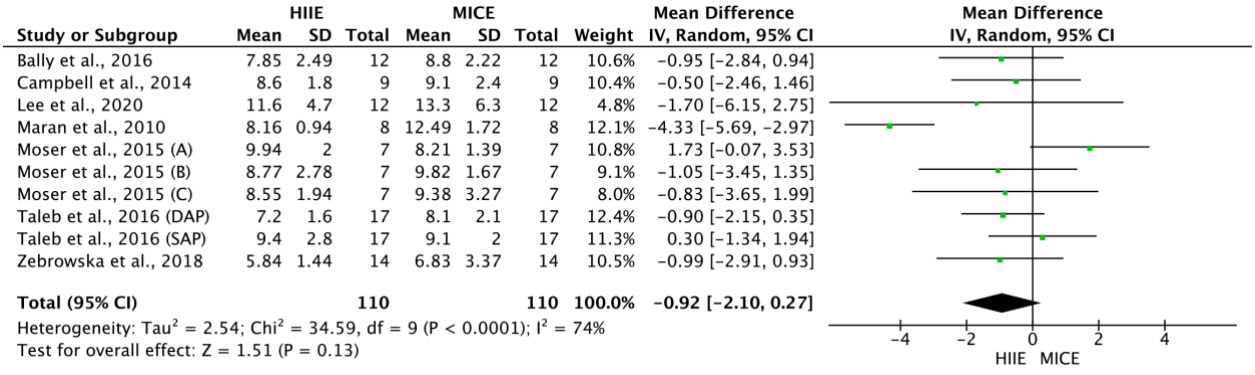

Figure 3.5 Meta-analysis of blood glucose levels during nocturnal period in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE)
Note: single-hormone artificial pancreas (SAP), dual-hormone artificial pancreas (DAP), mmol·L^{-1}

3.3.4.2 Metabolites (lactate and insulin)

Blood lactate was reported in 10 studies (Appendix A) and five studies (eight trials) were appropriate for meta-analysis (160; 164; 169; 170; 177). There was a statistically significant difference between HIIE and MICE in individuals with T1D for blood lactate levels, with a favourable result for the MICE (ES 2.41 mmol·L^{-1}, 95% CI 1.33 to 3.49; $p < 0.00001$) (Figure 3.6). Heterogeneity was found to be high between these studies (I^2 = 94%; Q = 1.69, T^2 = 100.56, df = 6, and $p < 0.00001$). Sensitivity analysis showed only minor shifts, and these shifts did not affect the overall significance of the mean effect.

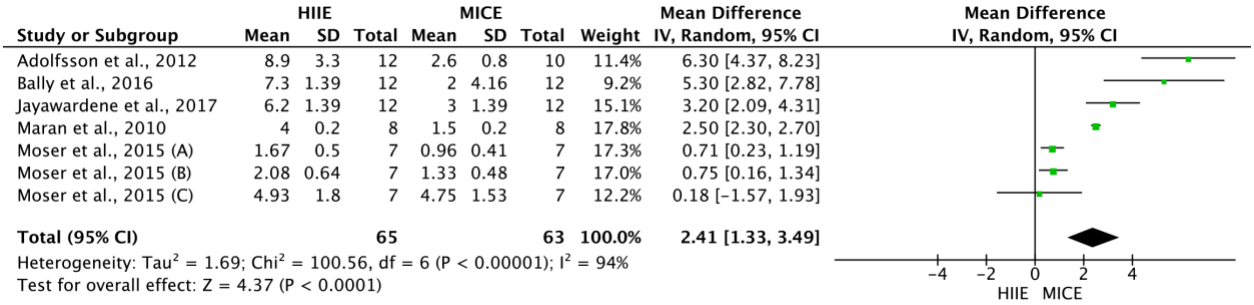

Figure 3.6 Meta-analysis of blood lactate levels in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE); mmol·L^{-1}

Circulating free insulin levels were reported in eight studies (Appendix A) and five trials (four studies) were appropriate for meta-analysis (160; 165; 169; 170). During exercise, circulating free insulin levels did not differ between MICE and HIIE (ES −0.00 mU·L^{-1}, 95% CI −2.99 to 2.99; p = 1.00) (Figure 3.7) in individuals with T1D. No significant heterogeneity was detected among these studies (I^2 = 0%; Q = 1.13, df = 4, and p = 0.89).

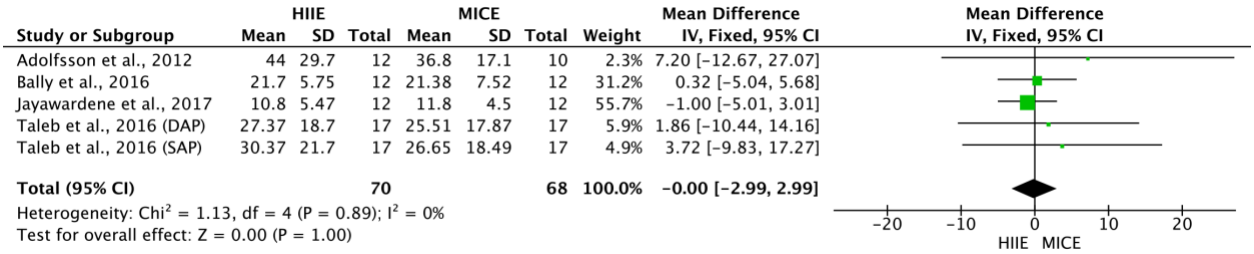

Figure 3.7 Meta-analysis of circulating insulin levels in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE); mU·L^{-1}

3.3.4.3 Counter-regulatory hormones (growth hormone, epinephrine, norepinephrine, cortisol, glucagon, dopamine)

Growth hormone was reported in six studies (Appendix B), however only three studies were appropriate for meta-analysis (160; 169; 170). From the pooled analysis of these three studies, growth hormone was significantly higher in responding to HIIE compared with MICE (ES 5.07

ng·mL^{-1}, 95% CI 1.18 to 8.96; p = 0.01) (Figure 3.8) in individuals with T1D. Heterogeneity was found to be low between these studies (I^2= 43%; Q = 3.50, T^2 = 5.07, df = 2, p = 0.17).

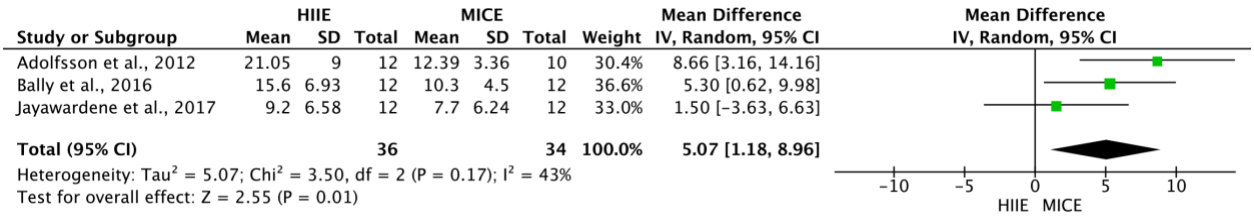

Figure 3.8 Meta-analysis of growth hormone levels in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE); ng·mL^{-1}

Epinephrine was reported in nine studies (Appendix B), however only four studies were appropriate for meta-analysis (163; 169; 170; 177). The comparison between MICE and HIIE presented a significant difference in epinephrine, with a mean difference (MD) of 135.86 pmol·L^{-1} (ES 135.86, 95% CI 57.93 to 213.78; p = 0.0006) (Figure 3.9) favourable to MICE. No significant heterogeneity among these studies was detected (I^2 = 0%; Q = 2.80, df = 3, p = 0.42).

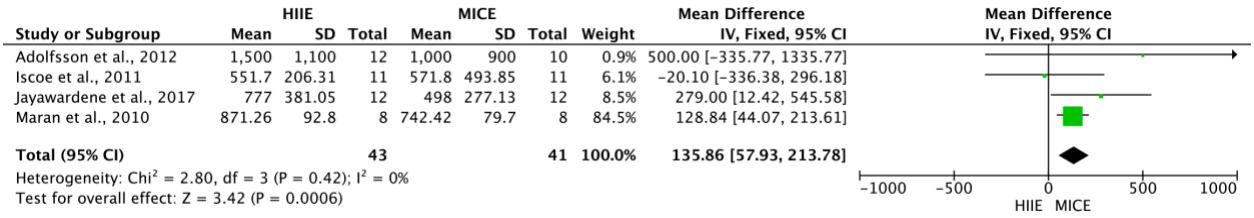

Figure 3.9 Meta-analysis of epinephrine in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE); pmol·L^{-1}

Norepinephrine was reported in nine studies (Appendix B), however only four studies were appropriate for meta-analysis (163; 169; 170; 177). The meta-analysis for the effect of HIIE and MICE on norepinephrine showed an effect size with 3.04 nmol·L^{-1} (95% CI, 0.50 to 5.59, p = 0.02) (Figure 3.10) favouring the MICE. There was high heterogeneity among these studies (I^2 = 77%;

Q = 13.31, df = 3, p = 0.004). Sensitivity analysis showed only minor shifts, and these shifts did not affect the overall significance of the mean effect.

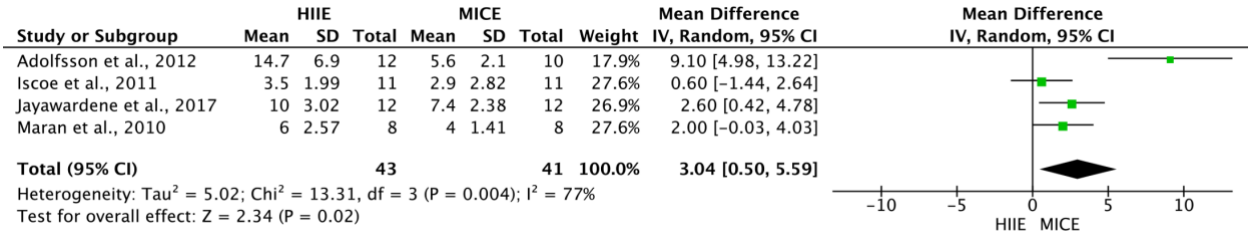

Figure 3.10 Meta-analysis of norepinephrine in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE); nmol·L^{-1}

Cortisol was reported in nine studies (Appendix A), however only three studies were appropriate for meta-analysis (160; 169; 170). In individuals with T1D, there was a statistically significant difference in serum cortisol levels during HIIE trials compared with MICE trials, with a favourable result for the MICE (ES 61.40 nmol·L^{-1}, 95% CI 12.62 to 110.17; p = 0.01) (Figure 3.11). No significant heterogeneity among these studies was detected (I^2 = 0%; Q = 0.11, df = 2, p = 0.95).

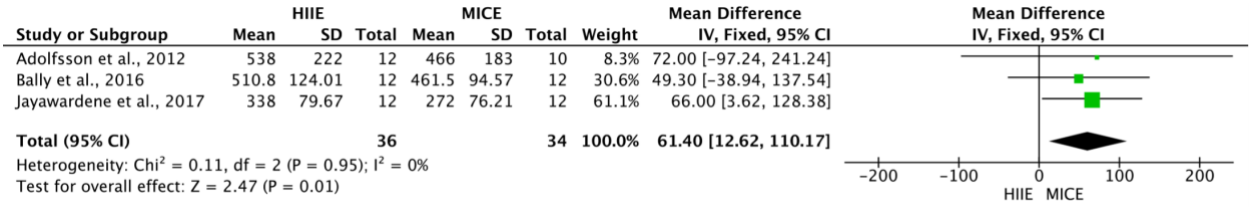

Figure 3.11 Meta-analysis of cortisol in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE); nmol·L^{-1}

Glucagon was measured in six studies (Appendix A) and there were insufficient data for meta-analysis. One study reported plasma glucagon increased during both MICE and HIIE in youth with T1D (169). One study with glucagon administration reported that more glucagon was needed during MICE than during HIIE (165). The remaining studies reported that glucagon was

not altered in response to MICE or HIIE, and there was no difference between the two intervention modes among these studies (160; 164; 170; 178). Dopamine was reported in three studies (Appendix A Table 3.2) and there was insufficient data for pooling meta-analysis. All three studies reported that dopamine increased during both MICE and HIIE in individuals with T1D, and the increase was greater for HIIE compared with MICE (164; 170; 185).

3.3.4.4 Adverse Events (hypoglycemia/hyperglycemia)

The type of data on hypoglycemia and hyperglycemia that authors investigated and reported is varied and few outcomes were appropriate for meta-analysis. Hypoglycemia was defined as an interstitial blood glucose concentration of $\leqslant$ 3.9 or < 4.0 mmol·L^{-1} in most included studies. Bally et al. and Campbell et al. defined hypoglycemia as a blood glucose concentration of < 3.5 mmol·L^{-1} (160; 167), Maran et al. and Mosser defined hypoglycemia as a blood glucose concentration of < 3.3 mmol·L^{-1} (177).

Most included studies reported the occurrence of hypoglycemia during exercise and in the immediate recovery stage (early-onset hypoglycemia). The meta-analysis of eight included studies (10 trials) showed a significant difference in the proportions of participants experiencing early-onset hypoglycemic events between HIIE and MICE (Risk Ratio, RR 0.57, 95% CI 0.38 to 0.86; p = 0.007) (Figure 3.12). No significant heterogeneity among these studies was detected (I^2 = 0%; Q = 2.81, df = 9, p = 0.97). However, there was no significant difference in the proportions of participants experiencing nocturnal hypoglycemic events between HIIE and MICE (RR 1.28, 95% CI 0.77 to 2.13; p = 0.34) (Figure 3.13). Heterogeneity was found to be low between these studies (I^2= 26%; T^2 = 0.11, and df = 5).

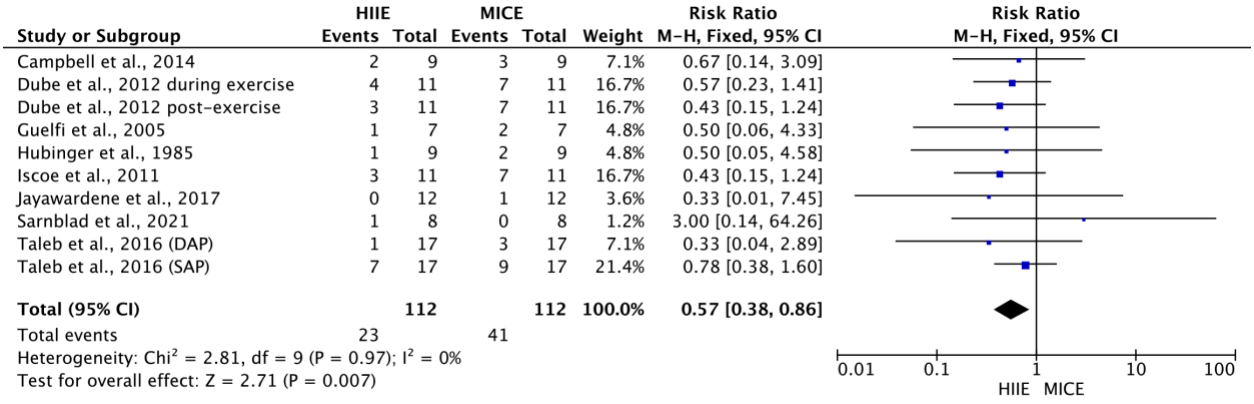

Figure 3.12 Meta-analysis of participants (n) who experienced early-onset hypoglycemic events in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE)

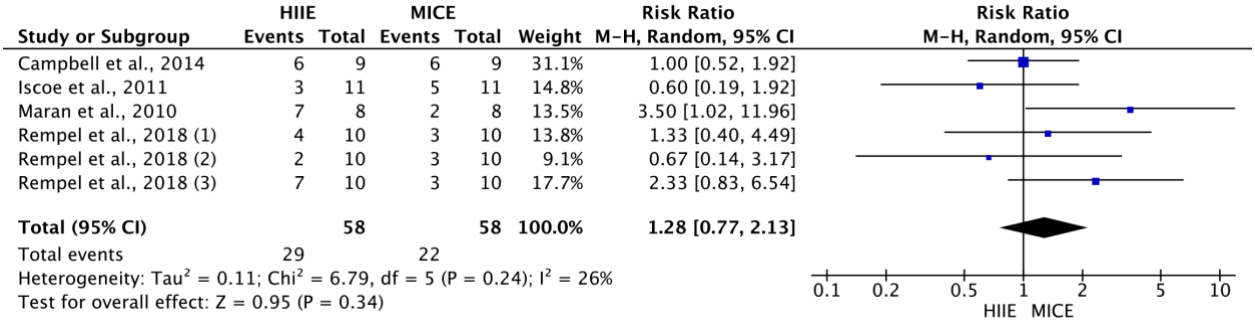

Figure 3.13 Meta-analysis of participants (n) who experienced nocturnal hypoglycemic events in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE)

Taleb et al. reported the percent time spent in hyperglycemia during exercise and in the immediate recovery stage (165), Bally et al., Lee et al., Scott et al. and Zaharieva et al. reported time or percent time spent in nocturnal hypoglycemia (160; 168; 180; 182). Campbell et al. and Scott et al. reported time or percentage time spent in hypoglycemia over 24 h post-exercise (167; 180). The pooled meta-analysis of these studies yielded a non-significant difference between the two arms in percent time spent in hypoglycemia (ES 1.48, 95% CI −0.59 to 3.54; $p = 0.16$) (Figure 3.14). No significant heterogeneity among these studies was detected ($I^2 = 0\%$; $Q = 7.41$, $df = 9$, $p = 0.59$).

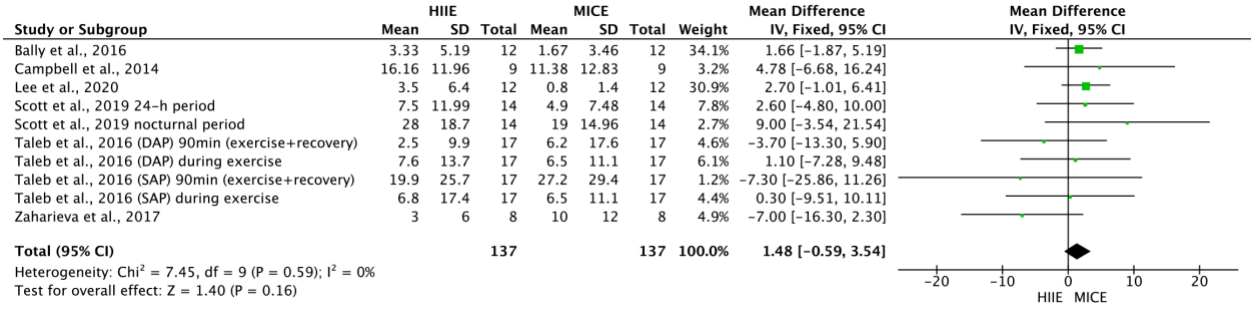

Figure 3.14 Meta-analysis of percentage of time spent in hypoglycemia in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE)

Hyperglycemia reported in most included studies was fasting blood glucose concentration of $\geqslant$ 7 mmol·L^{-1}and/or postprandial blood glucose $\geqslant$ 10 or 11 mmol·L^{-1}. Taleb et al. reported percentage time spent in hyperglycemia during exercise and in the immediate recovery stage (165), Bally et al., Lee et al., Scott et al. and Zaharieva et al. reported time or percentage time spent in nocturnal hyperglycemia (160; 168; 180; 182), Campbell et al., Lee et al., Scott et al. also reported time or percentage time spent in hyperglycemia over 24 h post-exercise (167; 168; 180). These data were pooled for meta-analysis and did not show a significant difference in percentage time spent in hyperglycemia between HIIE and MICE (ES −3.37, 95% CI −8.95 to 2.20; p = 0.24) (Figure 3.15). No significant heterogeneity among these studies was detected (I^2 = 0%; Q = 1.29, df = 8, p = 0.24).

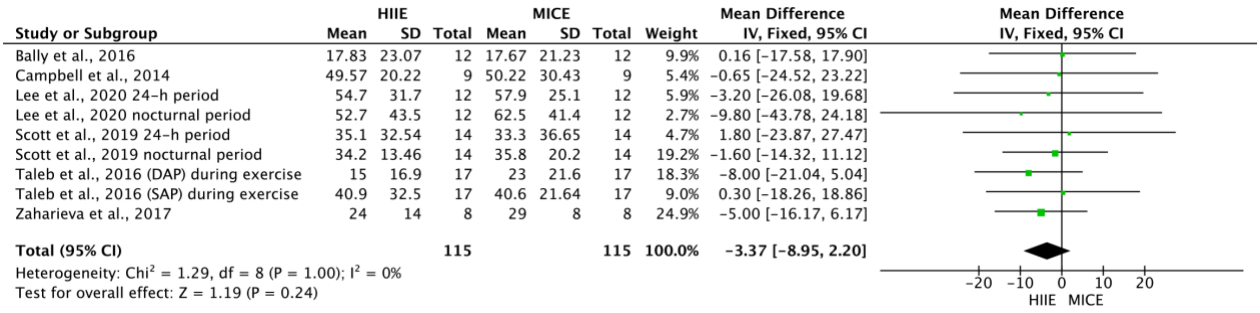

Figure 3.15 Meta-analysis of percentage of time spent in hyperglycemia in response to high-intensity interval exercise (HIIE) versus moderate-intensity continuous exercise (MICE)

3.4 Discussion

This systematic review and meta-analysis provided a comprehensive overview of metabolic and hormonal responses to MICE versus HIIE in individuals with T1D. To our knowledge, this is the first published meta-analysis quantifying the metabolic, hormonal responses, and adverse events in individuals living with T1D during exercise, in early recovery stage, and in the nocturnal period post-exercise. More specifically, the main results of our meta-analysis indicate the decline in blood glucose levels is less with HIIE compared with MICE in individuals with T1D and this is paralleled by increased levels of counter-regulatory hormones (mainly growth hormone and catecholamines), as well as substantially higher levels of lactate during HIIE. Moreover, the proportions of participants experiencing early-onset hypoglycemic events during HIIE exercise was lower than MICE. However, no significant difference was found with respect to the proportions of participants experiencing nocturnal hypoglycemic events, or percentage of time spent in hypoglycemia and hyperglycemia. Collectively, these findings reinforce the importance of understanding the metabolic and hormonal responses to exercise in the prevention of exercise-induced hypoglycemia.

This meta-analysis showed that blood glucose levels were 0.62 $mmol \cdot L^{-1}$ higher during the HIIE condition compared with the MICE condition, and the decline was 0.73 $mmol \cdot L^{-1}$ lower during HIIE compared with MICE. These results are in concordance with the glucose changes during exercise as reported by Guelfi et al. (51; 178) and Campbell et al. (167). The smaller decline in blood glucose levels with HIIE could be attributed to a greater increment in endogenous glucose production and attenuated glucose utilization. Guelfi et al. found that HIIE stimulated a more rapid and greater magnitude of increase in glucose production during exercise compared with the MICE session, whereas the increase in glucose utilization during HIIE was similar to MICE. Immediately

after exercise, glucose utilization rapidly declined after HIIE, while it remained elevated after MICE (51). Moreover, Campbell et al. suggested that the elevations in lactate concentrations during HIIE could serve to increase gluconeogenesis from baseline for 60 min post-exercise, and likely contributed to the attenuated decline in glucose (167).

The blood lactate levels during exercise in our meta-analysis were significantly higher, (2.41 mmol·L $^{-1}$), in response to HIIE versus MICE, supporting the results of other studies (160; 161; 164; 167; 176; 177). Furthermore, the increased of blood lactate was greater with HIIE compared with MICE (51; 170; 178). Campbell et al. suggested that the elevated lactate levels may contribute to attenuating the rates of blood glucose decline during HIIE and in early recovery by inhibiting the action of insulin on peripheral glucose uptake in skeletal muscle and increasing the production of glucose via hepatic gluconeogenesis (167).

This meta-analysis showed that there was no significant difference in circulating free insulin levels during exercise between HIIE and MICE, supporting the results of other studies (160; 176-178). In persons without T1D, insulin release from pancreatic β-cells decreases and glucagon secretion increases during MICE to ensure adequate fatty acids and glucose to fuel working muscles (186). For individuals with T1D, the destruction of the insulin-producing β-cells necessitates exogenous insulin. Thus, circulating insulin levels cannot be regulated endogenously and depend on the quantity and timing of insulin taken. Insulin levels are higher in individuals with T1D than individuals without T1D during MICE (169), which would result in limiting glucose production by the liver while stimulating glucose uptake by muscle, adipose, and liver cells for storage. Mallad et al. showed that reduced glucose levels in individuals with T1D is primarily due to the body's inability to lower circulating insulin levels (187). As a result, hypoglycemia is a

common occurrence with MICE unless insulin dosages are reduced appropriately or additional carbohydrates are supplemented before, during, or after exercise (87).

Growth hormone promotes lipolysis, potentially decreasing the body's reliance on circulating glucose. It is reported that HIIE can also increase growth hormone levels to a greater extent than MICE in T1D (51; 160; 178), which is consistent with the findings of this meta-analysis. Increasing the circulation of growth hormones in the blood would be associated with inhibition of insulin-mediated glucose uptake and attenuated declines in blood glucose levels (178). Guelfi et al. suggested that the attenuated declines in blood glucose levels in HIIE were attributed to the repeated bouts of HIIE stimulating a large increment in the levels of catecholamines and growth hormone (51). Similarly, Bally, Zueger et al. suggested HIIE induced a strong and persistent increase in catecholamines and growth hormone, and the high levels of growth hormone are associated with a comparably rapid reduction of peripheral glucose uptake and increased levels of catecholamines may also antagonize insulin-mediated glucose uptake in skeletal muscle (160). Additionally, Adolfsson et al. reported that growth hormone was 2.5-fold higher and 10-fold higher during and 30 min after HIIE than responses to MICE in individuals with T1D respectively (169). Similar findings have also been reported previously during both exercise and early recovery (161; 164). These meta-analyses are in agreement with the findings above and indicate that the increase in the circulating levels of growth hormones and catecholamines induced by HIIE may result in decreasing glucose uptake which contribute to the lesser decline of blood glucose compared with MICE.

These meta-analysis results indicate that HIIE carries a lower rate of early-onset hypoglycemia than MICE and that the rate of nocturnal hypoglycemia, the percentage time spent in hypoglycemia and hyperglycemia, were comparable between these two exercise modes. This suggests that individuals with T1D engaging in HIIE may be at a lower risk of early-onset

hypoglycemia without causing a higher occurrence of hyperglycemia and nocturnal hypoglycemia than those partaking in MICE. However, two studies reported that nocturnal hypoglycemia occurred more frequently after HIIE than MICE (177; 181). The evidence of the relative effect of HIIE and MICE on individuals' risk of experiencing hypoglycemic events is inconsistent. The reasons for the discrepancy in findings are unclear, but may be related to the age, gender, and physical fitness levels of the participants (188). In fact, metabolic and hormonal response to exercise in adult differs from children and adolescents (189), and hormonal response to exercise is higher in females than in males (190), but lower in untrained individuals compared with trained individuals (191).

Regular exercise is an important and integral component for effective treatment of T1D, as it is associated with numerous physiological benefits (192). However, glycemic management of exercise for individuals with T1D requires careful control, as it may require frequent glucose monitoring, insulin dosage adjustments, and carbohydrate intake modification before, during, and following exercise. Furthermore, determinants of the direction (increase/decrease) and magnitude of the glycemic response to exercise are varied and based on several factors, including the exercise duration and intensity (low vs. moderate or high intensity), individual characteristics (the effect of aerobic fitness to increase insulin sensitivity, and endogenous insulin sensitivity), and contextual factors (pre-exercise blood glucose level, insulin- and carbohydrates-on-board, and concentration of counter regulatory hormones) (193).

The SBGM used in previous studies often limited the follow-up period to a few hours post-exercise. Continuous glucose monitoring (CGM) has emerged in the last ten years as a valuable tool to monitor the glycemic response up to 24 h or more after exercise in individuals with T1D. Moreover, exercise-induced hypoglycemia can be managed by adjusting the dosage of exogenous

insulin and nutritional intake to maintain blood glucose levels in the target range before, during, and after exercise.

3.5 Strengths and Limitations

We performed a comprehensive literature search and systematic literature review and identified 17 crossover studies as relevant to our meta-analysis. Whilst this meta-analysis provides useful updated information for health-care workers and exercise professionals who work with individuals with T1D on managing blood glucose around HIIE and MICE, the results should be considered with the following limitations. First, most meta-analyses had substantial to considerable heterogeneity, our sensitivity analyses attempted to identify studies for heterogeneity and reduced heterogeneity. We could not carry out subgroup analyses of adults and adolescents, and males and females due to the small number of studies and insufficient data. Second, from the current findings, it is not clear which is the best strategy (insulin dosage modification, carbohydrate adjustments, or a combination of both) for prevention of hypoglycemic events during and following exercise. Fifteen to twenty grams of carbohydrate supplementation before exercise may be useful to prevent hypoglycemia but may also promote hyperglycemia during exercise. Carbohydrate intake is needed if blood glucose levels presented below 4 $mmol \cdot L^{-1}$. A twenty-five to seventy five percent bolus insulin reduction depending on exercise intensity and duration was recommended to avoid hypoglycemia before or after exercise.

However, these recommendations should be considered with limitations as there are many variabilities between different study designs including type of exercise and time of exercise. Therefore, more standardization of protocols is needed for the evaluation of the effects of HIIE versus MICE in persons with T1D. Furthermore, there was high interindividual variability in blood glucose responses to exercise and a small number of participants in each included study. These extensive variabilities make recommendations challenging. Thus, the insulin adjustment and

carbohydrate strategies recommended in these included studies should be taken simply as starting points. Specificity of each variable-related intervention is required to see beneficial metabolic controls of HIIE and T1D, and to provide evidence-based carbohydrate and insulin recommendations specifically designed for HIIE for individuals with T1D. Future research using larger sample sizes should carefully examine the minimal and optimal dosages of carbohydrate and insulin requirements for health benefits in persons living with T1D. In particular, additional research is warranted that more closely examines the relationships between carbohydrate/insulin volumes and glycemia control, and hypo/hyperglycemia before, during, after HIIE and MICE.

3.6 Conclusions

Our findings support the idea that acute increases in the circulating levels of growth hormones and catecholamines induced by HIIE may result in decreased glucose uptake, which contributes to less of a decline in blood glucose compared with MICE. High-intensity interval exercise may carry a lower risk of early-onset hypoglycemia without causing higher occurrence of hyperglycemia and nocturnal hypoglycemia than MICE. However, these effects were not clearly detectable from heterogeneity. Further examination using larger sample size of the minimal and optimal dosages of carbohydrate and insulin requirements is needed with greater standardization of exercise protocols for health benefits in persons living with T1D is necessary.

Chapter 4: Association between Physical Activity Level and Cardiovascular Risk Factors in Adolescents Living with Type 1 Diabetes: A Cross-sectional Study

4.1 Background

Type 1 diabetes is associated with high risk of microvascular and macrovascular complications, as well as other (CVD) risk factors, including obesity, hypertension, hyperglycemia, dyslipidemia, insulin resistance, and physical inactivity (18). Cardiovascular disease is the most frequent cause of premature death and disability in this population (194). In fact, the childhood-onset of T1D has been associated with a higher risk of developing CVD in adulthood when compared with the general population (195). In a cross-sectional study, 76% of children and adolescents with T1D were found to have one or more risk factors for CVD (i.e., obesity, hypertension, hyperglycemia, or dyslipidemia) and have a much higher prevalence of cardiovascular risk factors compared to non-diabetic individuals (196). There is an urgent need for prevention and treatment strategies to reduce CVD risk factors in children and youth living with T1D.

One recent systematic review and meta-analysis showed that exercise training can decrease risk factors for CVD by improving cardiovascular fitness and lipid profiles in individuals living with T1D (18). Furthermore, the review also demonstrated that exercise training can reduce the severity of CVD risk factors (such as obesity and body composition, high blood pressure, and worsened lipid lipoprotein profile) (18). The American College of Sports Medicine (ACSM) guidelines for exercise testing and prescription recommend that individuals living with T1D undertake 150 min of exercise at 40 - 59% of their oxygen uptake reserve (VO_2R) or 75 mins of

vigorous intensity exercise (60% - 89%VO_2R) per week, or 30 min or more of daily low to moderate intensity physical activity participation (155). Moreover, the 2018 Diabetes Canada clinical practice guidelines recommend that even smaller amounts of physical activity can provide some health benefits (197).

Despite the clear potential health benefits, individuals living with T1D may fear or be discouraged from regular physical activity participation due to the lack of adequate knowledge about exercise management and concerns of hypoglycemic episodes (39). According to a large German and Austrian study of self-reported physical activity, 82.7% of youth aged 3-18 years with T1D did not meet daily physical activity recommendations and regular physical activity was linked with a beneficial CVD risk profile (198). In a Canadian study, adolescents with T1D, surveyed using the Habitual Activity Estimation Scale, were shown to spend more time being less active than their peers without T1D and physical activity was associated with improved CVD risk profile (199). However, these studies have significant limitations: firstly, objective assessments of physical activity such as continuous heart rate monitoring and triaxial accelerometry (activity monitors that measure position and motion) provide more valid data than self-reports of physical activity (200). Secondly, these observational studies have focused on largely adult Caucasian populations, and CVD risk factors may vary between ethnic groups. One recent study found that African immigrants had lower rates of age-standardized hypertension, diabetes mellitus, overweight/obesity, high cholesterol, and prevalent smoking than African Americans (201). Collectively, there is limited research examining the relationships between objectively measured physical activity and CVD risk profile, particularly among Chinese youth living with T1D.

Accordingly, the primary objective of this study was to assess CVD risk factors in Chinese youth living with T1D in comparison with apparently healthy peers not living with T1D. The

second objective was to evaluate the relationship between objectively measured daily physical activity levels and markers of CVD. We hypothesized that the CVD risk profile (blood pressure, lipid profile, physical fitness) in youth with T1D would be proatherogenic compared with the profile of apparently healthy peers without diabetes, and that higher physical activity levels would be associated with improved CVD risk factors among Chinese youth with T1D.

4.2 Methods

4.2.1 Study design and participants

We conducted a cross-sectional study including 48 adolescents living with T1D (World Health Organization (WHO) criteria) and 19 apparently healthy peers without diabetes (aged 12-17 years). The participants with T1D were all Chinese recruited via snowball sampling, and social media. Individuals living with T1D for at least 6 months with HbA1c greater than or equal to 7.5% in the last three months, with normal renal function, and free from previous CVD and chronic kidney disease were eligible for participation. Participants with significant diabetic complications (diabetic foot, retinopathy, severe neuropathy), uncontrolled hypertension, diabetic keto-acidosis, CVD (defined as any form of clinical coronary heart disease, stroke or peripheral vascular disease), severe hypoglycemia episodes within the past 3 months were excluded. Participants on lipid lowering therapy were also excluded.

Peers without diabetes (apparently healthy) participants were recruited from local schools via snowball sampling and were selected to match the diabetic group in age and sex distribution. This apparently healthy group had no known history of chronic disease and no clinical or laboratory evidence of hypertension, cardiac disease, or other problems that would have contraindicated or limited their participation in regular physical activity. Participants that took any medications, which could influence cardiovascular function, lipid lipoprotein profiles, and/or glucose metabolism were excluded from study.

Recruitment of adolescents with T1D was done via advertisements in social media platform (e.g., Diabetes WeChat groups), by distributing initial letters to the individuals with T1D who visited local hospitals, and via snowball sampling. A total of 88 individuals with T1D aged 12-17 years were recruited for this study, and nine of whom had one or more exclusion criteria were excluded. Seventy-nine participants were eligible for participation and 48 consented to participate the study. In total, 67 participants were included, of which 48 had T1D and 19 participants were peers without diabetes.

4.2.2 Anthropometric measurements

Height was measured in bare feet to the nearest 0.1 cm using a wall-mounted stadiometer. Body mass was measured in light clothing to the nearest 0.1 kg using BC-418 segmental body composition analyzer (Tanita, Tokyo, Japan). Body mass index was calculated as weight (kg) divided by height squared (m^2) and adjusted for age and sex to give a BMI standard deviation score (BMI z-score). BMI z-score was calculated using the WHO Reference 2007 growth data for the age group 5-19 years with SPSS software (https://www.who.int/growthref/tools/en/). Waist circumference was measured in triplicate with a flexible tape at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest following WHO guidance (202). Blood pressure was measured after 10 min of rest in the seated position and the average of three measurements taken one minute apart was used in the analysis. The cuff was chosen to be of the appropriate size for the participant's upper arm, with a bladder width that is at least 40% of the arm circumference at a point midway between the olecranon and the acromion and a bladder length to cover 80-100% of the circumference of the arm.

4.2.3 Body composition assessment

Body composition measurements were performed by dual energy X-ray absorptiometry (DXA) using the iDXA instrument (GE Medical Systems, Madison, WI) with Encore 2011 software (version 13.6). All study participants underwent a whole-body scan (Lunar iDXA, GE Healthcare, WI), in which the participant was placed in the supine position, centralized in the DXA scan table.

4.2.4 Puberty and diabetes assessment

Puberty was assessed via a validated self-report questionnaire using pubertal staging images and the children were categorized as prepubertal (Tanner 1), in early puberty (Tanner 2), mid puberty (Tanner 3-4) or post puberty (Tanner 5) (203). This questionnaire has been validated in Chinese children (204). Participants living with T1D were asked to complete questionnaires (Appendix C, D, E) upon arrival at the testing location, which included: diabetes history, age, duration of diabetes, complications, insulin regimen, medications, and physical activity levels. Peers without T1D were asked to complete a questionnaire about their medical history and physical levels (Appendix C, D).

4.2.5 Biochemical investigations

All participants were studied after a 12-h overnight fast and, in the case of T1D individuals, before their morning insulin injections. Fasting capillary (fingertip) blood glucose samples were taken for analysis of HbA1c, total cholesterol, LDL-C, HDL-C, and triglycerides. Total cholesterol, LDL-C, HDL-C and triglycerides were analyzed using the Cardiochek PA Blood Analyser (Polymer Technology Systems Inc., Indianapolis, IN, USA) and HbA1c were

analyzed using the A1cNow+ (Metrika Inc., Sunnyvale, CA, USA). Both devices have been validated previously (205; 206).

4.2.6 Physical activity assessment

Physical activity levels were objectively measured (24 h per day) using triaxial accelerometers (wGT3x-BT ActiGraph LLC, Pensacola, FL, USA). Participants were asked to wear the accelerometers on their non-dominant wrist for seven consecutive days (5 weekdays), except in the water, as the device is water-resistant, but not waterproof. We collected data at 50 Hz, as this sampling frequency has shown to sufficiently capture body movement and allow for five weekdays and two weekend days of data collection (207). Participants were given a paper calendar-style tracking log on which they were instructed to write down the time they put the accelerometer on and the time they removed it in order to support wear-time compliance.

Data were downloaded with the manufacturer's software (ActiLife Version 6) and processed using 60-s epochs to derive the following daily physical activity parameters: metabolic equivalent of task (METs, $kcal \cdot h^{-1} \cdot kg^{-1}$; as an index of the intensity of activities), total daily physical activity counts (CPM), the percentage of time spent in sedentary behaviour, daily average time spent in light intensity physical activity, daily average time spent in moderate-to-vigorous intensity physical activity (MVPA), and the percentage of time spent in MVPA. Sedentary behaviour period ($\leq$ 100 CPM), light intensity physical activity (101-2295 CPM), moderate intensity physical activity (2296-4011 CPM) and vigorous intensity physical activity ($\geq$ 4012 CPM) established cut-offs were used (208). Moderate-to-vigorous intensity physical activity time accumulated in bouts (prolonged periods) of 10 or more consecutive min following physical activity guidelines was also derived (209). Sedentary time accumulated in bouts of 20 or more consecutive min, which has been shown to have a negative effect on cardio-metabolic biomarkers

(210), was also derived. The non-wear period was defined as a minimum of 60 min of continuous zero counts according to ActiLife's default option and at least 600 min of wear time per day without excessive counts (> 20,000 CPM) was required to be considered valid (211). At least three valid wear days were required to be included in the analysis.

Resting energy expenditure was estimated from accelerometer counts and age-specific prediction equations to derive the metabolic equivalent of MET intensity levels. The equation was: METs = 2.757 + (0.0015*CPM) – (0.08957*age) – (0.000038*CPM*age) (212).

4.2.7 Physical fitness assessment

Participants were screened for any cardiovascular complications and the readiness for exercise testing using the Physical Activity Readiness Questionnaire for Everyone (PAR-Q+) (213) prior to physical fitness test. The Leger 20-metre shuttle run test was used for aerobic fitness assessment. The frequency of the sound signals increased in such a way that running speed was increased by 0.5 $km \cdot h^{-1}$ each min from a starting speed of 8.5 $km \cdot h^{-1}$. The test stopped when the participants were no longer able to follow the set pace. If participants experienced hypoglycemia during their laboratory stay, a 15 g carbohydrate bolus was administered (Glucose drinks, Henan Three Connaught food Co., LTD, China). Hypoglycemia was defined as a blood glucose concentration of ≤ 3.9 $mmol \cdot L^{-1}$ and hyperglycemia ≥ 10.9 $mmol \cdot L^{-1}$ (214).

4.2.8 Statistical analysis

All statistical analyses were performed using the SPSS 20 for Windows (Statistical Package for the Social Sciences, IBM Corp., Armonk, N.Y., USA). Data were screened for normal distribution. The chi-square test was used for comparison of proportion (categorical variable including sex and pubertal status) between groups, and independent-samples t-tests were used for

comparison of the continuous variables (i.e., age, height, body mass, body composition, BMI, cardiovascular risk factors and daily physical activity variables) between groups. Cohen's d effect size was calculated for t-tests and described as small (d = 0.2), moderate (d = 0.5) and large (d = 0.8) based on benchmarks suggested by Cohen (215). We included BMI z-score as a covariate in an analysis of covariance (ANCOVA) for statistical differences between groups by reducing the error variance because BMI z-score correlates with the blood pressure, daily physical activity variables, lipid profiles, and aerobic fitness. The non-parametric test (Mann-Whitney) was used to compare time spent in MVPA and the percentage of time in MVPA among groups as the distributions were not normal. Effect size statistic for the Mann-Whitney test is r, which was calculated by dividing Z by the square root of total number of samples ($r = Z/\sqrt{N}$) and described as small (r = 0.1), moderate (r = 0.3) and large (r = 0.5). Results were summarized using means and standard deviation (SD) for normally distributed variables, medians and 25-75th quartile for non-normally distributed variables and using frequencies and percentages for categorical variables.

The associations between aerobic fitness, daily physical activity variables and cardiovascular risk factors were assessed with univariate linear regression analysis (Step 1) in T1D group and apparently healthy peers without diabetes, and multivariate linear regression analysis (Step 2) adjusting for age, sex, insulin treatment, and pubertal stage in individuals with T1D and adjusting for age, sex, and pubertal stage in apparently healthy peers not living with diabetes. The probability was considered to be statistically significant at p value < 0.05.

4.3 Results

The demographic characteristics and laboratory results of individuals with T1D and apparently healthy peers without diabetes are presented in Table 4.1. Specific descriptive data in

youth with T1D are presented in Table 4.2. No significant differences were shown between groups for age, sex, pubertal stage, body fat percentage, BMI, waist circumference, and blood pressure (all $p > 0.05$). T1D participants showed significantly higher values of total cholesterol (4.03 ± 0.81 vs. 3.14 ± 0.67 mmol·L^{-1}, $p = 0.001$, d = 1.20), LDL-C (2.31 ± 0.72 vs. 1.74 ± 0.38 mmol·L^{-1}, $p = 0.035$, d = 0.99), triglycerides (0.89 ± 0.31 vs. 0.60 ± 0.40 mmol·L^{-1}, $p = 0.012$, d = 0.81) compared to apparently healthy peers without diabetes. The BMI z-score was significantly lower in individuals with T1D than their peers without T1D (−0.27 ± 1.16 vs. 0.50 ± 1.01, $p = 0.018$). However, the body fat percent in T1D was higher than peers without T1D (29.08 ± 9.54 vs. 28.42 ± 6.61 %, $p = 0.084$), although this is only trended towards a significant difference.

Individuals living with T1D had significantly lower maximal aerobic power (VO_2max) (35.48 ± 8.72 vs. 44.43 ± 8.29 mL·kg^{-1}·min^{-1}, $p = 0.003$, d = 1.05), total daily physical activity counts (346.87 ± 101.97 vs. 451.01 ± 133.52 CPM, $p = 0.004$, d = 0.88), and daily light physical activity (335.93 ± 120.16 vs. 449.33 ± 89.55 min, $p = 0.002$, d = 1.07), while higher percentage of time spent in sedentary behaviour (36.34 ± 11.04 vs. 28.86 ± 12.56, $p = 0.04$, d = 0.63) compared with healthy participants. In persons living with T1D, median MVPA [(53.19 (35.68 - 63.16) vs 89.57 (61.00 - 124.14) min, $p = 0.001$, r = 0.40] and median percentage of time spent in MVPA [(8.56 (6.18 - 10.12) vs 11.91 (7.74 - 16.22) %, $p = 0.038$, r = 0.25] were significantly lower compared to apparently healthy peers without diabetes. Because of the observed differences in BMI z-score, the *p* value of main outcomes adjusted for the differences were also calculated (Table 4.1). ANCOVA of controlling BMI z-score did not impact the overall significance of the main outcomes between two groups (Table 4.1).

Table 4.1 Comparison of descriptive data between young people with T1D and apparently healthy peers without T1D

	T1D (n = 48)		Peers without diabetes (n = 19)			
	Mean	SD	Mean	SD	*p*	Adjusted *p*
Sex (male/ female) (%)	37.5/62.5		42.1/57.9		0.129	
Pubertal stage (n)					0.543	
Stage 1 (Not started)	18		7			
Stage 2 (Barely started)	8		1			
Stage 3 (Definitely underway)	12		6			
Stage 4 (Seems completed)	5		1			
Stage 5 (Completed)	5		4			
Ages (y)	14.0	2.9	13.6	3.5	0.601	
Body mass (kg)	49.48	12.56	52.34	15.45	0.452	
Height (m)	1.60	0.13	1.59	0.13	0.772	
BMI ($kg \cdot m^{-2}$)	18.97	3.10	20.38	3.32	0.119	
BMI z-score	−0.27	1.16	0.50	1.01	0.018*	
Body fat (%)	29.28	9.54	28.42	6.61	0.765	0.084
Waist circumference (cm)	67.63	7.96	73.65	8.22	0.055	0.151
Systolic blood pressure (mmHg)	106.07	16.72	107.07	15.45	0.837	0.778
Diastolic blood pressure (mmHg)	65.24	11.65	65.75	9.88	0.878	0.821
Total cholesterol ($mmol \cdot L^{-1}$)	4.03	0.81	3.14	0.67	0.001*	0.001
HDL-C ($mmol \cdot L^{-1}$)	1.48	0.28	1.29	0.42	0.078	0.184
LDL-C ($mmol \cdot L^{-1}$)	2.31	0.72	1.74	0.38	0.005*	0.008
Triglycerides ($mmol \cdot L^{-1}$)	0.89	0.31	0.60	0.40	0.012*	0.007
Estimated VO_2max ($mL \cdot kg^{-1} \cdot min^{-1}$）	35.48	8.72	44.43	8.29	0.003*	0.003
METs ($kcal \cdot h^{-1} \cdot kg^{-1}$) ‡	2.09	0.41	2.41	0.60	0.066	0.075
Physical activity counts (CPM)‡	346.87	101.97	451.01	133.52	0.004*	0.033
Light physical activity ($min \cdot day^{-1}$) ‡	335.93	120.16	449.33	89.55	0.002*	0.003
Percentage of time spent in Sedentary behaviour (%)‡	36.34	11.04	28.86	12.56	0.04*	0.095

Data are presented as means and standard deviation (SD). T1D, type 1 diabetes; n, number; y, year; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VO_2max, maximal aerobic power; METs, metabolic equivalent; CPM, counts-per-minute; adjusted *p*, ANCOVA adjusted for BMI z-score. *Statistically significant difference ($p < 0.05$) between T1D and apparently healthy peers without diabetes; ‡ Sixteen of 19 apparently healthy participants not living with diabetes and 40 of 48 participants with T1D had valid physical activity data.

Table 4.2 Specific descriptive data in young people living with T1D

	Type 1 diabetes (n = 48)	
	Mean	SD
Diabetes duration (y)	3.6	2.3
Pubertal Stage (n)		
Prepubertal (Tanner 1)	18	
Early puberty (Tanner 2)	8	
Mid-puberty (Tanner 3-4)	17	
Post-puberty (Tanner 5)	5	
MDI	30	
CSII	18	
CGM	26	
SMBG	22	
HbA1c ($mmol \cdot mol^{-1}$)	61	9
HbA1c (%)	7.70	2.47
Insulin dose ($unit \cdot kg^{-1} \cdot day^{-1}$)	0.87	0.29

Data are presented as means and standard deviation (SD); MDI, multiple daily injection; CSII, continuous subcutaneous insulin infusion; CGM, Continuous Glucose Monitoring; SMBG, self-monitoring of blood glucose; HbA1c, Glycosylated hemoglobin.

We investigated the within-group relationships between CVD risk factors (blood pressure, HbA1c, HDL-C, LDL-C, total cholesterol, and triglycerides) and physical fitness or daily physical activity variables with bivariate analysis. For participants with T1D, the METs correlated positively with HDL-C (r = 0.410, p = 0.030) and negatively with triglycerides (r = −0.456, p = 0.015) (Table 4.3). Also, there is a significant correlation between triglycerides and time spent in sedentary behaviour (r = 0.395, p = 0.041), and physical activity counts (r = −0.453, p = 0.018) (Table 4.3). No similar relationships were shown in healthy participants ($p > 0.05$).

Table 4.3 Correlation between cardiovascular risk factors and daily physical activity variables in young people living with T1D

		(1)	(2)	(3)	(4)	(5)
(1) HDL−C	Pearson's r	—				
	p	—				
(2) Triglycerides	Pearson's r	−0.450	—			
	p	0.010*	—			
(3) METs	Pearson's r	0.410	−0.456	—		
	p	0.030*	0.015*	—		
(4) Physical activity counts	Pearson's r	0.331	−0.453	0.837	—	
	p	0.091	0.018*	0.000*	—	—
(5) Time spent in sedentary behavior	Pearson's r	−0.254	0.395	−0.509	−0.446	—
	p	0.201	0.041*	0.003*	0.010*	—

HDL-C, high-density lipoprotein cholesterol; METs, metabolic equivalents; *Statistically significant difference ($p < 0.05$).

Linear regression models are presented in Table 4.4 and showed that HDL-C in persons with T1D were positively associated with METs (β = 0.29, $p = 0.030$, model $R^2 = 0.168$), but the results changed after adjusting for age, sex, pubertal stage, BMI z-score (β = 0.305, $p = 0.195$, model $R^2 = 0.54$). Linear regression models adjusted for age, sex, pubertal stage, BMI z-score, and insulin treatment showed that there was a trend for a negative association between HDL-C in T1D and time spent in sedentary behaviour (β = -0.002, $p = 0.060$, model $R^2 = 0.597$). HDL-C in apparently healthy peers without diabetes was not significantly associated with daily physical activity variables and VO_2max. Triglycerides were negatively associated with daily physical activity counts (β = −0.001, $p = 0.018$, model $R^2 = 0.205$) and METs (β = −0.359, $p = 0.015$, model $R^2 = 0.208$), positively associated with time spent in sedentary behaviour (β = 0.002, $p = 0.041$, model $R^2 = 0.156$) in persons with T1D, but the results changed to non-significance after adjusting for age, sex, pubertal stage, and BMI z-score (Table 4.5).

Table 4.4 Linear regression model examining the association between HDL-C and physical activity variables after adjusting by potential confounders in young people living with T1D

	dependent variable: HDL-C					
Independent variables	β	95%CI		*p*	Adjusted R^2	R^2
METs (kcal·h^{-1}·kg^{-1})						
Step 1 (unadjusted)	0.290	0.030	0.551	0.030	0.136	0.168
Step 2 (adjusted†)	0.305	−0.172	0.781	0.195	0.537	0.305
Sedentary behaviour (min·day^{-1})						
Step 1 (unadjusted)	−0.001	−0.003	0.001	0.201	0.027	0.065
Step 2 (adjusted†)	−0.002	−0.003	0.000	0.060	0.383	0.597

METs, metabolic equivalents; HDL-C, high-density lipoprotein cholesterol; β, estimated value; CI, confidence interval; R^2, coefficient of determinations; † adjusted for age, sex, insulin treatment, and pubertal stage

Table 4.5 Linear regression model examining the association between triglycerides and physical activity variables after adjusting by potential confounders in young people living with T1D

	dependent variable: Triglycerides					
Independent variables	β	95%CI		*p*	Adjusted R^2	R^2
Physical activity counts (CPM)						
Step 1 (unadjusted)	−0.001	−0.003	0.000	0.018	0.173	0.205
Step 2(adjusted †)	−0.001	−0.002	0.001	0.344	0.178	0.463
METs ($kcal \cdot h^{-1} \cdot kg^{-1}$)						
Step 1 (unadjusted)	−0.359	−0.641	−0.077	0.015	0.178	0.208
Step 2(adjusted†)	−0.272	−0.839	0.295	0.326	0.202	0.468
Sedentary behaviour ($min \cdot day^{-1}$)						
Step 1 (unadjusted)	0.002	0.000	0.003	0.041	0.122	0.156
Step 2(adjusted†)	0.001	−0.001	0.003	0.299	0.187	0.468

CPM, counts-per-minute; METs, metabolic equivalents; β, estimated value; CI, confidence interval; R^2, coefficient of determinations; † adjusted for age, sex, insulin treatment, and pubertal stage

4.4 Discussion

Similar to the finding in other ethnicities (198; 199), increased levels of risk factors for CVD were found in Chinese youth living with T1D compared with peers without diabetes. A significant correlation among physical activity levels and components of lipid profile was found including confounders of age, sex, pubertal stage, BMI z-score, and insulin treatment. Our findings emphasize the importance of promoting daily physical activity among youth living with T1D.

The SEARCH study showed that the prevalence of overweight children and adolescents (aged 3-19 years) with T1D was higher than those without diabetes (22.1% vs. 16.1%) (14). Conversely, the Norwegian Study Group reported a lower prevalence of obesity (4.4%), possibly due to the younger age and ethnicity and life-style difference (216). Similarly, there was only one out of 48 participants living with T1D who was overweight in our study, and the BMI z-score is lower in diabetic group than non-diabetic group. These findings, though, are often misunderstood and may lead one to believe that those living with T1D with low BMIs are not at risk for developing CVD. In our study, we found that body fat percentage tended to be higher in the T1D group compared to the non T1D group, but not significantly ($p = 0.084$). In a previous study, it was shown that individuals with a normal BMI and high body fat percentage demonstrated a high prevalence

of high blood pressure, hyperglycemia, and dyslipidemia (217). Therefore, even our T1D participants with a normal BMI could have a greater risk of developing these other CVD risk factors because of their above-average body fat percentage. This is likely ascribed to parent's knowledge, beliefs, and fear about diabetes. For example, we learned from our participants reported experiences that their parents limited their food intake to reduce insulin doses, because their parents believe that there are too many side-effects of insulin. Diabetes education and training to parents and individuals with T1D, especially outside of major urban areas, are still inadequate in China. Future research is warranted to confirm this finding.

A large proportion (45%) of T1D individuals are exposed to a high risk of early all-cause mortality and premature cardiovascular disease (218; 219). Adults living with T1D have a high prevalence of dyslipidemia (8; 220). Youth with T1D have proteomic alterations in their HDL compared to peers without diabetes and are at increased risk of CVD (221). Corroborating this, our results showed that youth living with T1D had increased total cholesterol, LDL-C, and triglycerides compared to apparently healthy peers without diabetes. Similarly, a previous study showed that youth with T1D (aged 5-15 years) had elevated values of total cholesterol and LDL-C compared to peers without diabetes (222). Lipids levels are very important in predicting adverse cardiovascular outcomes (136). Previous studies showed that LDL-C independently correlated with abnormal plethysmography responses (23), endothelial dysfunction (223), cIMT (224), and aIMT (225) in youth living with T1D. Moreover, Katz et al showed lack of knowledge and parental concerns regarding controlling blood pressure and lipid levels at a young age as patient-related reasons for undertreatment of CVD risk factors in youth with T1D (226). Of note, the median duration of diabetes in our study was less than four years, which suggests that the functional changes in lipid profiles start very early in the course of the disease and likely deteriorate over time, previous studies have similarly demonstrated atherogenic lipoprotein profiles in youth with

a short duration of diabetes (220), which highlights the importance of optimizing the management of T1D for lifelong habits and increases awareness of early treatment of CVD risk factors in youth with T1D.

The management of T1D is challenging as individuals with T1D must strategically manage their insulin administration, carbohydrate intake, ketones, exercise, and possible other hormones to maintain their blood glucose levels in the target range (227). Regular exercise is an important and integral component of effective treatment of T1D, but glycemic management of exercise is particularly difficult for individuals with T1D because determinants of the direction (increase/decrease) and magnitude of the glycemic response to exercise are variable and based on several factors, including the duration and intensity (high vs. moderate or low intensity) of exercise, an individual's characteristics (endogenous insulin sensitivity, and the effect of aerobic fitness to increase insulin sensitivity), and contextual factors (pre-exercise blood glucose level, insulin- and carbohydrates-on-board, and concentration of counter regulatory hormones) (193). Our results showed no significant associations between daily physical activity variables and HbA1c in youth with T1D. Similar results have been demonstrated in previous studies. Ligtenberg et al. found that glycemic control was not associated with physical activity in adults (aged 18-45 years) living with T1D (228). Wieliczko et al. reported that there was no correlation between the time spent every week participating in sports and HbA1c levels in children and adolescents with T1D (229). On the contrary, Herbst et al. found increasing physical activity was associated with better HbA1c levels in 23,251 children living with T1D (198). Valerio et al. have reported that regular physical activity was associated with better metabolic control and lipid profile in 138 children and adolescents with T1D (230). One of the possible reasons for the inconsistency could be differences in sample size between studies, with larger sample sizes often yielding more reliable and more significant findings. The other reasons could be possible variation in carbohydrate intake and insulin dosage

(for avoiding hypoglycemia episodes that caused by exercise), stress or stricter medical monitoring, which may all influence glycemic status.

Regular exercise, physical activity participation, and reduced sedentary behaviour are important for CVD risk management (98). Physical activity can improve the metabolic profile, bone mineral density, cardiorespiratory fitness and insulin sensitivity while lowering mortality risk in children with T1D, and physical activity habits developed during childhood and the associated health benefits may carry forward into adulthood (231). Contrary to this belief, a recent study with small sample size (n = 14) indicates that vigorous exercise (56% of VO_2max) in hot environment (35 ℃, relative humidity ~ 20%) can exacerbate reductions in cardiac autonomic modulation in young individuals with T1D (232). Further larger-scale confirmatory studies are warranted to confirm the potential risks of vigorous exercise in this population. The latest guidelines published in 2018 by the ISPAD recommend that children (aged 5-11 years) and adolescents (aged 12-17 years) should aim for 60 min or more per day of MVPA physical activity and minimize sedentary time, and participate in vigorous intensity exercise, muscle and bone strengthening exercise at least three times a week (20). In our study, individuals living with T1D did not achieve the minimal time of daily MVPA (60 min). Moreover, total daily physical activity count and the time spent in MVPA were significantly lower in individuals with T1D than apparently healthy peers without diabetes (mean difference −36 min). We learned from our participants' reported experiences that many physicians in China believed that individuals with T1D were too unfit to participant in physical activity and that physical activity would cause challenges of achieving target blood glucose control and hypoglycemia and many individuals with T1D and clinicians demonstrated a lack of awareness of the importance of exercise on the management of diabetes. This also has been similarly demonstrated in previous research in type 2 diabetes in France (233).

Reduced and insufficient physical activity during childhood is an important risk factor for CVD (234). Results of an observational study of children and adolescents (aged 4-18 years) demonstrated associations between increased time spent in sedentary activities with decreased levels of physical activity and related cardiovascular risk factors (27). Furthermore, cardiorespiratory fitness was significantly reduced in individuals with T1D compared with apparently healthy peers without diabetes in our study. Similarly, previous research also found that adolescents with T1D have a lower aerobic exercise capacity when compared with normal controls (235; 236). However, well-documented evidence from RCTs showed that there was improvement in cardiorespiratory fitness with exercise training (116; 154; 237; 238). These results highlight the importance to engage in regular physical exercise for persons living with T1D. Importantly, very small volumes of physical activity appear to have significant health benefits (222).

A positive association between HDL-C and METs, and a trend for a negative association between HDL-C and time spent in sedentary behaviour was found in the T1D group. Furthermore, triglycerides were negatively associated with daily physical activity counts and METs, and positively associated with time spent in sedentary behaviour in youth with T1D, while these relationships were not shown in the apparently healthy peers without diabetes. These results are in agreement with previous studies in youth with T1D that regular physical activity was associated with improved metabolic control and lipid profile in adolescents with T1D (28; 230). However, age, sex, pubertal stage, BMI z-score, and insulin treatment may affect an individual's physical activity variables and lipid profiles. Therefore, it is expected in multivariable analyses that potential confounding factors (age, sex, pubertal stage, BMI z-score, and insulin treatment) would decrease the association with physical activity variables and lipid profiles. Martin and colleagues revealed that each MET (approximately 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$) increase in cardiorespiratory fitness was

associated with a 25% reduction in all-cause mortality (239). Furthermore, in a systematic review and meta-analysis of physical activity and major chronic diseases showed that increased exercise, from achieving 11.25 MET-hours per week (675 MET-minutes per week), may be effective to decrease incidence and mortality of cardiovascular disease by 17% and 23%, respectively (240). Therefore, our observation suggests that increased daily physical activity has positive effects on CVD risk factors. Interpretation of these findings should be considered with the confounding effects of age, sex, pubertal stage, BMI z-score, and insulin treatment. Further research in this field is warranted.

4.5 Strengths and Limitations

The major strengths of the study include a well characterized cohort of Chinese youth living with T1D and apparently healthy peers without diabetes and the use of a reliable, device-assessed method to measure the physical activity levels and aerobic fitness. There were some potential limitations with our study. First, because of small sample size, our study may not have been large enough to detect significant changes in some variables. Second, wGT3x-BT triaxial accelerometers are water-resistant, but not waterproof, participants were required to remove the device when they engaged in aquatic activities such as swimming, which would lead to a potential underestimation of total physical activity levels. We only measured physical activity for one week, and this may not reflect the annual physical activity pattern. Third, the cross-sectional nature of this study does not allow determining causality; however, there was compelling information demonstrating important relationships between regular physical activity and the risk for CVD in youth living with T1D. A randomized controlled trial including a structured exercise training program would be required. Furthermore, there was a potential for selection bias since not all individuals who were approached agreed to participate in the study (48 out of 79 participants with T1D consented to participate the

study). It is possible that the individuals who were more sedentary or inactive may have been less willing to participate in the study. Additionally, the sample size in apparently healthy group was less than T1D group, and the power is based on the smaller sample.

4.6 Conclusions

Our findings provide evidence that, despite their young age and short duration of diabetes, Chinese youth living with T1D exhibit proatherogenic lipid profiles characterized by higher total cholesterol, LDL-C, and triglycerides compared to their peers without T1D, which is similar to that of other ethnicities. Furthermore, Chinese youth living with T1D showed lower physical activity levels and VO_2max compared to apparently healthy peers not living with diabetes. Being physically active may reduce the risk for CVD in youth living with T1D, included confounders of age, sex, pubertal stage, BMI z-score, and insulin treatment. As such, further larger-scale experimental design studies (e.g. RCTs) are warranted to confirm the findings. Accordingly, this study provides compelling evidence supporting the promotion of physical activity in youth living with T1D to reduce the risk for cardiovascular risk factors.

Chapter 5: Associations between Sleep Characteristics and Cardiovascular Risk Factors in Adolescents Living with Type 1 Diabetes

5.1 Introduction

Cardiovascular disease (CVD) is the most prevalent cause of premature death and disability in individuals living with type 1 diabetes (T1D). Cardiovascular risk factors associated with T1D can develop in childhood and adolescence. Previous research show that 76% of children and adolescents with T1D were found to have one or more risk factors for CVD (i.e., obesity, hypertension, hyperglycemia, or dyslipidemia) (196). In fact, the childhood onset of T1D has been associated with a higher risk for developing CVD in adulthood (195).

Short or very long durations of sleep and/or poor sleep quality in childhood are associated with higher the risk of CVD in adulthood (241), and may negatively impact the child's long-term cardiovascular health (242). Moreover, poor sleep patterns are related to CVD morbidity and mortality in adulthood (243). Previous research has shown that acute changes in CVD risk factors, including blood pressure, heart rate, glucose and insulin metabolic indices, and inflammation, often occur when are deprived healthy participants of sleep for varying lengths of time (244).

Emerging evidence has compared sleep duration among youths with T1D versus youths without T1D, and have identified some degree of disturbed sleep characterized by a reduction in sleep duration (30; 245). This includes an increase in overnight awakenings (246; 247), alterations in sleep architecture (30; 248), and poor sleep quality (30). However, most of these studies are based on subjective self-reporting, known to inaccurately estimate both sleep quantity and quality and many include small sample sizes (249). Moreover, sleep problems and disruption can affect insulin sensitivity and glucose regulation (250; 251). There is currently limited research that investigates how sleep quality affects cardiometabolic risk in adolescent living with T1D. Sleep

has physiological and behavioral impacts on diabetes outcomes, yet little is known about the impact of sleep disturbances on CVD risk factors in children with T1D.

Accordingly, the primary objective of this study was to compare objectively measured sleep in adolescents with T1D and with peers living without T1D. The second objective was to investigate the relationship between sleep and CVD risk factors. We hypothesized that sleep would be disturbed in adolescents living with T1D in comparison to adolescents without T1D, and poor sleep quality and shorter sleep duration would be associated with proatherogenic CVD risk factors.

5.2 Methods

5.2.1 Participants

This study used data from the same project that has been published previously (192). A cross-sectional study including 48 adolescents living with T1D (World Health Organization (WHO) criteria) and 19 apparently healthy peers without diabetes (aged 12 to 17 years) was conducted. We completed the recruitment of adolescents with T1D via advertisements using social media platforms (e.g., Diabetes WeChat groups), by distributing initial letters to individuals with T1D, and snowball sampling. The inclusion criteria for individuals living with T1D are: 1) at least 6 months of diagnosis of T1D; and 2) with HbA1c greater than or equal to 7.5% in the last three months; and 3) with normal renal function; and 4） free from previous CVD and chronic kidney disease. The exclusion criteria of participants are: 1) with any significant diabetic complications (diabetic foot, retinopathy, severe neuropathy); or 2) with uncontrolled hypertension; or 3) with diabetic keto-acidosis; or 4) with CVD (defined as any form of clinical coronary heart disease, stroke or peripheral vascular disease); or 5) with severe hypoglycemia episodes within the past 3 months.

We recruited peers without diabetes with matching for age and sex to the group with T1D from local schools via snowball sampling. The included healthy peers had no known history of chronic disease and no clinical or laboratory evidence of CVD, or other problems that would have contraindicated/limited their participation in regular physical activity. We excluded healthy participants without T1D who took any medications, which could influence cardiovascular function, lipid profiles, and/or glucose metabolism.

5.2.2 Demographic and anthropometric data collection

We measured height in bare feet to the nearest 0.1 cm with a wall-mounted stadiometer and body mass in light clothing to the nearest 0.1 kg with BC-418 segmental body composition analyzer (Tanita, Tokyo, Japan). We calculated body mass index (BMI) was as weight (kg) divided by height squared (m^2). We assessed puberty by a validated self-report questionnaire with pubertal staging images and the adolescents were categorized as prepubertal (Tanner 1), in early puberty (Tanner 2), mid puberty (Tanner 3-4) or post puberty (Tanner 5) (203). This questionnaire has been validated for Chinese children (204). Participants living with T1D were asked to complete questionnaires (Appendix C, D, E) upon arrival at the testing location, which included: diabetes history, age, duration of diabetes, complications, insulin regimen, medications, and physical activity levels. Peers without T1D were asked to complete a questionnaire about their medical history and physical levels (Appendix C, D). We measured waist circumference in triplicate using a flexible tape at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (202). We measured blood pressure after 10 min of rest in the seated position and the average of three measurements taken one minute apart was used in the analysis.

5.2.3 Cardiovascular outcomes

Waist circumference was measured in triplicate with a flexible tape at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (202). Blood pressure was measured after 10 min of rest in the seated position and the average of three measurements taken one minute apart was used in the analysis. Body composition was scanned by dual energy X-ray absorptiometry (DXA) using the iDXA instrument (GE Medical Systems, Madison, WI) with Encore 2011 software (version 13.6). All participants were studied after a 12-h overnight fast and before morning insulin injections for T1D individuals. We took fasting capillary (fingertip) blood samples for analysis of HDL-C, LDL-C, total cholesterol, and triglycerides. These lipid profiles were analyzed using the Cardiochek PA Blood Analyser (Polymer Technology Systems Inc., Indianapolis, IN, USA). We used the A1cNow+ (Metrika Inc., Sunnyvale, CA, USA) to analyze HbA1c and both devices have been previously validated (205; 206).

5.2.4 Accelerometry assessment of composition of the day

Sleep data were collected using an accelerometer (wGT3x-BT ActiGraph LLC, Pensacola, FL, USA) and analyzed using the manufacturer's software (ActiLife Version 6). Sandeh sleeping scoring algorithm (252) was used to analyze the sleep data. This algorithm determines a participant's sleep state by examining the activity counts over an 11 min window. Probability analysis is used to define each minute of recorded activity (using an 11-min sliding window) as either a sleep or awake epoch by weighting the activity scores of the surrounding minutes. If the probability is zero, the specific epoch is scored as sleep; otherwise, it is scored as awake (252). At least four nights of wear time (three weekdays and one weekend) was required to be considered valid.

Objective sleep measures included the following variables: estimates of sleep timing (sleep onset and sleep offset), total sleep time (time between falling asleep and final awakening from which, the time spent awake in between is subtracted), sleep onset latency (time between lying down in bed and falling asleep), sleep efficiency (total sleep time divided by total time in bed, in %), number of awakenings (the number of different awakening episodes as scored by the algorithm, wake after sleep onset (time awake between falling asleep and final awakening), and length of awakenings (the average length of all awakening episodes). An awakening does not necessarily mean the participant is awake, but rather that there was enough movement within the epoch (minute) to mark that epoch as "awake").

5.2.5 Statistical analyses

All statistical analyses were conducted using the SPSS 20 for Windows (Statistical Package for the Social Sciences, IBM Corp., Armonk, N.Y., USA) and data were screened for normal distribution. The chi-square test was used for comparison of proportion (categorical variables including sex and pubertal status) between groups, and independent-samples t-tests were used for comparison of the continuous variables (age, height, body mass, body composition, BMI, and sleep variables) between groups. A non-parametric test (Mann-Whitney) was used to compare sleep onset and sleep offset among groups. Results were summarized using medians and 25-75th quartile for non-normally distributed variables, using frequencies and percentages for categorical variables, and means and standard deviation (SD) for normally distributed variables. The associations between sleep characteristics and CVD risk factors were assessed with univariate linear regression analysis (Step 1) in the T1D group and apparently healthy peers without diabetes. With multivariate linear regression analysis (Step 2) adjusting for age, sex, and pubertal stage in

individuals with T1D and in apparently healthy peers not living with diabetes. The *p* value less than 0.05 was considered to be statistically significant.

5.3 Results

The demographic characteristics of participants with T1D and peers without diabetes are displayed in Table 5.1. No significant differences were found in age, sex, pubertal stage, height, body mass, body fat percentage, BMI, waist circumference, or blood pressure. T1D participants showed significantly higher values of total cholesterol (4.03 ± 0.81 vs. 3.14 ± 0.67 mmol·L^{-1}, p = 0.001), LDL-C (2.31 ± 0.72 vs. 1.74 ± 0.38 mmol·L^{-1}, p = 0.035), and triglycerides (0.89 ± 0.31 vs. 0.60 ± 0.40 mmol·L^{-1}, p = 0.012) compared to peers without diabetes.

Table 5.1 Comparison of descriptive data between adolescents with T1D and peers without diabetes

	T1D (n = 48)		**Peers without T1D (n = 19)**		
	Mean	SD	Mean	SD	*p*
Sex (male/ female) (%)	37.5/62.5		42.1/57.9		0.129
Pubertal stage (n)					0.543
Stage 1 (Not started)	18		7		
Stage 2 (Barely started)	8		1		
Stage 3 (Definitely underway)	12		6		
Stage 4 (Seems completed)	5		1		
Stage 5 (Completed)	5		4		
Ages (y)	14.0	2.9	13.6	3.5	0.601
Body mass (kg)	49.48	12.56	52.34	15.45	0.452
Height (m)	1.60	0.13	1.59	0.13	0.772
BMI (kg·m^{-2})	18.97	3.10	20.38	3.32	0.119
Body fat (%)	29.28	9.54	28.42	6.61	0.765
Waist circumference (cm)	67.63	7.96	73.65	8.22	0.055
Systolic blood pressure (mmHg)	106.07	16.72	107.07	15.45	0.837
Diastolic blood pressure (mmHg)	65.24	11.65	65.75	9.88	0.878
Total cholesterol (mmol·L^{-1})	4.03	0.81	3.14	0.67	0.001*
HDL-C (mmol·L^{-1})	1.48	0.28	1.29	0.42	0.078
LDL-C (mmol·L^{-1})	2.31	0.72	1.74	0.38	0.005*
Triglycerides (mmol·L^{-1})	0.89	0.31	0.60	0.40	0.012*
Diabetes duration (y)	3.64	2.29			
MDI (n)	30				

CSII (n)	18	
CGM (n)	26	
SMBG (n)	22	
HbA1c (%)	7.70	2.47
Insulin dose (unit·kg^{-1}·day^{-1})	0.87	0.29

Data are presented as means and standard deviation (SD). T1D, type 1 diabetes; n, number; y, year; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VO_2max, maximal aerobic power; METs, metabolic equivalent; CPM, counts-per-minute; *Statistically significant difference ($p < 0.05$) between T1D and apparently healthy peers without diabetes; MDI, multiple daily injection; CSII, continuous subcutaneous insulin infusion; CGM, Continuous Glucose Monitoring; SMBG, self-monitoring of blood glucose; HbA1c, Glycosylated hemoglobin.

Table 5.2 Comparison of sleep characteristics between adolescents with T1D and peers without diabetes

Sleep parameters	T1D (n = 33) Mean (SD)	Peers without diabetes (n = 16)	*p*-value
Sleep onset time (hh:mm) §	22:51 (22:06-23:06)	22:42 (22:08-23:12)	0.932
Sleep offset time (hh:mm) §	6:54 (6:33-7:30)	6:54 (6:33-7:30)	0.757
Sleep latency (min) §	1.78 (0.86-5.29)	2.17 (1.08-3.74)	0.662
Sleep efficiency (%)	86.30 (4.70)	86.43 (6.00)	0.933
Total sleep time (min)	421.30 (62.30)	432.02 (38.05)	0.534
Wake after Sleep onset (min)	62.23 (24.10)	66.71 (32.49)	0.589
Number of Awakenings (n)	20.82 (5.94)	21.21 (8.34)	0.848
Length of awakenings (min)	62.23 (24.10)	69.62 (39.64)	0.422

§ Data are presented as medians and 25-75th

There are no significant differences in sleep characteristics between adolescents with T1D and without T1D (Table 5.2). We investigated the within-group relationships between CVD risk factors (blood pressure, HbA1c, HDL-C, LDL-C, total cholesterol, and triglycerides) and sleep parameters with bivariate analysis. In adolescents with T1D, no significant associations were found between CVD risk factors and sleep characteristics. In healthy peers without T1D, the LDL-C and triglycerides both correlated negatively with sleep efficiency ($r = -0.554$, $p = 0.026$ and $r = -0.617$, $p = 0.011$) and no significant associations were found between any other CVD risk factors and sleep characteristics.

Linear regression models are presented in Table 5.3 and showed that LDL-C in healthy adolescents without T1D was negatively associated with sleep efficiency ($\beta = -0.554$, $p = 0.026$,

model $R^2 = 0.307$), but the results changed to a trend for a negative relation after adjusting for age, gender, and pubertal stage ($\beta = -0.04$, $p = 0.071$, model $R^2 = 0.395$), although less significant, the relationship became stronger.

Table 5.3 Linear regression model examining the association between LDL-C and sleep parameters after adjusting by potential confounders in adolescents living with T1D

Dependent variable: LDL-C						
Independent variables	β	95%CI		*p*	Adjusted R^2	R^2
Sleep efficiency (%)						
Step 1 (unadjusted)	−0.554	−0.07	−0.005	0.026	0.258	0.307
Step 2 (adjusted†)	−0.04	−0.084	0.004	0.071	0.175	0.395
Total sleep time (min·day^{-1})						
Step 1 (unadjusted)	−0.001	−0.003	0.001	0.201	0.027	0.065
Step 2 (adjusted†)	−0.002	−0.003	0.000	0.060	0.383	0.597

† Adjusted for age, sex, and pubertal stage

In all participants (n=49), we performed multivariate linear regression analysis including CVD risk factors as dependent variables, and disease, age, pubertal stage, and sleep characteristics (sleep efficiency and sleep duration) as independent variables. We found sleep efficiency was independently associated with LDL-C ($\beta = -0.045$, $p = 0.018$, model $R^2 = 0.230$) and triglycerides ($\beta = -0.027$, $p = 0.012$, model $R^2 = 0.222$).

Table 5.4 Linear regression model examining the association between sleep efficiency after adjusting by potential confounders in the entire sample

Independent variables: sleep efficiency						
Dependent variable:	β	95%CI		*p*	Adjusted R^2	R^2
LDL-C (mmol·L^{-1})						
Step 2 (adjusted)	−0.045	−0.082	−0.008	0.018	0.120	0.230
Triglycerides (mmol·L^{-1})						
Step 2 (adjusted††)	−0.027	−0.048	−0.006	0.012	0.111	0.222

†† Adjusted for sleep duration, age, sex, diabetes, and pubertal stages

5.4 Discussion

On average, adolescents with T1D and without T1D, slept less than the recommended eight hours per night in our study. A significant correlation between sleep efficiency and LDL-C and triglycerides was observed when confounders of age, sex, and pubertal stage were included in healthy peers without T1D and in the entire sample adjusted for T1D, age, sex, and pubertal stage. Similar to the findings in previous research, our study did not find any significant differences in sleep duration (248), efficiency (253; 254), sleep onset and offset, or frequency of awakenings (253) between persons with T1D and peers without T1D.

Our study found no significant differences in sleep duration between adolescents with T1D and peers without T1D. Similar results have been demonstrated by Perfect et al. (248) and Macaulay et al. (254). However, a systematic review and meta-analysis of sleep characteristics and associations with glycemic control in T1D showed that children and adolescents slept an average of 26 min, by objective measurement, less than peers without diabetes. Interpretation of these findings should be considered with caution as only three small studies with a total sample size of 70 participants with T1D were included (30). The inconsistency of these results is unclear; however, the results are likely due to the small sample size of each individual study or strict inclusion criteria of participants without chronic complications. Manin et al. reported that the prevalence of obstructive sleep apnea was high among men with T1D (24). In addition, obstructive sleep apnea was independently associated with macrovascular complications and retinopathy (255). Our study excluded participants living with chronic complications may explain the non-difference between adolescents with T1D and their peers without T1D.

The latest guidelines, based on available evidence of the impact of sleep duration on health outcomes, published in 2016 by the American Academy of Sleep Medicine recommend that children (aged 6-12 years) should obtain 9-12 h of sleep per 24 h (25). Moreover, adolescents (aged

13-18 years) should obtain 8-10 h of sleep per 24 h (256) and adults should obtain seven or more hours of sleep per 24 h (257). In our study, both adolescents living with and without T1D did not achieve the minimal time of daily sleep (8 h). We found that individuals with T1D slept 58.7 min and peers without T1D slept 47.98 min less than these recommendations. Previous research reported insufficient sleep duration in Chinse adolescents were due to heavy academic burdens (258). A growing body of evidence reported similar results in American (259), Canadian (260), German (261), and Australian (262) children and adolescents, and insufficient sleep has been identified as an international public health concern.

Evidence suggests that inadequate sleep quality and quantity are causally linked to sleepiness, inattention, cognitive and behavioral deficits, and long-term functional development (263). Previous cross-sectional and longitudinal studies have established associations between inadequate sleep and increased prevalence of overweight and obesity among children and adolescents (264; 265). Further, previous studies have linked shorter sleep duration to metabolic dysfunction in children and adolescents (266-269). Spruyt et al. found that shorter sleep duration was associated with obesity and poorer metabolic health including glucose, insulin, cholesterol, triglycerides, and high-sensitivity C-reactive protein in 4-10-year-old children (266). These findings highlight the importance for children and adolescents to obtain an adequate amount of good sleep on a regular basis.

We found no significant association between sleep duration and glycemic control in children and adolescents living with T1D who had no CVD complications. Similarly, Perfect et al. found objectively measured sleep duration was not related to glycemic control in children living with T1D (8). This finding is also supported by Reutrakul et al.'s meta-analysis (30). In contrast, findings in Reutrakul et al.'s systematic review highlighted shorter self-reported sleep duration and poorer self-reported sleep quality was associated with increased HbA1c, with a mean difference in

HbA1c of 0.19% and 0.24%, respectively in adults with T1D (30). On the other hand, Hazen and colleagues found that, in addition to poorer glycemic control and higher average blood glucose levels, parent reports of their children sleeping more than other children were associated with poorer T1D management. Collectively, these findings suggest that obtaining sleep outside the recommended range (whether too little or too much) may have a negative impact on glycemic control for individuals with T1D. The optimal and minimal amounts of sleep duration and quality for beneficial changes in the cardiovascular risk profile of those living with T1D remains to be determined.

A significant inverse relation between sleep efficiency and LDL-C was found in healthy peers without T1D, and there is still a trend for an inverse relation after adjusting for sex, age, and pubertal stage. However, we found no significant association between sleep efficiency and HbA1c and other CVD risk factors in children and adolescents living with T1D. In contrast, von Schnurbein et al. reported that self-reported increases in average sleep quality were correlated with a small decrease in HbA1c among T1D (270). The lack of correlation in our study is likely due to potential confounders of insulin therapy modality and diabetes management, excluding individuals with T1D who had diabetic complications and a small sample size. With multiple regression analysis, the association between sleep efficiency and LDL-C and triglycerides is independent of sleep duration after adjusting for confounders (diabetes, sex, age, and pubertal stage) in our study. Similarly, Narang et al. found poor sleep quality was independently associated with cardiovascular risk factor abnormalities in healthy adolescents. Additionally, Jarrin et al. found that sleep quality was negatively linked with obesity in children and adolescents (271). These observations highlight the importance of optimizing sleep quality and sleep duration for the management of T1D and increase the awareness of early treatment of CVD risk factors in youth with T1D.

5.5 Strengths and Limitations

To our knowledge, this is the first study investigating the associations between sleep characteristics and CVD risk factors in adolescents with T1D. The major strengths of the study include a well characterized cohort of adolescents living with T1D and apparently healthy peers without diabetes, and the use of an objective and reliable method to assess the sleep characteristics over multiple days. However, we did not collect subjective sleep data, which may provide useful insights into group differences as to how those with T1D perceive their own sleep quality. Furthermore, we could not perform subgroup analyses of CGM and SMBG or CSII and MDI due to small sample size of our study. Future research should assess the effects of technological advancements on sleep in T1D. Additionally, the sample size in peers without T1D group was less than T1D group, and the power is based on the smaller sample. In addition, we excluded diabetic individuals with complications. Furthermore, the cross-sectional nature of this study does not allow determining causality. Therefore, future research with a larger sample size including diabetic individuals who have complications is warranted. Moreover, an interventional study would allow for greater exploration of the potential mechanisms linking sleep and CVD risk factors in adolescents with T1D. This study was conducted in Chinese adolescents living with T1D and therefore cautions are needed when generalizing our study findings to other populations with different characteristics.

5.6 Conclusions

On average, adolescents with T1D and without T1D, sleep less than the recommended 8 h per night. The association between sleep efficiency and LDL-C and triglycerides is independent of sleep duration, regardless of sex, age, pubertal stage. Future research with a larger sample size including diabetic individuals who has complications is warranted to explore sleep-promoting interventions on glycemic control and other CVD risk factors in adolescents living with T1D.

Chapter 6: Associations between 24 h Movement Behaviours and Cardiovascular Risk Factors in Adolescents Living with Type 1 Diabetes: A Novel Compositional Data Analysis

6.1 Introduction

Sedentary lifestyle, lack of physical activity, and poor treatment compliance are considered the important causative factors in obesity, hypertension, hyperglycemia, dyslipidemia, insulin resistance and ultimately increased cardiovascular disease (CVD) risk in individuals with T1D (8). Type 1 diabetes is also related to cardiovascular abnormalities (such as increased carotid intima-media thickness, arterial stiffness, endothelial dysfunction and reduced myocardial function) that may increase the risk for the development of chronic heart failure (95). Previous research has shown that 76% of children and adolescents with T1D were found to have one or more risk factors for CVD (196). Additionally, cardiovascular disease is the major cause of premature death and disability in T1D. Therefore, knowledge of effective preventive strategies for reducing CVD risk factors is needed, especially among high-risk populations, such as T1D.

Physical behaviours such as physical activity, sedentary behaviour (SB), and sleep are associated with CVD risk factors in youth (192; 272; 273). An observational study of children and adolescents (aged 4-18 years) demonstrated associations between increased time spent in sedentary activities with decreased time spent in physical activity, and related CVD risk factors (27). A systematic review has shown regular physical activity has positive effects on cardiovascular health including improved glycemic control, aerobic fitness, and self-rated quality of life , and reduced insulin requirements, CVD risk factors, body mass, and body fat in individuals living with type 1 diabetes (18). Moreover, sleep duration that is too short has also been shown be associated with obesity markers (272).

Most previous studies on physical activity levels and sleep in T1D used self-reported measures of physical activity (199; 274) and sleep (275) which have been shown to be less accurate and reliable compared with accelerometer measurements (276). Objective assessments of accelerometry provide more objective data on how people spend their time in different movement-related behaviours throughout the 24 h continuum (276). Time spent in physical activity, sedentary behaviour, and sleep constitutes mutually exclusive components of the complete day (24 h), thus increasing time spent in one behaviour can only occur at the displacement of time available for other behaviours within that day. All of these behaviours are co-dependent on the amount of time spent in the other behaviours and compositional in nature (277). Therefore, they should be analyzed and interpreted in relation to each other.

Compositional Data Analysis (CoDA) deals with each behaviour that is a proportion of a finite sum (24 h) and enables studying the effect of each behaviour relative to each other rather than in isolation (277). It has recently been used in studies of associations between physical behaviours that individuals engage in on a daily basis and CVD risk factors (278-281). Chastin et al., using compositional data analysis, reported the distribution of time spent in sleep, SB, LIPA and MVPA collectively associated with a variety of cardiometabolic health markers and reallocating equivalent time from one behaviour to another was associated with changes in these health indicators (280). Powell et al. reported reallocating 30 min from sleep, SB, or standing, to LIPA in older adults was associated with significant decreases in BMI, body fat, and fat mass (281). A study by McGregor et al. has clearly shown that the whole 24-h movement behaviour is associated with healthy outcomes across the lifespans (282). These studies provide a starting point towards a better understanding of the combined effects of 24-h movement behaviours on various CVD risk factors in the general population.

However, to our knowledge, no study has used CoDA to examine the association between the full 24-h movement behaviour composition and CVD risk factors in persons living with T1D. Therefore, the purpose of this study is to investigate associations between time spent in any 24-h movement-related behaviours, relative to the other behaviours, and the CVD risk factors in adolescents with T1D.

6.2 Methods

6.2.1 Population

This study used data from the a project that has been published previously (192). A cross-sectional study including 48 adolescents living with T1D (World Health Organization (WHO) criteria) and 19 apparently healthy peers without diabetes (aged 12-17 years) was conducted. We completed the recruitment of adolescents with T1D via advertisements using social media platforms (e.g., Diabetes WeChat groups), by distributing initial letters to individuals with T1D, and snowball sampling. The inclusion criteria for individuals living with T1D are: 1) at least 6 months of diagnosis of T1D; and 2) with HbA1c greater than or equal to 7.5% in the last three months; and 3) with normal renal function; and 4) free from previous CVD and chronic kidney disease. The exclusion criteria of participants are: 1) with any significant diabetic complications (diabetic foot, retinopathy, severe neuropathy); or 2) with uncontrolled hypertension; or 3) with diabetic keto-acidosis; or 4) with CVD (defined as any form of clinical coronary heart disease, stroke or peripheral vascular disease); or 5) with severe hypoglycemia episodes within the past 3 months.

We recruited peers without diabetes with matching for age and sex to the group with T1D from local schools via snowball sampling. The included healthy peers had no known history of chronic disease and no clinical or laboratory evidence of CVD, or other problems that would have contraindicated/limited their participation in regular physical activity. We excluded healthy

participants without T1D who took any medications, which could influence cardiovascular function, lipid profiles, and/or glucose metabolism.

6.2.2 Cardiovascular outcomes

We measured waist circumference in triplicate using a flexible tape at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest (202). We measured blood pressure after 10 min of rest in the seated position and the average of three measurements taken one minute apart was used in the analysis. Body composition was scanned by dual energy X-ray absorptiometry (DXA) using the iDXA instrument (GE Medical Systems, Madison, WI) with Encore 2011 software (version 13.6). All participants were studied after a 12-h overnight fast and, in the case of T1D individuals, before their morning insulin injections. We took fasting capillary (fingertip) blood samples for analysis of HDL-C, LDL-C, total cholesterol, and triglycerides. These lipid profiles were analyzed using the Cardiochek PA Blood Analyser (Polymer Technology Systems Inc., Indianapolis, IN, USA). We used the A1cNow+ (Metrika Inc., Sunnyvale, CA, USA) to analyze HbA1c and both devices have been previously validated (205; 206).

6.2.3 Accelerometry assessment of composition of the day

We conceptualized the 24 h movement behaviour composition as consisting of MVPA, LIPA, SB, and sleep. Data were downloaded and analyzed using the manufacturer's software (ActiLife Version 6). Time spent in SB, LIPA and MVPA was assessed objectively following the method detailed previously (192), using an accelerometer (wGT3x-BT ActiGraph LLC, Pensacola, FL, USA). A sleep algorithm (252) was used to analyze the sleep data. This algorithm determines a participant's sleep state by examining the activity counts over an 11-min sliding window. Probability analysis is used to define each minute of recorded activity (using an 11-min sliding window) as either a sleep or awake epoch by a weighting the activity scores of the surrounding

minutes. If the probability is zero or greater, the specific epoch is scored as sleep; otherwise, it is scored as awake. After selecting sleep end and sleep offset, each minute of sleep data is analyzed this way, including night awakenings (252).

At least four valid wear days (> 16 h of wear time) were required to be included in the analysis. The researcher manually removed invalid days and all participants with < 4 valid days. Time spent in four behaviours was summed, with daily average wear time of 22.9 h, and normalized to the proportion of the total time so that the total daily time was always 24 h (283).

6.2.4 Potential confounding variables

We measured height in bare feet to the nearest 0.1 cm with a wall-mounted stadiometer and body mass in light clothing to the nearest 0.1 kg with BC-418 segmental body composition analyzer (Tanita, Tokyo, Japan). We calculated body mass index (BMI) was as weight (kg) divided by height squared (m^2). We assessed puberty by a validated self-report questionnaire with pubertal staging images and the adolescents were categorized as prepubertal (Tanner 1), in early puberty (Tanner 2), mid puberty (Tanner 3-4) or post puberty (Tanner 5) (203). This questionnaire has been validated for Chinese children (204). Participants living with T1D were asked to complete questionnaires (Appendix C, D, E) upon arrival at the testing location, which included: diabetes history, age, duration of diabetes, complications, insulin regimen, medications, and physical activity levels. Peers without T1D were asked to complete a questionnaire about their medical history and physical levels (Appendix C, D).

6.2.5 Statistical analyses

All statistical analyses were performed using the SPSS 20 (Statistical Package for the Social Sciences, IBM Corp., Armonk, N.Y., USA) and RStudio software (version 1.4.1106). Specifically, CoDA was performed using the 'Compositions' R packages (https://cran.r-project.org) and Shiny

(Shiny V.1.0.5, RStudio, Boston, USA, 2017) that was made available through the OpenCoDa website (https://opencoda.net).

Compositional means were calculated by normalizing the geometric means of time spent in four behaviours (MVPA, LIPA, SB, Sleep) so as to add up to 100%. Differences of time spent in each behaviour between T1D and peers without T1D groups were tested using MANOVA and a CoDA approach based on isometric log-ratio transformed data. Bar plots of geometric means were used to illustrate proportions of the time spent in each behavior, stratified by T1D and peers without T1D groups.

First, we examined whether there was an association between the entire composition and each CVD risk factor using the ANOVA test of deviance of the regressions. Then we analyzed whether each movement-related behaviour relative to the other behaviours was significantly associated with the CVD risk factors. For the analysis, the total 24-h (1440 min) day was partitioned in proportions of time spent in four behaviours (MVPA, LIPA, SB, sleep). Each participant's daily time-use composition was transformed into a set of three isometric log-ratio (*ilr*) coordinates, which map the compositions in real space (unconstrained by time) and preserve all relative information about the four compositional behaviours (280). Thus, for MVPA, ilr_1 expresses the ratio of time in MVPA to time in all other (MVPA, LIPA, SB, sleep) behaviours, ilr_2 considers the ratio of time in LIPA to non-active time (SB and sleep), and ilr_3 expresses the ratio of sedentary time to time in sleep. First, the associations between CVD risk factors (dependent/response variables) and the first *ilr* coordinate of each behaviour were explored using multiple linear regression models in adolescents living with T1D (i.e., adjusted for age, sex, and pubertal stage). Second, the associations between CVD risk factors (dependent/response variables) and the set of three *ilr* coordinates for each behaviour (explanatory variables) were explored using multiple linear regression models (i.e., adjusted for age, sex, and pubertal stage). Therefore, one compositional

linear regression model was conducted for each CVD outcome with four different sets of *ilr* coordinates (three *ilr* coordinates for each movement-related behaviour). The following is an example *ilr* transformation of MVPA, LIPA, SB, and sleep. The probability was statistically significant at p value < 0.05.

MVPA

$$ilr1 = \sqrt{\frac{3}{4}} \ln \frac{MVPA}{(LIPA * SB * Sleep)^{1/3}}$$

$$ilr2 = \sqrt{\frac{2}{3}} \ln \frac{LIPA}{(SB * Sleep)^{1/2}}$$

$$ilr3 = \sqrt{\frac{1}{2}} \ln \frac{SB}{Sleep}$$

LIPA

$$ilr1 = \sqrt{\frac{3}{4}} \ln \frac{LIPA}{(MVPA * SB * Sleep)^{1/3}}$$

$$ilr2 = \sqrt{\frac{2}{3}} \ln \frac{MVPA}{(SB * Sleep)^{1/2}}$$

$$ilr3 = \sqrt{\frac{1}{2}} \ln \frac{Sleep}{SB}$$

SB

$$ilr1 = \sqrt{\frac{3}{4}} \ln \frac{SB}{(MVPA * SB * Sleep)^{1/3}}$$

$$ilr2 = \sqrt{\frac{2}{3}} \ln \frac{Sleep}{(LIPA * MVPA)^{1/2}}$$

$$ilr3 = \sqrt{\frac{1}{2}} \ln \frac{LIPA}{MVPA}$$

Sleep

$$ilr1 = \sqrt{\frac{3}{4}} \ln \frac{Sleep}{(MVPA * SB * Sleep)^{1/3}}$$

$$ilr2 = \sqrt{\frac{2}{3}} \ln \frac{SB}{(LIPA * MVPA)^{1/2}}$$

$$ilr3 = \sqrt{\frac{1}{2}} \ln \frac{MVPA}{LIPA}$$

6.3 Results

Forty-nine participants had valid accelerometer data (at least four days of valid wake time data and at least four nights of valid sleep data). Participants were predominantly female (63.2%) and were aged 13.61 years on average (SD 3.13). A total of 33 participants living with T1D and 16 participants living without T1D had complete data for analyzing associations of 24 h movement behaviours with CVD risk factors. Descriptive statistics for each group are presented in Table 6.1. Specific descriptive data in youth with T1D are presented in Table 6.2.

Table 6.1 Descriptive data for adolescents with T1D and healthy peers without T1D

		T1D (n = 33)		Peers without T1D (n = 16)	
		Mean	SD	Mean	SD
Covariates	Sex (male/ female) (%)	30.3/69.7		50/50	
	Pubertal stage (n)				
	Stage 1 (Not started)	14		7	
	Stage 2 (Barely started)	7		1	
	Stage 3 (Definitely underway)	5		3	
	Stage 4 (Seems completed)	3		1	
	Stage 5 (Completed)	4		4	
	Ages (y)	13.8	2.9	13.2	3.5
Cardiovascular risk factors	BMI ($kg \cdot m^{-2}$)	19.13	3.06	20.96	3.86
	BMI z-score	−0.12	0.98	0.75	1.02
	Body fat (%)	29.03	9.72	29.57	6.75
	Waist circumference (cm)	68.49	7.97	74.19	8.32
	Systolic blood pressure (mmHg)	106.51	17.26	104.82	13.27
	Diastolic blood pressure (mmHg)	65.35	11.02	68.02	9.91
	Total cholesterol ($mmol \cdot L^{-1}$)	3.96	0.81	3.47	1.09
	HDL-C ($mmol \cdot L^{-1}$)	1.48	0.29	1.30	0.41
	LDL-C ($mmol \cdot L^{-1}$)	2.23	0.70	1.98	0.41
	Triglycerides ($mmol \cdot L^{-1}$)	0.89	0.32	0.67	0.37
Compositional mean for 24-h movement behaviours	MVPA (min) ‡	56.51	4%	93.86	6%
	LIPA (min)‡	347.06	23%	449.33	31%
	SB (min) ‡	615.13	43%	464.79	32%
	Sleep (min)‡	421.30	30%	424.80	31%

Data are presented as means and standard deviation (SD). ‡ Compositional mean for movement-related behaviours and % of 24 h, T1D, type 1 diabetes; n, number; y, year; BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; VO2max, maximal aerobic power; MVPA, moderate to vigorous physical activity; LIPA, light intensity physical activity; SB, sedentary behaviour;

Table 6.2 Specific descriptive data in young people living with T1D

	T1D (n = 33)	
	Mean	SD
Diabetes duration (y)	3.6	2.2
Pubertal Stage (n)		
Prepubertal (Tanner 1)	14	
Early puberty (Tanner 2)	7	
Mid-puberty (Tanner 3-4)	8	
Post-puberty (Tanner 5)	4	
MDI	19	
CSII	14	
CGM	19	
SMBG	14	
HbA1c ($mmol \cdot mol^{-1}$)	66	
HbA1c (%)	8.14	2.99
Insulin dose ($unit \cdot kg^{-1} \cdot day^{-1}$)	0.85	0.27

Data are presented as means and standard deviation (SD). T1D, type 1 diabetes; MDI, multiple daily injection; CSII, continuous subcutaneous insulin infusion; CGM, Continuous Glucose Monitoring; SMBG, self-monitoring of blood glucose; HbA1c, Glycosylated hemoglobin

The variability of the data for the entire sample is summarized in the compositional variation matrix (Table 6.3). A value close to zero indicates that the times spent in the two behaviours included in the ratio are highly proportional. The highest variances were observed for MVPA and SB, which demonstrated that time spent in MVPA was the least co-dependent on SB. The smallest variance was observed for sleep and LIPA with 0.0736, which implies high co-dependence between sleep and LIPA.

Table 6.3 Compositional variation matrix of time spent by the entire sample in Sleep, SB, LIPA, and MVPA

	Sleep	LIPA	MVPA	SB
Sleep	0	0.0736	0.2472	0.1242
LIPA	0.0736	0	0.1559	0.4193
MVPA	0.2472	0.1559	0	0.7992
SB	0.1242	0.4193	0.7992	0

SB, Sedentary Behaviour; LIPA, Light Intensity Physical Activity; MVPA, Moderate-to-Vigorous Physical Activity.

Time spent in SB, LIPA, MVPA, and sleep were statistically significant different between T1D and peers living without T1D groups. Compositional geometric mean bar plots comparing the compositional mean of the entire sample with the compositional mean of participants with T1D

group, and the peers without diabetes for SB, LIPA, MVPA, and sleep (Fig. 6.5). The proportion of time spent in SB was higher and the proportion of time spent in sleep, LIPA, and MVPA was lower in the persons with T1D than the entire sample (Fig. 6.5). The proportion of time spent in SB was lower and the proportion of time spent in sleep, LIPA, and MVPA was higher in the peers without diabetes than the entire sample (Fig. 6.5).

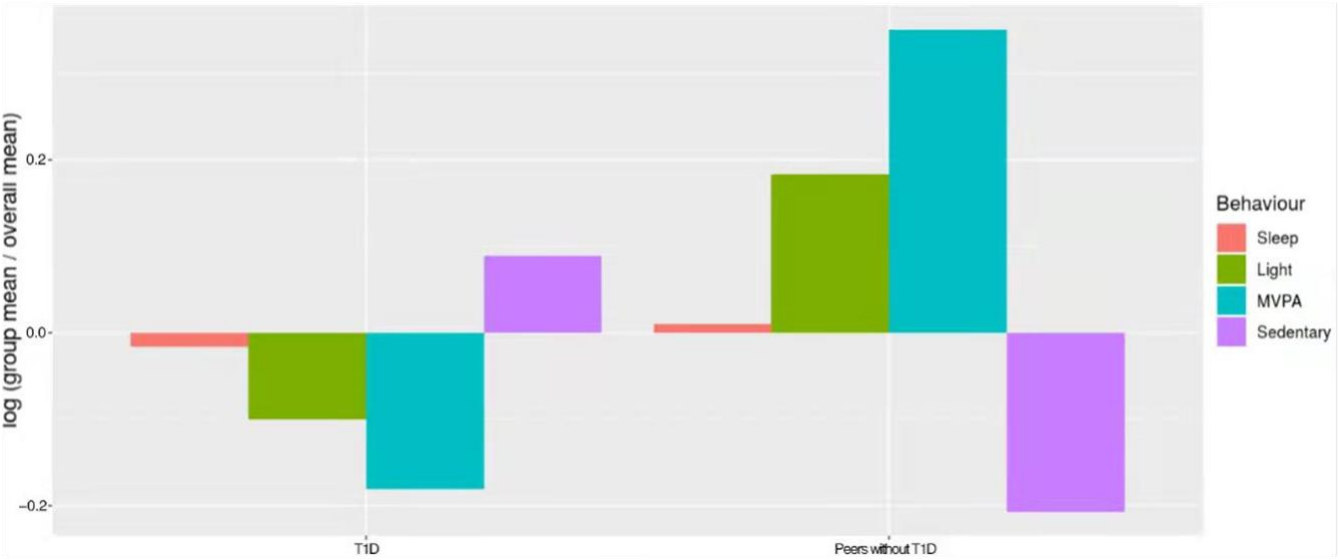

Figure 6.1 Compositional analysis of the group mean time spent in sleep, SB, LIPA and MVPA with respect to the overall mean time composition by group of T1D and Peers without T1D

Note: Geometric mean bar plot indicating the time spent each behaviour (i.e., MVPA, LIPA, SB, and sleep), in terms of differences from the geometric mean value of the entire sample. Each bar represents the ratio on a logarithmic scale (left axis) between the geometric mean of the specific group and the mean of the entire sample.

For individuals living with T1D, the entire movement composition is significantly associated with body fat percentage and tended to be associated with BMI, BMI z-score, and triglycerides when adjusted for age, sex, and pubertal stages (Table 6.4). For all participants, the entire movement composition was significantly associated with BMI when adjusted for diabetes, and was significantly associated with BMI, BMI z-score and body fat percentage when fully adjusted for diabetes, age, sex, and pubertal stages (Table 6.5). We did not find any significance

between the entire movement composition and other CVD risk factors in individuals with or without T1D.

Table 6.4 The p-values from the ANOVA test of deviance of the regression, examining the association of the entire 24 h movement composition with each cardiovascular outcome in adolescents living with T1D

Cardiovascular outcomes	Adjusted p-value
BMI	0.0863
BMI z-score	0.0811
Waist circumference	0.4207
Systolic blood pressure	0.6151
Diastolic blood pressure	0.1591
HDL-C	0.2244
LDL-C	0.1831
Total cholesterol	0.4931
Triglycerides	0.0803
Body fat percentage	0.0347*

All models are adjusted for age, sex, and pubertal stages. BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MVPA, moderate to vigorous physical activity; LIPA, light intensity physical activity; SB, sedentary behaviour; *Statistically significant difference ($p < 0.05$)

Table 6.5 The p-values from the ANOVA test of deviance of the regression, examining the association of the entire 24 h movement composition with each cardiovascular outcome in the entire sample

Cardiovascular outcomes	Adjusted p-value	Fully adjusted p-value
BMI	0.0110*	0.0296*
BMI z-score	0.0572	0.0176*
Waist circumference	0.2118	0.3070
Systolic blood pressure	0.5498	0.8313
Diastolic blood pressure	0.0968	0.1227
HDL-C	0.2712	0.1787
LDL-C	0.2712	0.2490
Total cholesterol	0.4816	0.8173
Triglycerides	0.2059	0.3195
Body fat percentage	0.5824	0.0372*

Adjusted models include diabetes, fully adjusted model includes the covariance age, sex, and pubertal stages and diabetes, BMI, body mass index; HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol, MVPA, moderate to vigorous physical activity, LIPA, light intensity physical activity, SB, sedentary behaviour, *Statistically significant difference ($p < 0.05$)

When only the first coordinates (which contained all the relevant information in a participant's movement behaviour composition) of each behaviour were included in the regression model, we found time spent in sleep, relative to all other behaviours, was significantly positively associated with BMI, BMI z-score, and LDL-C. Triglycerides were significantly positively associated with time spent in SB , significantly negatively associated with time spent in LIPA and MVPA separately relative to all other behaviours (Table 6.6). However, some associations were

not significant when the second and third coordinates of each behaviour were included in the regression models. After including all three coordinates of each behaviour in each regression model, time spent in sleep relative to the other movement behaviours was positively associated with BMI (β = 4.52; p = 0.0247), BMI z-score (β = 1.75; p = 0.0231) and body fat percentage (β = 25.71; p = 0.0160) (Table 6.7) in individuals living with T1D and the portion of variance in BMI explained by the composition of movement behaviours was 38%.

Table 6.6 Compositional behaviour model for select cardiovascular risk factors in adolescents living with T1D for the proportion of the day spent in MVPA, LIPA, SB and sleep

Cardiovascular outcomes	MVPA		LIPA		SB		Sleep	
	β	p	β	p	β	p	β	p
BMI z-score	0.03	0.9450	−1.22	0.141	−0.32	0.5520	1.43	0.0433*
BMI	−0.47	0.6943	−3.42	0.1135	−0.15	0.9184	4.04	0.0270
Body fat (%)	−2.82	0.6160	−5.22	0.6540	5.23	0.5431	13.73	0.0799
Triglycerides ($mmol \cdot L^{-1}$)	−0.32	0.0187*	−0.16	0.560	0.38	0.0274	0.42	0.104
HDL-C ($mmol \cdot L^{-1}$)	0.23	0.0752	0.01	0.9890	−0.32	0.04887	−0.10	0.6733
LDL-C ($mmol \cdot L^{-1}$)	0.33	0.3380	−0.71	0.2660	0.24	0.589	1.29	0.0326*

All models are adjusted for age, sex, and pubertal stages. Table shows the beta coefficients and p-values only for the first isometric log ratio coordinate that describes time spent in a specific behaviour, relative to time in the remaining behaviours; MVPA, moderate to vigorous physical activity, LIPA, light intensity physical activity, SB, sedentary behaviours, *Statistically significant difference ($p < 0.05$)

Table 6.7 Compositional behaviour model for select cardiovascular risk factors in adolescents living with T1D for the proportion of the day spent in MVPA, LIPA, SB and sleep

Cardiovascular outcomes	Model adjusted R^2	Model p value	MVPA		LIPA		SB		Sleep	
			β	p	β	p	β	p	β	p
BMI	0.38	0.0117*	−0.05	0.9641	−3.16	0.1340	−1.30	0.4306	4.52	0.0247*
BMI z-score	0.12	0.2094	0.13	0.7953	−1.17	0.1457	−0.71	0.2643	1.75	0.0231*
Body fat (%)	0.41	0.0902	−7.55	0.2287	8.93	0.4126	26.55	0.0655	25.17	0.0160*

All models are adjusted for age, sex, and pubertal stages. BMI: body mass index, Table shows the beta coefficients and p-values only for three isometric log ratio coordinates that describes time spent in a specific behaviour, relative to time in the remaining behaviour; MVPA, moderate to vigorous physical activity; LIPA, light intensity physical activity; SB, sedentary behaviour; *Statistically significant difference ($p < 0.05$)

For the entire sample, time spent in LIPA relative to other movement behaviours was negatively associated with BMI (β = −4.17; p = 0.0027) and BMI z-score (β = −1.58; p = 0.0214)

(Table 6.8). Time spent in Sleep relative to other movement behaviours was positively associated with BMI (β = 4.17; p = 0.0190), BMI z-score (β = 1.65; p = 0.0131), and body fat percentage (β = 18.17; p = 0.0090) (Table 6.8).

Table 6.8 Compositional behaviour model for select cardiovascular disease risk factors in the entire sample for the proportion of the day spent in MVPA, LIPA, SB and sleep

Cardiovascular outcomes	Model adjusted R^2	Model p value	MVPA		LIPA		SB		Sleep	
			β	p	β	p	β	p	β	p
BMI	0.48	0.0001*	−0.65	0.5647	−4.17	0.0227*	−0.64	0.6386	4.17	0.0190*
BMI z-score	0.29	0.0093*	−0.40	0.3425	−1.58	0.0214*	−0.48	0.3520	1.65	0.0131*
Body fat (%)	0.35	0.0324*	−3.50	0.4276	−1.20	0.8661	13.47	0.0622	18.17	0.0090*

All models are adjusted for age, sex, pubertal stages, and diabetes. Table shows the beta coefficients and p-values only for the first isometric log ratio coordinate that describes time spent in a specific behaviour, relative to time in the remaining behaviours; MVPA, moderate to vigorous physical activity; LIPA, light intensity physical activity; SB, sedentary behaviour; *Statistically significant difference ($p < 0.05$)

6.4 Discussion

To our knowledge, our study investigated associations between the 24-h movement composition (consisting of MVPA, LIPA, SB, and sleep) and select CVD risk outcomes is the first study to apply a compositional data analysis on a population with T1D. Our main findings showed that more time spent in LIPA relative to the other behaviours was beneficially associated with select CVD risk factors whereas more time spent in sleep relative to the other movement behaviours was detrimentally associated with CVD risk factors.

For adolescents living with T1D, the proportion of time spent in SB was higher and the proportion of time spent in sleep, LIPA, and MVPA was lower than the entire sample. For healthy peers without T1D, the proportion of time spent in sleep, LIPA, and MVPA was higher while the proportion of time spent in SB was lower than the entire sample. These findings are in line with our previous reports that adolescents with T1D spent more time in SB and less time in physical activity compared to their peers without T1D (192). Reduced physical activity and increased SB

during childhood is an important risk factor for CVD (234). Results of an observational study of children and adolescents (aged 9-10 years) demonstrated an independent significant inverse association between objectively measured PA and clustered metabolic risk (284). Therefore, it is very important for adolescents living with T1D to increase physical activity levels and reduce SB to prevent cardiovascular disease.

When only the first coordinate was included in the regression model (285), we found time spent in sleep, relative to all other behaviours, was positively associated with BMI, BMI z-score, and LDL-C and time spent in LIPA and MVPA relative to all other behaviours were negatively associated with triglycerides and time spent in SB relative to other behaviours was positively associated with triglycerides. The first *ilr* coordinate only contains the information regarding one behaviour at a time in relation to all other behaviours (285). Therefore, significant associations of relative time spent in one behaviour relative to the remaining behaviours may or may not be found, regardless of whether the entire composition is significantly associated with an outcome. Therefore, in our study, for adolescents living with T1D, it was only time spent in sleep, relative to all other behaviours that was associated with BMI, BMI z-score, and LDL-C, irrespective of how time was distributed among the other behaviours. As well, only time spent in LIPA and MVPA relative to all other behaviours was negatively associated with triglycerides and time spent in SB relative to all other behaviours was positively associated with triglycerides, irrespective of how time was distributed among the other behaviours. Our findings continue to support the importance of movement behaviours for optimal health in adolescents living with T1D. However, some associations were removed after the second and third coordinates were included in regression models. This is probably because one joint p value for a set of three *ilr* coordinates and the outcome were calculated and the association of each behaviour with the outcomes adequately adjusted for the time spent in the other behaviours (286). Therefore, interventions targeting only one behaviour

may be less effective for improving CVD risk factors among adolescents living T1D and, thus, taking into account how other movement behaviours change when targeted movement behaviours increase, or decrease may help to further improve the efficacy of interventions.

We found the entire compositional behaviour accounted for 38% of variance of BMI in adolescents living with T1D and time spent in sleep relative to the other movement behaviours was positively associated with BMI, BMI z-score and body fat percentage after adjusted age, sex, and pubertal stages. The findings from current literature on associations between sleep duration and obesity markers are largely inconsistent. A cross-sectional study of 723 adolescents (25.6% of participants were overweight/obesity) showed negative linear relationship between sleep duration and BMI (287). However, Hassan et al. found null association between insufficient sleep and childhood obesity (288). Interestingly, Sivertsen et al. found the association between sleep duration and BMI for girls (14.6% of girls were overweight/obesity) was U-shape and linear for boys (18.3% of boys were overweight/obesity) (289). Similarly, Danielsen et al. found shorter and longer sleep durations were significantly related to higher BMI (the odds ratio of overweight/obesity ranged from 1.6%-12.8%). The BMI of our participants living with T1D are normal and ranged from 13.35 to 23.44 $kg \cdot m^{-2}$ (mean = 19.13 $kg \cdot m^{-2}$) and we found the positive association between sleep duration with BMI, BMI z-score and body fat percentage. Of note, the BMI z-score in our study of T1D was significantly lower than their peers without T1D, which probably suggest that more time spent in sleep in T1D relative to all other behaviours may be helpful to get their BMI z-score comparable to their peers without T1D. Our finding was in our sample under the conditions of this study. Future epidemiological studies with larger sample sizes regarding the associations between sleep duration and obesity should include individuals with T1D who are obese and be carefully designed to minimize the selection bias.

The majority of current literature on individuals with T1D is focused on sleep characteristics in T1D and its associations with glycemic control rather than associations between sleep characteristics and CVD risk factors. One study reported that adolescents with T1D experienced more sleep disturbances and shorter sleep durations compared to their healthy peers and inadequate sleep is associated with negative mental health and physical health outcomes (290). In our study, the proportion of time spent in sleep for adolescents living with T1D, was lower than their peers without T1D. Therefore, sleep is an important component of effective treatment recommendation for T1D management and should be a behaviour to emphasize in diabetes education.

In all participants, we found that the compositional behaviour accounted for 48%, 29%, 35% of the variance of BMI, BMI z-score and body fat percentage separately after adjusting for diabetes, age, sex, and pubertal stages. Furthermore, an important finding of our study was that time spent in LIPA relative to other movement behaviours was negatively associated with BMI and BMI z-score. A previous systematic review of the relationships between objectively measured physical activity and health indicators in school-aged adolescents reported that LIPA was favourably associated with cardiometabolic biomarkers, which is consistent with our results (291). These findings highlight the potential benefits of LIPA. The absence of statistical significance in our study for other behaviours relative to the remaining behaviours and other CVD risk factors may reflect the smaller sample size, with larger sample sizes being needed to find significant findings.

6.5 Strengths and Limitations

This was the first study to use compositional analyses to examine the relationships between movement behaviours and select CVD risk factors in adolescents living with T1D. Strengths of this study are that we included a well characterized adolescent cohort living with T1D and peers living without T1D and a range of CVD risk factors. Furthermore, the analysis of time use covered

the entire 24 h spectrum of accelerometer-measured movement-related behaviours, thus increasing the likelihood of capturing an objective and reliable representation of the participants' movement behaviours. Additionally, the novel analytical approach allowed for an integrated assessment of the association between each movement behaviour and select CVD risk factors by taking the compositional nature of time use data into account. However, there are some potential limitations of this study that should be considered. First, the cross-sectional nature of this study does not allow determining the direction of causality in the relationships observed; however, there was compelling information demonstrating important relationships between 24 h movement behaviour and the risk factors for CVD in adolescents. Further experimental design studies (e.g., RCTs) are warranted to confirm the findings. Second, subjective sleep data were not available, and sleep time was based on sustained inactivity bouts (11-min window) within a predefined angular range of arm motion. Third, because of the small sample size, our study may have been underpowered to detect significant changes in some variables. Future work should look at the impact of 24-hour physical behaviour compositions on CVD risk factors in a larger sample of people with T1D. In addition, LIPA, MVPA and SB were based on acceleration thresholds; especially, LIPA and SB were less accurate than postural allocation, which may lead to different results. Furthermore, it should be noted that the need for participants to remove the accelerometer for water-based activities likely missed some physical activity, such as showering and swimming, which may lead to potential underestimation of total physical activity levels.

6.6 Conclusions

Adolescents living with T1D showed less active and more sedentary when compared to their peers without T1D and increased sleep and decreased LIPA have negative consequences in cardiovascular health among adolescents living with T1D. Optimizing these behaviours may lead to better cardiovascular health outcomes in these individuals. Further experimental design studies

(e.g., RCTs) on a larger scale are warranted to confirm the findings. Accordingly, this study provides novel insights into collective cardiovascular health implications of 24-h movement behaviours in adolescents living with T1D and can facilitate interesting avenues for future investigations.

Chapter 7: Summary of Findings and Future Research

7.1 Summary of Findings

This project describes empirical studies from peer-reviewed publications, consolidates findings from recent investigations of movement behaviours and CVD risk factors in individuals living with T1D, and offers suggestions for future directions for movement behaviours as a target in diabetes clinical care and research endeavours. The movement behaviours of individuals with T1D typically interfere with their cardiovascular health. Multiple improvements in cardiovascular health indicators firmly remark that physical activity is important in the management of T1D. Cardiovascular health promotion in individuals with T1D must be based on movement behaviours, especially regular physical activity, less sedentary behaviour, and adequate sleep in accordance with specific guidance.

Chapter 2 has presented a systematic review and meta-analysis of published, controlled studies, both randomized and non-randomized, examining how exercise-training interventions reduce risk factors for cardiovascular disease among individuals living with T1D, and our findings have confirmed that, in individuals living with T1D, exercise training is associated with the development of a beneficial cardiovascular profile; this includes improvements in lipid profile, glycemic control (decreased daily insulin dosage and HbA1c), and aerobic fitness level. In addition, we also found that exercise training has greater beneficial effects when it involves a combination of aerobic exercise and resistance training, and we see better results with more frequent training, and with longer durations of study. This study provides useful, updated information regarding exercise as the primary form of cardiovascular disease prevention to further emphasise healthcare providers and policymakers the importance of exercise as a cornerstone in diabetes management and health promotion for individuals living with T1D.

In Chapter 3, a systematic review was conducted to compare the acute effects of HIIE with MICE on metabolic outcomes and hormonal responses in individuals with T1D. We found the decline of levels blood glucose to be less with HIIE compared with MICE. This is paralleled by increased levels of counter-regulatory hormones (mainly growth hormone and catecholamines), as well as substantially higher levels of lactate in HIIE. In addition, the probability of early-onset hypoglycemia after HIIE was lower compared with MICE, and there was no difference between HIIE and MICE regarding the onset of hyperglycemia and nocturnal hypoglycemia. These findings provide evidence that HIIE may prevent exercise-induced acute hypoglycemia. High-intensity interval exercise may be safer than MICE as it carries a lower risk of early-onset hypoglycemia compared to MICE with no difference in the frequency of hyperglycemia and nocturnal hypoglycemia. The results of our studies call for researchers, clinicians, and front-line exercise professionals to design and develop targeted exercise interventions for effective management of T1D.

Chapter 4 assessed CVD risk factors in Chinese youth living with T1D in comparison with their healthy peers not affected by T1D and evaluated the relationship between objectively measured daily physical activity levels and markers of CVD. We found increased levels of risk factors for CVD in Chinese youth living with T1D, compared with the group consisting of their heathy peers, and this finding highlights the importance of identifying cardiovascular risk factors at an early stage in life for individuals living with T1D. Furthermore, Chinese youth living with T1D showed lower levels of both physical activity and aerobic fitness compared to their peers not affected by diabetes. Being physically active may push to eliminate the risk factors for CVD in adolescents living with T1D. Therefore, physicians and health professionals should encourage adolescents with T1D to explore engagement in physical activity as part of a regimen for a healthy lifestyle.

Chapter 5 examined objectively measured sleep characteristics in adolescents living with T1D in comparison with healthy peers not with T1D and evaluated the relationship between sleep characteristics and markers of CVD in adolescents. We found that both adolescents with T1D and without T1D, sleep less than the recommended 8 h per night. The association between sleep efficiency and LDL-C and triglycerides is independent of sleep duration, regardless of gender, age, and pubertal stage. Our findings provide updated information in the development of evidence-based sleep recommendations for individuals with T1D.

Chapter 6 used compositional data analysis to investigate associations between time spent in any 24-h movement-related behaviours, relative to the other behaviours, and the CVD risk factors in adolescents with T1D. We found that increased time spent in sleep and decreased time spent in LIPA is associated with higher BMI in adolescents living with T1D. Optimizing these behaviours may lead to better cardiovascular health outcomes in these individuals. This knowledge is important for future physical activity and future sleep guidelines aimed at optimizing cardiovascular health in pediatric populations with T1D should consider an integrated movement behaviour approach.

7.2 Future Research

The research around T1D and CVD risk factors is evolving rapidly, and the important role of daily movement behavioural intervention can play in the prevention and management of CVD is becoming increasingly recognized by clinicians, policy makers, and patients. However, additional studies, especially experimental and longitudinal with larger sample sizes, are needed to fully understand the benefits of movement behaviours on cardiovascular health outcomes. The following specific recommendations are based on each study to move the field forward.

For Chapter 2, as mentioned previously, future research should more carefully examine the minimal and optimal dosages of physical activity for health benefits in persons living with T1D. In

particular, additional RCTs are warranted that more closely examines the relationships between physical activity volumes (and/or intensities) and glycemia control, insulin dosages, aerobic fitness, and quality of life. Studies in this area will provide important information in the development of evidence-based exercise recommendations for individuals with T1D.

For Chapter 3, Larger, well-designed, RCTs are needed to determine the long-term effects of including more high-intensity exercise into regular physical activity sessions on health-related outcomes, in particular glycemic control, hypoglycemia, and nocturnal hypoglycemia in youth with T1D. Furthermore, the insulin adjustment and carbohydrate strategies recommendations are very important for individuals living with T1D. Optimizing these strategies is required to see beneficial metabolic controls of HIIE in T1D, and to provide evidence-based carbohydrate and insulin recommendations specifically designed for HIIE for individuals with T1D. For example, future research using a larger sample size should carefully examine the minimal and optimal dosages of carbohydrate and insulin required for health benefits in persons living with T1D. Additionally, research is warranted that more closely examines the relationships between carbohydrate/insulin volumes and glycemia control, and hypo/hyperglycemia before, during, after HIIE and MICE. Designing a randomized controlled trial using this protocol of training is a future perspective.

Based on our findings in Chapter 4, observational studies with larger sample sizes investigating the specific timing, frequency, duration, and intensity of exercise interventions required to see beneficial results for cardiovascular risk factors and to provide evidence-based activity recommendations specifically designed for T1D in daily practice. In addition, critical steps still need to be made in translating the research finding into clinical practice, especially, improving the awareness of the importance of physical activity in the management of diabetes among individuals living with T1D and physicians, and helping individuals with T1D promote physical activity effectively and safely.

The results of Chapter 5 warrant further investigation into the association between sleep behaviours and weight gain, and CVD risk factors among T1D youth who have complications. A new wave of research is warranted to better evaluate the relationships between sleep, glycemic control, and cardiovascular risk factors. Future studies should incorporate multiple, detailed and validated measures of sleep. They should be longitudinal, experimental, stratified by sex and designed to address causal direction. Additionally, future research is needed to establish if the reported findings of sleep patterns hold among other ethnic groups living with T1D and diverse pediatric populations with a broad range of BMI and diabetes complications. In addition, it may also be beneficial to consider the relationships between sleep and psychosocial outcomes like depression and quality of life among individuals living with T1D.

Based on the findings in Chapter 6, more studies with larger sample sizes are required to examine the relative contributions of multicomponent of movement behaviours and differential glycemic control treatment strategies. To further investigate the relationship between 24-h movement behaviours and cardiovascular health in T1D, and to guide the planning of 24-h movement behavioural interventions and health policy, future compositional data analyses should be performed on longitudinal and experimental data and may be stratified by sex. Moreover, future studies should consider adjusting for potential confounders such as diabetes-related information (e.g., duration of diabetes and insulin regimen), participants' diet quality and other health factors (e.g., obesity, chronic disease status). It may also be of interest to consider the relationships between 24-h movement behaviours and neurobehavioural outcomes like depression and quality of life in individuals living with T1D.

References

1. Mathis D, Vence L, Benoist C. β-Cell death during progression to diabetes. Nature 2001;414:792

2. American Diabetes Association. 2. Classification and Diagnosis of Diabetes. Diabetes Care 2015;38:S8-S16

3. Katsarou A, Gudbjörnsdottir S, Rawshani A, Dabelea D, Bonifacio E, Anderson BJ, Jacobsen LM, Schatz DA, Lernmark Å. Type 1 diabetes mellitus. Nature Reviews Disease Primers 2017;3:17016

4. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Research and Clinical Practice 2019;157:107843

5. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. Diabetes Care 2018;41:S13-S27

6. Stephens E. Insulin therapy in type 1 diabetes. Medical Clinics 2015;99:145-156

7. Gourgari E, Dabelea D, Rother K. Modifiable risk factors for cardiovascular disease in children with type 1 diabetes: can early intervention prevent future cardiovascular events? Current Diabetes Reports 2017;17:134

8. Snell-Bergeon JK, Nadeau K. Cardiovascular Disease Risk in Young People with Type 1 Diabetes. Journal of Cardiovascular Translational Research 2012;5:446-462

9. Dabelea D, Talton JW, D'Agostino R, Wadwa RP, Urbina EM, Dolan LM, Daniels SR, Marcovina SM, Hamman RF. Cardiovascular risk factors are associated with increased arterial stiffness in youth with type 1 diabetes: the SEARCH CVD study. Diabetes Care 2013;36:3938-3943

10. Cleary PA, & Backlund, J. Y. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. New England Journal of Medicine 2005;353:2643-2653

11. McCrimmon RJ, Sherwin RS. Hypoglycemia in type 1 diabetes. Diabetes 2010;59:2333-2339

12. Pena AS, Couper JJ, Harrington J, Gent R, Fairchild J, Tham E, Baghurst P. Hypoglycemia, but not glucose variability, relates to vascular function in children with type 1 diabetes. Diabetes Technology & Therapeutics 2012;14:457-462

13. Skyler JS, Bergenstal R, Bonow RO, Buse J, Deedwania P, Gale EA, Howard BV, Kirkman MS, Kosiborod M, Reaven P. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. Journal of the American College of Cardiology 2009;53:298-304

14. Liu LL, Lawrence JM, Davis C, Liese AD, Pettitt DJ, Pihoker C, Dabelea D, Hamman R, Waitzfelder B, Kahn HS. Prevalence of overweight and obesity in youth with diabetes in USA: the SEARCH for Diabetes in Youth study. Pediatric Diabetes 2010;11:4-11

15. Haffner SM. Dyslipidemia management in adults with diabetes. Diabetes Care 2004;27:S68

16. Lee SH, Kim JH, Kang MJ, Lee YA, Yang SW, Shin CH. Implications of nocturnal hypertension in children and adolescents with type 1 diabetes. Diabetes Care 2011;34:2180-2185

17. Silverstein J, Klingensmith G, Copeland K, Plotnick L, Kaufman F, Laffel L, Deeb L, Grey M, Anderson B, Holzmeister LA. Care of children and adolescents with type 1 diabetes: a statement of the American Diabetes Association. Diabetes Care 2005;28:186-212

18. Wu N, Bredin SS, Guan Y, Dickinson K, Kim DD, Chua Z, Kaufman K, Warburton DE. Cardiovascular health benefits of exercise training in persons living with type 1 diabetes: a systematic review and meta-analysis. Journal of Clinical Medicine 2019;8:253

19. MacMillan F, Kirk A, Mutrie N, Matthews L, Robertson K, Saunders DH. A systematic review of physical activity and sedentary behavior intervention studies in youth with type 1 diabetes: study characteristics, intervention design, and efficacy. Pediatric Diabetes 2014;15:175-189

20. Adolfsson P, Riddell MC, Taplin CE, Davis EA, Fournier PA, Annan F, Scaramuzza AE, Hasnani D, Hofer SE. ISPAD Clinical Practice Consensus Guidelines 2018: Exercise in children and adolescents with diabetes. Pediatric Diabetes 2018;19:205-226

21. Alman AC, Talton JW, Wadwa RP, Urbina EM, Dolan LM, Daniels SR, Hamman RF, D'agostino RB, Marcovina SM, Mayer-Davis EJ. Cardiovascular health in adolescents with type 1 diabetes: the SEARCH CVD study. Pediatric Diabetes 2014;15:502-510

22. Brazeau A-S, Rabasa-Lhoret R, Strychar I, Mircescu H. Barriers to physical activity among patients with type 1 diabetes. Diabetes Care 2008;31:2108-2109

23. Nadeau KJ, Regensteiner JG, Bauer TA, Brown MS, Dorosz JL, Hull A, Zeitler P, Draznin B, Reusch JE. Insulin resistance in adolescents with type 1 diabetes and its relationship to cardiovascular function. The Journal of Clinical Endocrinology & Metabolism 2010;95:513-521

24. Church TS, LaMonte MJ, Barlow CE, Blair SN. Cardiorespiratory fitness and body mass index as predictors of cardiovascular disease mortality among men with diabetes. Archives of Internal Medicine 2005;165:2114-2120

25. Carter S, Hartman Y, Holder S, Thijssen DH, Hopkins ND. Sedentary behavior and cardiovascular disease risk: mediating mechanisms. Exercise and Sport Sciences Reviews 2017;45:80-86

26. Melo EASd, Ferreira LEdS, Cavalcanti RJF, Botelho Filho CAdL, Lopes MR, Barbosa RHdA. Nuances between sedentary behavior and physical inactivity: cardiometabolic effects and cardiovascular risk. Revista da Associação Médica Brasileira 2021;67:335-343

27. Raitakari OT, Taimela S, Porkka K, Telama R, Välimäki I, Akerblom H, Viikari J. Associations between physical activity and risk factors for coronary heart disease: the Cardiovascular Risk in Young Finns Study. Medicine and Science in Sports and Exercise 1997;29:1055-1061

28. Michaliszyn SF, Faulkner MS. Physical activity and sedentary behavior in adolescents with type 1 diabetes. Research in Nursing & Health 2010;33:441-449

29. Association AD. Standards of medical care in diabetes—2017 abridged for primary care providers. Clinical Diabetes: a Publication of the American Diabetes Association 2017;35:5

30. Reutrakul S, Thakkinstian A, Anothaisintawee T, Chontong S, Borel A-L, Perfect MM, Janovsky CCPS, Kessler R, Schultes B, Harsch IA. Sleep characteristics in type 1 diabetes and associations with glycemic control: systematic review and meta-analysis. Sleep Medicine 2016;23:26-45

31. Hazen RA, Fehr KK, Fidler A, Cousino MK, MacLeish SA, Gubitosi-Klug R. Sleep disruption in adolescents with Type 1 diabetes mellitus: relationships with adherence and diabetes control. Diabetes Management 2015;5:257

32. Wolfsdorf J. Improving diabetes control in adolescents with type 1 diabetes. Practical Psychology for Diabetes Clinicians 2002:149-159

33. Moy CS, Songer TJ, LaPorte RE, Dorman JS, Kriska AM, Orchard TJ, Becker DJ, Drash AL. Insulin-dependent diabetes mellitus, physical activity, and death. American Journal of Epidemiology 1993;137:74-81

34. LaPorte R, Dorman J, Tajima N, Cruickshanks K, Orchard T, Cavender D, Becker D, Drash A. Pittsburgh insulin-dependent diabetes mellitus morbidity and mortality study: physical activity and diabetic complications. Pediatrics 1986;78:1027-1033

35. Rabasa-Lhoret R, Bourque J, Ducros F, Chiasson J-L. Guidelines for premeal insulin dose reduction for postprandial exercise of different intensities and durations in type 1 diabetic subjects

treated intensively with a basal-bolus insulin regimen (ultralente-lispro). Diabetes Care 2001;24:625-630

36. MacDonald MJ. Postexercise late-onset hypoglycemia in insulin-dependent diabetic patients. Diabetes Care 1987;10:584-588

37. Association AD. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. Diabetes Care 2006;29:2200-2204

38. Guelfi KJ, Jones TW, Fournier PA. New insights into managing the risk of hypoglycaemia associated with intermittent high-intensity exercise in individuals with type 1 diabetes mellitus. Sports Medicine 2007;37:937-946

39. Johnson S, Cooper M, Davis E, Jones T. Hypoglycaemia, fear of hypoglycaemia and quality of life in children with Type 1 diabetes and their parents. Diabetic Medicine 2013;30:1126-1131

40. Patton SR, Dolan LM, Henry R, Powers SW. Parental fear of hypoglycemia: young children treated with continuous subcutaneous insulin infusion. Pediatric Diabetes 2007;8:362-368

41. Adolfsson P, Riddell MC, Taplin CE, Davis EA, Fournier PA, Annan F, Scaramuzza AE, Hasnani D, Hofer SE. ISPAD Clinical Practice Consensus Guidelines 2018: Exercise in children and adolescents with diabetes. Pediatric Diabetes 2018;19 Suppl 27:205-226

42. Sigal RJ, Armstrong MJ, Bacon SL, Boule NG, Dasgupta K, Kenny GP, Riddell MC. Physical activity and diabetes. Canadian Journal of Diabetes 2018;42:S54-S63

43. Yardley JE, Sigal RJ. Exercise strategies for hypoglycemia prevention in individuals with type 1 diabetes. Diabetes Spectrum 2015;28:32-38

44. Adolfsson P, Nilsson S, Albertsson-Wikland K, Lindblad B. Hormonal response during physical exercise of different intensities in adolescents with type 1 diabetes and healthy controls. Pediatr Diabetes 2012;13:587-596

45. Calles J, Cunningham JJ, Nelson L, Brown N, Nadel E, Sherwin RS, Felig P. Glucose turnover during recovery from intensive exercise. Diabetes 1983;32:734-738

46. Marliss EB, Vranic M. Intense exercise has unique effects on both insulin release and its roles in glucoregulation: implications for diabetes. Diabetes 2002;51:S271-S283

47. Bussau VA, Ferreira LD, Jones TW, Fournier PA. A 10-s sprint performed prior to moderate-intensity exercise prevents early post-exercise fall in glycaemia in individuals with type 1 diabetes. Diabetologia 2007;50:1815-1818

48. Bussau VA, Ferreira LD, Jones TW, Fournier PA. The 10-s maximal sprint: a novel approach to counter an exercise-mediated fall in glycemia in individuals with type 1 diabetes. Diabetes Care 2006;29:601-606

49. Davey RJ, Bussau VA, Paramalingam N, Ferreira LD, Lim EM, Davis EA, Jones TW, Fournier PA. A 10-s sprint performed after moderate-intensity exercise neither increases nor decreases the glucose requirement to prevent late-onset hypoglycemia in individuals with type 1 diabetes. Diabetes Care 2013;36:4163-4165

50. Fahey A, Paramalingam N, Davey R, Davis E, Jones T, Fournier P. The effect of a short sprint on postexercise whole-body glucose production and utilization rates in individuals with type 1 diabetes mellitus. The Journal of Clinical Endocrinology & Metabolism 2012;97:4193-4200

51. Guelfi K, Ratnam N, Smythe G, Jones T, Fournier P. Effect of intermittent high-intensity compared with continuous moderate exercise on glucose production and utilization in individuals with type 1 diabetes. American Journal of Physiology-Endocrinology And Metabolism 2007;292:E865-E870

52. Guelfi KJ, Jones TW, Fournier PA. Intermittent high-intensity exercise does not increase the risk of early postexercise hypoglycemia in individuals with type 1 diabetes. Diabetes Care 2005;28:416-418

53. Campbell MD, West DJ, Bain SC, Kingsley MI, Foley P, Kilduff L, Turner D, Gray B, Stephens JW, Bracken RM. Simulated games activity vs continuous running exercise: a novel comparison of the glycemic and metabolic responses in T1DM patients. Scandinavian Journal of Medicine & Science in Sports 2015;25:216-222

54. Sills IN, Cerny FJ. Responses to continuous and intermittent exercise in healthy and insulin-dependent diabetic children. Medicine and Science in Sports and Exercise 1983;15:450-454

55. Brazeau A, Leroux C, Mircescu H, Rabasa-Lhoret R. Physical activity level and body composition among adults with type 1 diabetes. Diabetic Medicine 2012;29:e402-e408

56. Bohn B, Herbst A, Pfeifer M, Krakow D, Zimny S, Kopp F, Melmer A, Steinacker JM, Holl RW. Impact of physical activity on glycemic control and prevalence of cardiovascular risk factors in adults with type 1 diabetes: a cross-sectional multicenter study of 18,028 patients. Diabetes Care 2015;38:1536-1543

57. Herbst A, Bachran R, Kapellen T, Holl RW. Effects of regular physical activity on control of glycemia in pediatric patients with type 1 diabetes mellitus. Archives of Pediatrics & Adolescent Medicine 2006;160:573-577

58. Åman J, Skinner T, De Beaufort C, Swift PG, Aanstoot HJ, Cameron F, Diabetes HSGoC. Associations between physical activity, sedentary behavior, and glycemic control in a large cohort of adolescents with type 1 diabetes: the Hvidoere Study Group on Childhood Diabetes. Pediatric Diabetes 2009;10:234-239

59. Aouadi R, Khalifa R, Aouidet A, Ben Mansour A, Ben Rayana M, Mdini F, Bahri S, Stratton G. Aerobic training programs and glycemic control in diabetic children in relation to exercise frequency. Journal of Sports Medicine and Physical Fitness 2011;51:393

60. Campaigne BN, Gilliam TB, Spencer ML, Lampman RM, Schork MA. Effects of a physical activity program on metabolic control and cardiovascular fitness in children with insulin-dependent diabetes mellitus. Diabetes Care 1984;7:57-62

61. D'hooge R, Hellinckx T, Van Laethem C, Stegen S, De Schepper J, Van Aken S, Dewolf D, Calders P. Influence of combined aerobic and resistance training on metabolic control, cardiovascular fitness and quality of life in adolescents with type 1 diabetes: a randomized controlled trial. Clinical Rehabilitation 2011;25:349-359

62. Landt KW, Campaigne BN, James FW, Sperling MA. Effects of exercise training on insulin sensitivity in adolescents with type I diabetes. Diabetes Care 1985;8:461-465

63. Maggio AB, Rizzoli RR, Marchand LM, Ferrari S, Beghetti M, Farpour-Lambert NJ. Physical activity increases bone mineral density in children with type 1 diabetes. Medicine and Science in Sports and Exercise 2012;44:1206-1211

64. Rowland TW, Swadba LA, Biggs DE, Burke EJ, Reiter EO. Glycemic control with physical training in insulin-dependent diabetes mellitus. American Journal of Diseases of Children 1985;139:307-310

65. Salem MA, AboElAsrar MA, Elbarbary NS, ElHilaly RA, Refaat YM. Is exercise a therapeutic tool for improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial. Diabetology & Metabolic Syndrome 2010;2:47

66. Robertson K, Adolfsson P, Scheiner G, Hanas R, Riddell MC. Exercise in children and adolescents with diabetes. Pediatric Diabetes 2009;10:154-168

67. Zuijdwijk C, Vukovic R, Marks BE, Mandilou SVM, Ng SM, Wright N, Krogvold L, Barrett T, Agwu JC. Proceedings of 20th ISPAD science school for physicians 2021. Pediatric Diabetes 2021;22:843-849

68. Tsalikian E, Kollman C, Tamborlane WB, Beck RW, Fiallo-Scharer R, Fox L, Janz KF, Ruedy KJ, Wilson D, Xing D, Weinzimer SA. Prevention of hypoglycemia during exercise in children with type 1 diabetes by suspending basal insulin. Diabetes Care 2006;29:2200-2204

69. Admon G, Weinstein Y, Falk B, Weintrob N, Benzaquen H, Ofan R, Fayman G, Zigel L, Constantini N, Phillip M. Exercise with and without an insulin pump among children and adolescents with type 1 diabetes mellitus. Pediatrics 2005;116:e348-355

70. Taplin CE, Cobry E, Messer L, McFann K, Chase HP, Fiallo-Scharer R. Preventing post-exercise nocturnal hypoglycemia in children with type 1 diabetes. Journal of Pediatrics 2010;157:784-788.e781

71. Miller A, Nebesio T, DiMeglio L. Insulin dose changes in children attending a residential diabetes camp. Diabetic Medicine 2011;28:480-486

72. Campbell MD, Walker M, Trenell MI, Jakovljevic DG, Stevenson EJ, Bracken RM, Bain SC, West DJ. Large pre- and postexercise rapid-acting insulin reductions preserve glycemia and prevent early- but not late-onset hypoglycemia in patients with type 1 diabetes. Diabetes Care 2013;36:2217-2224

73. Perrone C, Laitano O, Meyer F. Effect of carbohydrate ingestion on the glycemic response of type 1 diabetic adolescents during exercise. Diabetes Care 2005;28:2537-2538

74. Riddell MC, Milliken J. Preventing exercise-induced hypoglycemia in type 1 diabetes using real-time continuous glucose monitoring and a new carbohydrate intake algorithm: an observational field study. Diabetes Technology & Therapeutics 2011;13:819-825

75. Dube MC, Lavoie C, Weisnagel SJ. Glucose or intermittent high-intensity exercise in glargine/glulisine users with T1DM. Medicine and Science in Sports and Exercise 2013;45:3-7

76. Dube M-C, Lavoie C, Galibois I, Weisnagel SJ. Nutritional strategies to prevent hypoglycemia at exercise in diabetic adolescents. Medicine and Science in Sports and Exercise 2012;44:1427-1432

77. Soon W, Guelfi K, Davis E, Smith G, Jones T, Fournier P. Effect of combining pre-exercise carbohydrate intake and repeated short sprints on the blood glucose response to moderate-intensity exercise in young individuals with Type 1 diabetes. Diabetic Medicine 2019;

78. West DJ, Stephens JW, Bain SC, Kilduff LP, Luzio S, Still R, Bracken RM. A combined insulin reduction and carbohydrate feeding strategy 30 min before running best preserves blood glucose concentration after exercise through improved fuel oxidation in type 1 diabetes mellitus. Journal of Sports Sciences 2011;29:279-289

79. Riddell M, Perkins BA. Exercise and glucose metabolism in persons with diabetes mellitus: perspectives on the role for continuous glucose monitoring. Journal of Diabetes Science and Technology 2009;3:914-923

80. Galassetti P, Riddell MC. Exercise and type 1 diabetes (T1DM). Comprehensive Physiology 2013;3:1309-1336

81. Galassetti P, Tate D, Neill RA, Morrey S, Wasserman DH, Davis SN. Effect of antecedent hypoglycemia on counterregulatory responses to subsequent euglycemic exercise in type 1 diabetes. Diabetes 2003;52:1761-1769

82. Galassetti P, Tate D, Neill RA, Richardson A, Leu SY, Davis SN. Effect of differing antecedent hypoglycemia on counterregulatory responses to exercise in type 1 diabetes. American Journal of Physiology-Endocrinology and Metabolism 2006;290:E1109-1117

83. Tran BD, Galassetti P. Exercise in pediatric type 1 diabetes. Pediatric Exercise Science 2014;26:375-383

84. Gomez AM, Gomez C, Aschner P, Veloza A, Muñoz O, Rubio C, Vallejo S. Effects of performing morning versus afternoon exercise on glycemic control and hypoglycemia frequency in type 1 diabetes patients on sensor-augmented insulin pump therapy. Journal of Diabetes Science and Technology 2015;9:619-624

85. Metcalf KM, Singhvi A, Tsalikian E, Tansey MJ, Zimmerman MB, Esliger DW, Janz KF. Effects of moderate-to-vigorous intensity physical activity on overnight and next-day hypoglycemia in active adolescents with type 1 diabetes. Diabetes Care 2014;37:1272-1278

86. McMahon SK, Ferreira LD, Ratnam N, Davey RJ, Youngs LM, Davis EA, Fournier PA, Jones TW. Glucose requirements to maintain euglycemia after moderate-intensity afternoon exercise in adolescents with type 1 diabetes are increased in a biphasic manner. Journal of Clinical Endocrinology and Metabolism 2007;92:963-968

87. Riddell MC, Gallen IW, Smart CE, Taplin CE, Adolfsson P, Lumb AN, Kowalski A, Rabasa-Lhoret R, McCrimmon RJ, Hume C. Exercise management in type 1 diabetes: a consensus statement. The Lancet Diabetes & Endocrinology 2017;5:377-390

88. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, Garg S, Heinemann L, Hirsch I, Amiel SA. International consensus on use of continuous glucose monitoring. Diabetes Care 2017;40:1631-1640

89. Suzuki J, Urakami T, Yoshida K, Kuwabara R, Mine Y, Aoki M, Morioka I. Association between scanning frequency of flash glucose monitoring and continuous glucose monitoring-derived glycemic makers in children and adolescents with type 1 diabetes. Pediatrics International 2021;63:154-159

90. Mathis D, Vence L, Benoist C. Beta-Cell death during progression to diabetes. Nature 2001;414:792-798

91. Salem MA, AboElAsrar MA, Elbarbary NS, ElHilaly RA, Refaat YM. Is exercise a therapeutic tool for improvement of cardiovascular risk factors in adolescents with type 1 diabetes mellitus? A randomised controlled trial. Diabetology and Metabolic Syndrome 2010;2:47

92. Patterson CC, Karuranga S, Salpea P, Saeedi P, Dahlquist G, Soltesz G, Ogle GD. Worldwide estimates of incidence, prevalence and mortality of type 1 diabetes in children and adolescents: Results from the International Diabetes Federation Diabetes Atlas. Diabetes Research and Clinical Practice 2019;157:107842

93. Diabetes Atlas [article online], 2017. Available from http://www.diabetesatlas.org/. 2017

94. Waden J, Forsblom C Fau - Thorn LM, Thorn Lm Fau - Saraheimo M, Saraheimo M Fau - Rosengard-Barlund M, Rosengard-Barlund M Fau - Heikkila O, Heikkila O Fau - Lakka TA, Lakka Ta Fau - Tikkanen H, Tikkanen H Fau - Groop P-H, Groop PH. Physical activity and diabetes complications in patients with type 1 diabetes: the Finnish Diabetic Nephropathy (FinnDiane) Study. Diabetes Care 2008;31:230-232

95. Fuentes-Antras J, Picatoste B, Gomez-Hernandez A, Egido J, Tunon J, Lorenzo O. Updating experimental models of diabetic cardiomyopathy. Journal of Diabetes Research 2015;2015

96. Groop PH, Thomas Mc Fau - Moran JL, Moran Jl Fau - Waden J, Waden J Fau - Thorn LM, Thorn Lm Fau - Makinen V-P, Makinen Vp Fau - Rosengard-Barlund M, Rosengard-Barlund M Fau - Saraheimo M, Saraheimo M Fau - Hietala K, Hietala K Fau - Heikkila O, Heikkila O Fau - Forsblom C, Forsblom C. The presence and severity of chronic kidney disease predicts all-cause mortality in type 1 diabetes. Diabetes 2009;58:1651-1658

97. Warburton DE, Nicol CW, Bredin SS. Health benefits of physical activity: the evidence. Canadian Medical Association Journal 2006;174:801-809

98. Warburton DE, Bredin SS. Health benefits of physical activity: a systematic review of current systematic reviews. Current Opinion in Cardiology 2017;32:541-556

99. Yardley JE, Kenny GP, Perkins BA, Riddell MC, Balaa N, Malcolm J, Boulay P, Khandwala F, Sigal RJ. Resistance Versus Aerobic Exercise: Acute effects on glycemia in type 1 diabetes. Diabetes Care 2013;36:537-542

100. Codella R, Terruzzi I, Luzi L. Why should people with type 1 diabetes exercise regularly? Acta Diabetologica 2017;54:615-630

101. Warburton DE, Bredin SS. Lost in Translation: What Does the Physical Activity and Health Evidence Actually Tell Us? In *Lifestyle in Heart Health and Disease*, Elsevier, 2018, p. 175-186

102. Warburton DE, Bredin SS. Reflections on physical activity and health: what should we recommend? Canadian Journal of Cardiology 2016;32:495-504

103. Vanhees L, Geladas N, Hansen D, Kouidi E, Niebauer J, Reiner Ž, Cornelissen V, Adamopoulos S, Prescott E, Börjesson M. Importance of characteristics and modalities of physical activity and exercise in the management of cardiovascular health in individuals with cardiovascular risk factors: recommendations from the EACPR (Part II). European Journal of Preventive Cardiology 2012;19:1005-1033

104. Chudyk A, Petrella RJ. Effects of exercise on cardiovascular risk factors in type 2 diabetes: a meta-analysis. Diabetes Care 2011;34:1228-1237

105. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Medicine 2009;6:e1000097

106. PEDro Scare [article online], Available from https://www.pedro.org.au/. Accessed 11 Oct 2017

107. Gusso SA-Ohoo, Pinto T, Baldi JC, Derraik JGB, Cutfield WS, Hornung T, Hofman PL. Exercise Training Improves but Does Not Normalize Left Ventricular Systolic and Diastolic Function in Adolescents With Type 1 Diabetes. Diabetes Care 2017;40:1264-1272

108. Aouadi R, Khalifa R, Aouidet A, Ben Mansour A, Ben Rayana M, Mdini F, Bahri S, Stratton G. Aerobic training programs and glycemic control in diabetic children in relation to exercise frequency. Journal Sports Medicine and Physical Fitness 2011;51:393-400

109. Brazeau AS, Gingras V, Leroux C, Suppere C, Mircescu H, Desjardins K, Briand P, Ekoe JM, Rabasa-Lhoret R. A pilot program for physical exercise promotion in adults with type 1 diabetes: the PEP-1 program. Applied Physiology, Nutrition, and Metabolism 2014;39:465-471

110. Campaigne Bn Fau - Landt KW, Landt Kw Fau - Mellies MJ, Mellies Mj Fau - James FW, James Fw Fau - Glueck CJ, Glueck Cj Fau - Sperling MA, Sperling MA. The Effects of Physical Training on Blood Lipid Profiles in Adolescents With Insulin-Dependent Diabetes Mellitus. Diabetes Care 1985;7:57-62

111. Dahl-Jorgensen K Fau - Meen HD, Meen Hd Fau - Hanssen KF, Hanssen Kf Fau - Aagenaes O, Aagenaes O. The effect of exercise on diabetic control and hemoglobin A1 (HbA1) in children. Acta Paediatrica Scandinavica Supplement 1980;283:53-56

112. Durak EP, Jovanovic-Peterson L, Peterson CM. Randomized crossover study of effect of resistance training on glycemic control, muscular strength, and cholesterol in type I diabetic men. Diabetes Care 1990;13:1039-1043

113. Fuchsjager-Mayrl G, Pleiner J, Wiesinger GF, Sieder AE, Quittan M, Nuhr MJ, Francesconi C, Seit HP, Francesconi M, Schmetterer L, Wolzt M. Exercise training improves vascular endothelial function in patients with type 1 diabetes. Diabetes Care 2002;25:1795-1801

114. Heyman E, Toutain C, Delamarche P, Berthon P, Briard D, Youssef H, Dekerdanet M, Gratas-Delamarche A. Exercise training and cardiovascular risk factors in type 1 diabetic adolescent girls. Pediatric Exercise Science 2007;19:408-419

115. Huttunen NP, Lankela SL, Knip M, Lautala P, Kaar ML, Laasonen K, Puukka R. Effect of once-a-week training program on physical fitness and metabolic control in children with IDDM. Diabetes Care 1989;12:737-740

116. Laaksonen DE, Atalay M, Niskanen LK, Mustonen J, Sen CK, Lakka TA, Uusitupa M. Aerobic exercise and the lipid profile in type 1 diabetic men: a randomized controlled trial. Medicine and Science in Sports and Exercise 2000;32:1541-1548

117. Landt Kw Fau - Campaigne BN, Campaigne Bn Fau - James FW, James Fw Fau - Sperling MA, Sperling MA. Effects of exercise training on insulin sensitivity in adolescents with type I diabetes. Diabetes Care 1985;8:461-465

118. Newton KH, Wiltshire EJ, Elley CR. Pedometers and text messaging to increase physical activity: randomized controlled trial of adolescents with type 1 diabetes. Diabetes Care 2009;32:813-815

119. Perry TL, Mann JI, Lewis-Barned NJ, Duncan AW, Waldron MA, Thompson C. Lifestyle intervention in people with insulin-dependent diabetes mellitus (IDDM). European Journal of Clinical Nutrition 1997;51:757-763

120. Roberts L, Jones T, Fournier P. Exercise training and glycemic control in adolescents with poorly controlled type 1 diabetes mellitus. Journal of Pediatric Endocrinology & Metabolism 2002;15:621-627

121. Rowland Tw Fau - Swadba LA, Swadba La Fau - Biggs DE, Biggs De Fau - Burke EJ, Burke Ej Fau - Reiter EO, Reiter EO. Glycemic control with physical training in insulin-dependent diabetes mellitus. American Journal of Diseases of Children 1985;139:307-310

122. Stratton R, Wilson DP, Endres RK, Goldstein DE. Improved glycemic control after supervised 8-wk exercise program in insulin-dependent diabetic adolescents. Diabetes Care 1987;10:589-593

123. Tunar M, Ozen S, Goksen D, Asar G, Bediz CS, Darcan S. The effects of Pilates on metabolic control and physical performance in adolescents with type 1 diabetes mellitus. Journal of Diabetic Complications 2012;26:348-351

124. Wallberg-Henriksson H Fau - Gunnarsson R, Gunnarsson R Fau - Rossner S, Rossner S Fau - Wahren J, Wahren J. Long-term physical training in female type 1 (insulin-dependent) diabetic patients: absence of significant effect on glycaemic control and lipoprotein levels. Diabetologia 1986;29:53-57

125. Wong CH, Chiang YC, Wai JP, Lo FS, Yeh CH, Chung SC, Chang CW. Effects of a home-based aerobic exercise programme in children with type 1 diabetes mellitus. Journal of Clinical Nursing 2011;20:681-691

126. Yki-Jarvinen H Fau - DeFronzo RA, DeFronzo Ra Fau - Koivisto VA, Koivisto VA. Normalization of insulin sensitivity in type I diabetic subjects by physical training during insulin pump therapy. Diabetes Care 1984;7:520-527

127. Laaksonen DE, Atalay M, Niskanen LK, Mustonen J, Sen CK, Lakka TA, Uusitupa MI. Aerobic exercise and the lipid profile in type 1 diabetic men: a randomized controlled trial. Medicine & Science & Sports & Exercise 2000;32:1541-1548

128. Maggio AB, Rizzoli RR, Marchand LM, Ferrari S, Beghetti M, Farpour-Lambert NJ. Physical activity increases bone mineral density in children with type 1 diabetes. Medicine & Science & Sports & Exercise 2012;44:1206-1211

129. Al Khalifah R, Suppère C, Haidar A, Rabasa-Lhoret R, Ladouceur M, Legault L. Association of aerobic fitness level with exercise-induced hypoglycaemia in Type 1 diabetes. Diabetic Medicine 2016;33:1686-1690

130. Martin B-J, Arena R, Haykowsky M, Hauer T, Austford LD, Knudtson M, Aggarwal S, Stone JA. Cardiovascular fitness and mortality after contemporary cardiac rehabilitation. In *Mayo Clinic Proceedings*. Elsevier, p. 455-463

131. Kokkinos P, Myers J, Faselis C, Panagiotakos DB, Doumas M, Pittaras A, Manolis A, Kokkinos JP, Karasik P, Greenberg M. Exercise capacity and mortality in older men: a 20-year follow-up study. Circulation 2010;122:790-797

132. Eijsvogels TM, Molossi S, Lee D-c, Emery MS, Thompson PD. Exercise at the extremes: the amount of exercise to reduce cardiovascular events. Journal of the American College of Cardiology 2016;67:316-329

133. Einarson TR, Acs A, Ludwig C, Panton UH. Prevalence of cardiovascular disease in type 2 diabetes: a systematic literature review of scientific evidence from across the world in 2007–2017. Cardiovascular Diabetology 2018;17:1-19

134. De Ferranti SD, De Boer IH, Fonseca V, Fox CS, Golden SH, Lavie CJ, Magge SN, Marx N, McGuire DK, Orchard TJ. Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. Circulation 2014;130:1110-1130

135. Maahs D, Daniels S, de Ferranti S, Dichek H, Flynn J, Goldstein B, Kelly A, Nadeau K, Martyn-Nemeth P, Osganian S. American Heart Association Atherosclerosis, Hypertension and Obesity in Youth Committee of the Council on Cardiovascular Disease in the Young, Council on Clinical Cardiology, Council on Cardiovascular and Stroke Nursing, Council for High Blood Pressure Research, and Council on Lifestyle and Cardiometabolic Health. Cardiovascular disease risk factors in youth with diabetes mellitus: a scientific statement from the American Heart Association. Circulation 2014;130:1532-1558

136. Haskell WL, Lee I-M, Pate RR, Powell KE, Blair SN, Franklin BA, Macera CA, Heath GW, Thompson PD, Bauman A. Physical activity and public health: updated recommendation for adults from the American College of Sports Medicine and the American Heart Association. Circulation 2007;116:1081

137. Minges KE, Whittemore R, Weinzimer SA, Irwin ML, Redeker NS, Grey M. Correlates of overweight and obesity in 5529 adolescents with type 1 diabetes: The T1D Exchange Clinic Registry. Diabetes Research and Clinical Practice 2017;126:68-78

138. Nørgaard K, Feldt-Rasmussen B, Borch-Johnsen K, Saelan H, Deckert T. Prevalence of hypertension in type 1 (insulin-dependent) diabetes mellitus. Diabetologia 1990;33:407-410

139. Whelton SP, Chin A, Xin X, He J. Effect of aerobic exercise on blood pressure: a meta-analysis of randomized, controlled trials. Annals of Internal Medicine 2002;136:493-503

140. Lima LC, Assis GV, Hiyane W, Almeida WS, Arsa G, Baldissera V, Campbell CS, Simões HG. Hypotensive effects of exercise performed around anaerobic threshold in type 2 diabetic patients. Diabetes Research and Clinical Practice 2008;81:216-222

141. Kalyva E, Malakonaki E, Eiser C, Mamoulakis D. Health-related quality of life (HRQoL) of children with type 1 diabetes mellitus (T1DM): self and parental perceptions. Pediatric Diabetes 2011;12:34-40

142. Cai H, Li G, Zhang P, Xu D, Chen L. Effect of exercise on the quality of life in type 2 diabetes mellitus: a systematic review. Quality of Life Research 2017;26:515-530

143. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. Diabetes Care 2010;33:1389-1394

144. Zoungas S, Patel A, Chalmers J, De Galan BE, Li Q, Billot L, Woodward M, Ninomiya T, Neal B, MacMahon S. Severe hypoglycemia and risks of vascular events and death. New England Journal of Medicine 2010;363:1410-1418

145. Giménez M, López JJ, Castell C, Conget I. Hypoglycaemia and cardiovascular disease in Type 1 Diabetes. Results from the Catalan National Public Health registry on insulin pump therapy. Diabetes Research and Clinical Practice 2012;96:e23-e25

146. Kacerovsky M, Jones J, Schmid AI, Barosa C, Lettner A, Kacerovsky-Bielesz G, Szendroedi J, Chmelik M, Nowotny P, Chandramouli V. Postprandial and fasting hepatic glucose fluxes in longstanding type 1 diabetes. Diabetes 2011:DB_101001

147. Yardley JE, Iscoe KE, Sigal RJ, Kenny GP, Perkins BA, Riddell MC. Insulin pump therapy is associated with less post-exercise hyperglycemia than multiple daily injections: an observational study of physically active type 1 diabetes patients. Diabetes Technology & Therapeutics 2013;15:84-88

148. Iliodromiti S, Celis-Morales CA, Lyall DM, Anderson J, Gray SR, Mackay DF, Nelson SM, Welsh P, Pell JP, Gill JM. The impact of confounding on the associations of different adiposity measures with the incidence of cardiovascular disease: a cohort study of 296 535 adults of white European descent. European Heart Journal 2018;39:1514-1520

149. Quirk H, Blake H, Tennyson R, Randell TL, Glazebrook C. Physical activity interventions in children and young people with Type 1 diabetes mellitus: a systematic review with meta-analysis. Diabetic Medicine 2014;31:1163-1173

150. Tonoli C, Heyman E, Roelands B, Buyse L, Cheung SS, Berthoin S, Meeusen R. Effects of different types of acute and chronic (training) exercise on glycaemic control in type 1 diabetes mellitus. Sports Medicine 2012;42:1059-1080

151. Kennedy A, Nirantharakumar K, Chimen M, Pang TT, Hemming K, Andrews RC, Narendran P. Does exercise improve glycaemic control in type 1 diabetes? A systematic review and meta-analysis. PloS One 2013;8:e58861

152. Ostman C, Jewiss D, King N, Smart N. Clinical outcomes to exercise training in type 1 diabetes: A systematic review and meta-analysis. Diabetes Research and Clinical Practice 2018;139:380-391

153. Seeger J, Thijssen D, Noordam K, Cranen M, Hopman M, Nijhuis-van der Sanden M. Exercise training improves physical fitness and vascular function in children with type 1 diabetes. Diabetes, Obesity and Metabolism 2011;13:382-384

154. Fuchsjäger-Mayrl G, Pleiner J, Wiesinger GF, Sieder AE, Quittan M, Nuhr MJ, Francesconi C, Seit H-P, Francesconi M, Schmetterer L. Exercise training improves vascular endothelial function in patients with type 1 diabetes. Diabetes Care 2002;25:1795-1801

155. Riebe D, Ehrman JK, Liguori G, Magal M. *ACSM's Guidelines for Exercise Testing and Prescription*. Riebe D, Ehrman JK, Liguori G, Magal M, Eds., Philadelphia: Philadelphia : Wolters Kluwer, American College of Sports Medicine 2018;

156. American Diabetes Association. Physical activity/exercise and diabetes mellitus. Diabetes Care 2003;26:s73-s77

157. Tuominen JA, Karonen S-L, Melamies L, Bolli G, Koivisto V. Exercise-induced hypoglycaemia in IDDM patients treated with a short-acting insulin analogue. Diabetologia 1995;38:106-111

158. Farinha JB, Krause M, Rodrigues-Krause J, Reischak-Oliveira A. Exercise for type 1 diabetes mellitus management: General considerations and new directions. Medical Hypotheses 2017;104:147-153

159. Robertson K, Riddell MC, Guinhouya BC, Adolfsson P, Hanas R. Exercise in children and adolescents with diabetes. Pediatric Diabetes 2014;15:203-223

160. Bally L, Zueger T, Buehler T, Dokumaci AS, Speck C, Pasi N, Ciller C, Paganini D, Feller K, Loher H, Rosset R, Wilhelm M, Tappy L, Boesch C, Stettler C. Metabolic and hormonal response

to intermittent high-intensity and continuous moderate intensity exercise in individuals with type 1 diabetes: a randomised crossover study. Diabetologia 2016;59:776-784

161. Dube MC, Lavoie C, Weisnagel SJ. Glucose or intermittent high-intensity exercise in glargine/glulisine users with T1DM. Medicine and Science in Sports and Exercise 2013;45:3-7

162. Gluchowska B, Zebrowska A, Kaminski T. Glycaemic control in response to continuous and intermittent physical exercise in patients with type 1 diabetes. Diabetic Medicine 2016;33:25-26

163. Iscoe KE, Riddell MC. Continuous moderate-intensity exercise with or without intermittent high-intensity work: Effects on acute and late glycaemia in athletes with Type1 diabetes mellitus. Diabetic Medicine 2011;28:824-832

164. Moser O, Tschakert G, Mueller A, Groeschl W, Pieber TR, Obermayer-Pietsch B, Koehler G, Hofmann P. Effects of high-intensity interval exercise versus moderate continuous exercise on glucose homeostasis and hormone response in patients with type 1 diabetes mellitus using novel ultra-long-acting insulin. PloS One 2015;10

165. Taleb N, Emami A, Suppere C, Messier V, Legault L, Ladouceur M, Chiasson JL, Haidar A, Rabasa-Lhoret R. Efficacy of single-hormone and dual-hormone artificial pancreas during continuous and interval exercise in adult patients with type 1 diabetes: randomised controlled crossover trial. Diabetologia 2016;59:2561-2571

166. Zebrowska A, Hall B, Maszczyk A, Banas R, Urban J. Brain-derived neurotrophic factor, insulin like growth factor-1 and inflammatory cytokine responses to continuous and intermittent exercise in patients with type 1 diabetes. Diabetes Research and Clinical Practice 2018;144:126-136

167. Campbell MD, West DJ, Bain SC, Kingsley MI, Foley P, Kilduff L, Turner D, Gray B, Stephens JW, Bracken RM. Simulated games activity vs continuous running exercise: a novel

comparison of the glycemic and metabolic responses in T1DM patients. Scandinavian Journal of Medicine & Science in Sports 2015;25:216-222

168. Lee AS, Way KL, Johnson NA, Twigg SM. High-intensity interval exercise and hypoglycaemia minimisation in adults with type 1 diabetes: A randomised cross-over trial. Journal of Diabetes and its Complications 2020;34:107514

169. Adolfsson P, Nilsson S, Albertsson-Wikland K, Lindblad B. Hormonal response during physical exercise of different intensities in adolescents with type 1 diabetes and healthy controls. Pediatric Diabetes 2012;13:587-596

170. Jayawardene DC, McAuley SA, Horsburgh JC, Gerche AL, Jenkins AJ, Ward GM, MacIsaac RJ, Roberts TJ, Grosman B, Kurtz N, Roy A, O'Neal DN. Closed-loop insulin delivery for adults with type 1 diabetes undertaking high-intensity interval exercise versus moderate-intensity exercise: A randomized, crossover study. Diabetes Technology and Therapeutics 2017;19:340-348

171. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Medicine 2009:e1000097

172. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS, Eldridge SM. RoB 2: a revised tool for assessing risk of bias in randomised trials. British Medical Journal 2019;366

173. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Medical Research Methodology 2014;14:1-13

174. Hubinger A, Ridderskamp I, Lehmann E, Gries FA. Metabolic response to different forms of physical exercise in type I diabetics and the duration of the glucose lowering effect. European Journal of Clinical Investigation 1985;15:197-203

175. Särnblad S, Ponsot E, Leprêtre PM, Kadi F. Acute effects of aerobic continuous, intermittent and resistance exercise on glycemia in adolescents males with type 1 diabetes. Pediatric Diabetes 2021;

176. Bally L, Zueger T, Pasi N, Carlos C, Paganini D, Stettler C. Accuracy of continuous glucose monitoring during differing exercise conditions. Diabetes Research and Clinical Practice 2016;112:1-5

177. Maran A, Pavan P, Bonsembiante B, Brugin E, Ermolao A, Avogaro A, Zaccaria M. Continuous glucose monitoring reveals delayed nocturnal hypoglycemia after intermittent high-intensity exercise in nontrained patients with type 1 diabetes. Diabetes Technology & Therapeutics 2010;12:763-768

178. Guelfi KJ, Jones TW, Fournier PA. The decline in blood glucose levels is less with intermittent high-intensity compared with moderate exercise in individuals with type 1 diabetes. Diabetes Care 2005;28:1289-1294

179. Moser O, Mader JK, Tschakert G, Mueller A, Groeschl W, Pieber TR, Koehler G, Messerschmidt J, Hofmann P. Accuracy of Continuous Glucose Monitoring (CGM) during Continuous and High-Intensity Interval Exercise in Patients with Type 1 Diabetes Mellitus. Nutrients 2016;8

180. Scott SN, Cocks M, Andrews RC, Narendran P, Purewal TS, Cuthbertson DJ, Wagenmakers AJ, Shepherd SO. Fasted high-intensity interval and moderate-intensity exercise do not lead to detrimental 24-hour blood glucose profiles. The Journal of Clinical Endocrinology & Metabolism 2019;104:111-117

181. Rempel M, Yardley JE, MacIntosh A, Hay JL, Bouchard D, Cornish S, Marks SD, Hai Y, Gordon JW, McGavock J. Vigorous intervals and hypoglycemia in type 1 diabetes: a randomized cross over trial. Scientific Reports 2018;8:1-9

182. Zaharieva D, Yavelberg L, Jamnik V, Cinar A, Turksoy K, Riddell MC. The effects of basal insulin suspension at the start of exercise on blood glucose levels during continuous versus circuit-based exercise in individuals with type 1 diabetes on continuous subcutaneous insulin infusion. Diabetes Technology & Therapeutics 2017;19:370-378

183. Taleb N, Haidar A, Suppere C, Emami A, Messier V, Legault L, Ladouceur M, Chiasson JL, Remi RL. The efficacy of single-and dual-hormone artificial pancreas systems at regulating glucose levels during continuous and interval exercise in type 1 diabetes: Randomised four-way trial. Diabetes Technology and Therapeutics Conference: 9th International Conference on Advanced Technologies and Treatments for Diabetes, ATTD 2016;18

184. Särnblad S, Ponsot E, Leprêtre PM, Kadi F. Acute effects of aerobic continuous, intermittent, and resistance exercise on glycemia in adolescents males with type 1 diabetes. Pediatric Diabetes 2021;

185. Dubé M-C, Lavoie C, Weisnagel SJ. Effect of intermittent high intensity exercise on counter-regulatory hormones in type 1 diabetes glargine/glulisine users. Journal of Diabetes Research and Clinical Metabolism 2014;3:8

186. Wolfe RR, Nadel ER, Shaw J, Stephenson LA, Wolfe MH. Role of changes in insulin and glucagon in glucose homeostasis in exercise. The Journal of Clinical Investigation 1986;77:900-907

187. Mallad A, Hinshaw L, Schiavon M, Dalla Man C, Dadlani V, Basu R, Lingineni R, Cobelli C, Johnson ML, Carter R. Exercise effects on postprandial glucose metabolism in type 1 diabetes: a triple-tracer approach. American Journal of Physiology-Endocrinology and Metabolism 2015;308:E1106-E1115

188. Yardley JE, Brockman NK, Bracken RM. Could age, sex and physical fitness affect blood glucose responses to exercise in type 1 diabetes? Frontiers in Endocrinology 2018;9:674

189. Riddell MC. The endocrine response and substrate utilization during exercise in children and adolescents. Journal of Applied Physiology 2008;105:725-733

190. Silverman HG, Mazzeo RS. Hormonal responses to maximal and submaximal exercise in trained and untrained men of various ages. The Journals of Gerontology Series A: Biological Sciences and Medical Sciences 1996;51:B30-B37

191. Pritzlaff-Roy CJ, Widemen L, Weltman JY, Abbott R, Gutgesell M, Hartman ML, Veldhuis JD, Weltman A. Gender governs the relationship between exercise intensity and growth hormone release in young adults. Journal of Applied Physiology 2002;92:2053-2060

192. Wu N, Bredin SS, Jamnik VK, Koehle MS, Guan Y, Shellington EM, Li Y, Li J, Warburton DE. Association between physical activity level and cardiovascular risk factors in adolescents living with type 1 diabetes mellitus: a cross-sectional study. Cardiovascular Diabetology 2021;20:1-11

193. Chetty T, Shetty V, Fournier PA, Adolfsson P, Jones TW, Davis EA. Exercise management for young people with type 1 diabetes: a structured approach to the exercise consultation. Frontiers in Endocrinology 2019;10:326

194. Dawson SI, Willis J, Florkowski CM, Scott RS. Cause-specific mortality in insulin-treated diabetic patients: a 20-year follow-up. Diabetes Research and Clinical Practice 2008;80:16-23

195. Skrivarhaug T, Bangstad H-J, Stene L, Sandvik L, Hanssen K, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006;49:298-305

196. Steigleder-Schweiger C, Rami-Merhar B, Waldhör T, Fröhlich-Reiterer E, Schwarz I, Fritsch M, Borkenstein M, Schober E. Prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes in Austria. European Journal of Pediatrics 2012;171:1193-1202

197. Committee DCCPGE. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. Canadian Journal of Diabetes 2018;42:S1-S325

198. Herbst A, Kordonouri O, Schwab KO, Schmidt F, Holl RW. Impact of physical activity on cardiovascular risk factors in children with type 1 diabetes: a multicenter study of 23,251 patients. Diabetes Care 2007;30:2098-2100

199. Mohammed J, Deda L, Clarson CL, Stein RI, Cuerden MS, Mahmud FH. Assessment of habitual physical activity in adolescents with type 1 diabetes. Canadian Journal of Diabetes 2014;38:250-255

200. Sirard JR, Pate RR. Physical activity assessment in children and adolescents. Sports Medicine 2001;31:439-454

201. Turkson-Ocran RAN, Nmezi NA, Botchway MO, Szanton SL, Golden SH, Cooper LA, Commodore-Mensah Y. Comparison of Cardiovascular Disease Risk Factors Among African Immigrants and African Americans: An Analysis of the 2010 to 2016 National Health Interview Surveys. Journal of the American Heart Association 2020;9:e013220

202. World Health Organization . *Waist circumference and waist-hip ratio: report of a WHO expert consultation, Geneva, 8-11 December* 2008

203. Morris NM, Udry JR. Validation of a self-administered instrument to assess stage of adolescent development. Journal of Youth and Adolescence 1980;9:271-280

204. Chan NP, Sung RY, Kong AP, Goggins WB, So HK, Nelson EAS. Reliability of pubertal self-assessment in Hong Kong Chinese children. Journal of Paediatrics and Child Health 2008;44:353-358

205. Carter AW. An Analysis of the Assessment of Glycated Hemoglobin Using A1cNow+™ Point-of-Care Device Compared to Central Laboratory Testing—an Important Addition to

Pharmacist-Managed Diabetes Programs? Journal of Diabetes Science and Technology 2008;2:828-830

206. Panz VR, Raal FJ, Paiker J, Immelman R, Miles H. Performance of the CardioChekTM PA and Cholestech LDX (R) point-of-care analysers compared to clinical diagnostic laboratory methods for the measurement of lipids: cardiovascular topic. Cardiovascular Journal of South Africa 2005;16:112-116

207. Bouten CV, Koekkoek KT, Verduin M, Kodde R, Janssen JD. A triaxial accelerometer and portable data processing unit for the assessment of daily physical activity. IEEE Transactions on Biomedical Engineering 1997;44:136-147

208. Evenson KR, Catellier DJ, Gill K, Ondrak KS, McMurray RG. Calibration of two objective measures of physical activity for children. Journal of Sports Sciences 2008;26:1557-1565

209. Tremblay MS, Warburton DE, Janssen I, Paterson DH, Latimer AE, Rhodes RE, Kho ME, Hicks A, LeBlanc AG, Zehr L. New Canadian physical activity guidelines. Applied Physiology, Nutrition, and Metabolism 2011;36:36-46

210. Dunstan DW, Kingwell BA, Larsen R, Healy GN, Cerin E, Hamilton MT, Shaw JE, Bertovic DA, Zimmet PZ, Salmon J, Owen N. Breaking Up Prolonged Sitting Reduces Postprandial Glucose and Insulin Responses. Diabetes Care 2012;35:976-983

211. Biddle GJ, Edwardson CL, Rowlands AV, Davies MJ, Bodicoat DH, Hardeman W, Eborall H, Sutton S, Griffin S, Khunti K. Differences in objectively measured physical activity and sedentary behaviour between white Europeans and south Asians recruited from primary care: cross-sectional analysis of the PROPELS trial. BMC Public Health 2019;19:95

212. Freedson P, Pober D, Janz KF. Calibration of accelerometer output for children. Medicine & Science in Sports & Exercise 2005;37:S523-S530

213. Warburton DE, Jamnik V, Bredin SS, Shephard RJ, Gledhill N. The 2019 physical activity readiness questionnaire for everyone (PAR-Q+) and electronic physical activity readiness medical examination (ePARmed-X+). The Health & Fitness Journal of Canada 2018;11:80-83

214. Yardley JE, Kenny GP, Perkins BA, Riddell MC, Malcolm J, Boulay P, Khandwala F, Sigal RJ. Effects of performing resistance exercise before versus after aerobic exercise on glycemia in type 1 diabetes. Diabetes Care 2012;35:669-675

215. Cohen J. *Statistical power analysis for the behavioral sciences*. Academic press, 2013

216. Margeirsdottir H, Larsen J, Brunborg C, Øverby N, Dahl-Jørgensen K. High prevalence of cardiovascular risk factors in children and adolescents with type 1 diabetes: a population-based study. Diabetologia 2008;51:554-561

217. Kim JY, Han SH, Yang BM. Implication of high-body-fat percentage on cardiometabolic risk in middle-aged, healthy, normal-weight adults. Obesity 2013;21:1571-1577

218. Lee Y-B, Han K, Kim B, Lee S-E, Jun JE, Ahn J, Kim G, Jin S-M, Kim JH. Risk of early mortality and cardiovascular disease in type 1 diabetes: a comparison with type 2 diabetes, a nationwide study. Cardiovascular Diabetology 2019;18:157

219. Tecce N, Masulli M, Lupoli R, Della Pepa G, Bozzetto L, Palmisano L, Rivellese AA, Riccardi G, Capaldo B. Evaluation of cardiovascular risk in adults with type 1 diabetes: poor concordance between the 2019 ESC risk classification and 10-year cardiovascular risk prediction according to the Steno Type 1 Risk Engine. Cardiovascular Diabetology 2020;19:1-9

220. Gourgari E, Playford MP, Campia U, Dey AK, Cogen F, Gubb-Weiser S, Mete M, Desale S, Sampson M, Taylor A, Rother KI, Remaley AT, Mehta NN. Low cholesterol efflux capacity and abnormal lipoprotein particles in youth with type 1 diabetes: a case control study. Cardiovascular Diabetology 2018;17:158

221. Gourgari E, Ma J, Playford MP, Mehta NN, Goldman R, Remaley AT, Gordon SM. Proteomic alterations of HDL in youth with type 1 diabetes and their associations with glycemic control: a case–control study. Cardiovascular Diabetology 2019;18:1-11

222. Abregu AV, Carrizo TR, Prado MM, Velarde MS, Diaz EI, Perez AR, Fonio MC, Bazan MC. Cardiovascular risk factors in children with type 1 diabetes and their relationship with the glycemic control. Medicina 2005;65:385

223. Järvisalo MJ, Raitakari M, Toikka JO, Putto-Laurila A, Rontu R, Laine S, Lehtimäki T, Rönnemaa T, Viikari J, Raitakari OT. Endothelial dysfunction and increased arterial intima-media thickness in children with type 1 diabetes. Circulation 2004;109:1750-1755

224. Singh TP, Groehn H, Kazmers A. Vascular function and carotid intimal-medial thickness in children with insulin-dependent diabetes mellitus. Journal of the American College of Cardiology 2003;41:661-665

225. Harrington J, Peña AS, Gent R, Hirte C, Couper J. Aortic intima media thickness is an early marker of atherosclerosis in children with type 1 diabetes mellitus. The Journal of Pediatrics 2010;156:237-241

226. Katz ML, Guo Z, Cheema A, Laffel LM. Management of cardiovascular disease risk in teens with type 1 diabetes: perspectives of teens with and without dyslipidemia and parents. Pediatric Diabetes 2019;20:210-216

227. Johnson B, Norman P, Sanders T, Elliott J, Whitehead V, Campbell F, Hammond P, Ajjan R, Heller S. Working with Insulin, Carbohydrates, Ketones and Exercise to Manage Diabetes (WICKED): evaluation of a self-management course for young people with Type 1 diabetes. Diabetic Medicine 2019;36:1460-1467

228. Ligtenberg PC, Blans M, Hoekstra JB, van der Tweel I, Erkelens DW. No effect of long-term physical activity on the glycemic control in type 1 diabetes patients: a cross-sectional study. The Netherlands Journal of Medicine 1999;55:59-63

229. Wieliczko M, Gobert M, Mallet E. The participation in sports of diabetic children. A survey in the Rouen region. In *Annales de pediatrie*, 1991, p. 84-88

230. Valerio G, Spagnuolo MI, Lombardi F, Spadaro R, Siano M, Franzese A. Physical activity and sports participation in children and adolescents with type 1 diabetes mellitus. Nutrition, Metabolism and Cardiovascular Diseases 2007;17:376-382

231. Dimitri P, Joshi K, Jones N. Moving more: physical activity and its positive effects on long term conditions in children and young people. Archives of Disease in Childhood 2020;105:1035-1040

232. Macartney MJ, Notley SR, Herry CL, Seely AJ, Sigal RJ, Kenny GP. Cardiac autonomic modulation in type 1 diabetes during exercise-heat stress. Acta Diabetologica 2020;57:959-963

233. Lanhers C, Duclos M, Guttmann A, Coudeyre E, Pereira B, Ouchchane L. General practitioners' barriers to prescribe physical activity: the dark side of the cluster effects on the physical activity of their type 2 diabetes patients. PLoS One 2015;10:e0140429

234. Eisenmann JC. Physical activity and cardiovascular disease risk factors in children and adolescents: an overview. The Canadian Journal of Cardiology 2004;20:295-301

235. Komatsu WR, Gabbay MAL, Castro ML, Saraiva GL, Chacra AR, De Barros Neto TL, Dib SA. Aerobic exercise capacity in normal adolescents and those with type 1 diabetes mellitus. Pediatric Diabetes 2005;6:145-149

236. Williams B, Guelfi K, Jones T, Davis E. Lower cardiorespiratory fitness in children with type 1 diabetes. Diabetic Medicine 2011;28:1005-1007

237. Gusso S, Pinto T, Baldi JC, Derraik JG, Cutfield WS, Hornung T, Hofman PL. Exercise training improves but does not normalize left ventricular systolic and diastolic function in adolescents with type 1 diabetes. Diabetes Care 2017;40:1264-1272

238. Huttunen N-P, Lankela S-L, Knip M, Lautala P, Kaar M-L, Laasonen K, Puukka R. Effect of once-a-week training program on physical fitness and metabolic control in children with IDDM. Diabetes Care 1989;12:737-740

239. Martin B-J, Arena R, Haykowsky M, Hauer T, Austford LD, Knudtson M, Aggarwal S, Stone JA, Investigators A. Cardiovascular fitness and mortality after contemporary cardiac rehabilitation. In *Mayo Clinic Proceedings*, Elsevier, 2013, p. 455-463

240. Wahid A, Manek N, Nichols M, Kelly P, Foster C, Webster P, Kaur A, Friedemann Smith C, Wilkins E, Rayner M. Quantifying the association between physical activity and cardiovascular disease and diabetes: a systematic review and meta-analysis. Journal of the American Heart Association 2016;5:e002495

241. Cespedes EM, Rifas-Shiman SL, Redline S, Gillman MW, Peña MM, Taveras EM. Longitudinal associations of sleep curtailment with metabolic risk in mid-childhood. Obesity 2014;22:2586-2592

242. Morrison JA, Friedman LA, Gray-McGuire C. Metabolic syndrome in childhood predicts adult cardiovascular disease 25 years later: the Princeton Lipid Research Clinics Follow-up Study. Pediatrics 2007;120:340-345

243. Matthews KA, Pantesco EJ. Sleep characteristics and cardiovascular risk in children and adolescents: an enumerative review. Sleep Medicine 2016;18:36-49

244. Mullington JM, Haack M, Toth M, Serrador JM, Meier-Ewert HK. Cardiovascular, inflammatory, and metabolic consequences of sleep deprivation. Progress in Cardiovascular Diseases 2009;51:294-302

245. Perfect MM. The relations of sleep and quality of life to school performance in youth with type 1 diabetes. Journal of Applied School Psychology 2014;30:7-28

246. Pillar G, Schuscheim G, Weiss R, Malhotra A, McCowen KC, Shlitner A, Peled N, Shehadeh N. Interactions between hypoglycemia and sleep architecture in children with type 1 diabetes mellitus. The Journal of Pediatrics 2003;142:163-168

247. Matyka KA, Crawford C, Wiggs L, Dunger DB, Stores G. Alterations in sleep physiology in young children with insulin-dependent diabetes mellitus: relationship to nocturnal hypoglycemia. The Journal of Pediatrics 2000;137:233-238

248. Perfect MM, Patel PG, Scott RE, Wheeler MD, Patel C, Griffin K, Sorensen ST, Goodwin JL, Quan SF. Sleep, glucose, and daytime functioning in youth with type 1 diabetes. Sleep 2012;35:81-88

249. Lauderdale DS, Knutson KL, Yan LL, Liu K, Rathouz PJ. Sleep duration: how well do self-reports reflect objective measures? The CARDIA Sleep Study. Epidemiology (Cambridge, Mass) 2008;19:838

250. Spiegel K, Leproult R, Van Cauter E. Impact of sleep debt on metabolic and endocrine function. The Lancet 1999;354:1435-1439

251. Donga E, Van Dijk M, Van Dijk JG, Biermasz NR, Lammers G-J, Van Kralingen K, Hoogma RP, Corssmit EP, Romijn JA. Partial sleep restriction decreases insulin sensitivity in type 1 diabetes. Diabetes Care 2010;33:1573-1577

252. Sadeh A, Sharkey M, Carskadon MA. Activity-based sleep-wake identification: an empirical test of methodological issues. Sleep 1994;17:201-207

253. Kostkova M, Durdik P, Ciljakova M, Vojtkova J, Sujanska A, Pozorciakova K, Snahnicanova Z, Jancinova M, Banovcin P. Short-term metabolic control and sleep in children and adolescents with type 1 diabetes mellitus. Journal of Diabetes and its Complications 2018;32:580-585

254. Macaulay GC, Galland BC, Boucher SE, Wiltshire EJ, Haszard JJ, Campbell AJ, Black SM, Smith C, Elder D, Wheeler BJ. Impact of type 1 diabetes mellitus, glucose levels, and glycemic control on sleep in children and adolescents: a case–control study. Sleep 2020;43:zsz226

255. Manin G, Pons A, Baltzinger P, Moreau F, Iamandi C, Wilhelm J, Lenoble P, Kessler L, Kessler R. Obstructive sleep apnoea in people with Type 1 diabetes: prevalence and association with micro-and macrovascular complications. Diabetic Medicine 2015;32:90-96

256. Paruthi S, Brooks LJ, D'Ambrosio C, Hall WA, Kotagal S, Lloyd RM, Malow BA, Maski K, Nichols C, Quan SF. Recommended amount of sleep for pediatric populations: a consensus statement of the American Academy of Sleep Medicine. Journal of Clinical Sleep Medicine 2016;12:785-786

257. Panel CC, Watson NF, Badr MS, Belenky G, Bliwise DL, Buxton OM, Buysse D, Dinges DF, Gangwisch J, Grandner MA. Joint consensus statement of the American Academy of Sleep Medicine and Sleep Research Society on the recommended amount of sleep for a healthy adult: methodology and discussion. Sleep 2015;38:1161-1183

258. Luo J, Cao M, Sun F, Shi B, Wang X, Jing J. Association between outdoor activity and insufficient sleep in Chinese school-aged children. Medical Science Monitor: International Medical Journal of Experimental and Clinical Research 2020;26:e921617-921611

259. Spilsbury JC, Storfer-Isser A, Drotar D, Rosen CL, Kirchner LH, Benham H, Redline S. Sleep behavior in an urban US sample of school-aged children. Archives of Pediatrics & Adolescent Medicine 2004;158:988-994

260. Sluggett L, Wagner SL, Hardy C, Harris RL. Associations between sleep duration and indicators of cardiometabolic disease in Canadian children and adolescents: Analyses of the 2007–2009 Canadian Health Measures Survey. Childhood Obesity 2016;12:325-333

261. Loessl B, Valerius G, Kopasz M, Hornyak M, Riemann D, Voderholzer U. Are adolescents chronically sleep-deprived? An investigation of sleep habits of adolescents in the Southwest of Germany. Child: Care, Health and Development 2008;34:549-556

262. Olds T, Maher C, Blunden S, Matricciani L. Normative data on the sleep habits of Australian children and adolescents. Sleep 2010;33:1381-1388

263. Beebe DW. Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. Pediatric Clinics 2011;58:649-665

264. Cappuccio FP, Taggart FM, Kandala N-B, Currie A, Peile E, Stranges S, Miller MA. Meta-analysis of short sleep duration and obesity in children and adults. Sleep 2008;31:619-626

265. Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, Steer C, Sherriff A. Early life risk factors for obesity in childhood: cohort study. British Medical Journal 2005;330:1357

266. Spruyt K, Molfese DL, Gozal D. Sleep duration, sleep regularity, body weight, and metabolic homeostasis in school-aged children. Pediatrics 2011;127:e345-e352

267. Sung V, Beebe DW, VanDyke R, Fenchel MC, Crimmins NA, Kirk S, Hiscock H, Amin R, Wake M. Does sleep duration predict metabolic risk in obese adolescents attending tertiary services? A cross-sectional study. Sleep 2011;34:891-898

268. Hitze B, Bosy-Westphal A, Bielfeldt F, Settler U, Plachta-Danielzik S, Pfeuffer M, Schrezenmeir J, Mönig H, Müller M. Determinants and impact of sleep duration in children and adolescents: data of the Kiel Obesity Prevention Study. European Journal of Clinical Nutrition 2009;63:739-746

269. Narang I, Manlhiot C, Davies-Shaw J, Gibson D, Chahal N, Stearne K, Fisher A, Dobbin S, McCrindle BW. Sleep disturbance and cardiovascular risk in adolescents. Canadian Medical Association Journal 2012;184:E913-E920

270. von Schnurbein J, Boettcher C, Brandt S, Karges B, Dunstheimer D, Galler A, Denzer C, Denzer F, Vollbach H, Wabitsch M. Sleep and glycemic control in adolescents with type 1 diabetes. Pediatric Diabetes 2018;19:143-149

271. Jarrin DC, McGrath JJ, Drake CL. Beyond sleep duration: distinct sleep dimensions are associated with obesity in children and adolescents. International Journal of Obesity 2013;37:552-558

272. Garaulet M, Ortega F, Ruiz J, Rey-Lopez J, Beghin L, Manios Y, Cuenca-Garcia M, Plada M, Diethelm K, Kafatos A. Short sleep duration is associated with increased obesity markers in European adolescents: effect of physical activity and dietary habits. The HELENA study. International Journal of Obesity 2011;35:1308-1317

273. Júdice PB, Hetherington-Rauth M, Northstone K, Andersen LB, Wedderkopp N, Ekelund U, Sardinha LB, Collaborators ICsAD. Changes in Physical Activity and Sedentary Patterns on Cardiometabolic Outcomes in the Transition to Adolescence: International Children's Accelerometry Database 2.0. The Journal of Pediatrics 2020;225:166-173. e161

274. Herbst A, Kordonouri O, Schwab KO, Schmidt F, Holl RW. Impact of physical activity on cardiovascular risk factors in children with type 1 diabetes: a multicenter study of 23,251 patients. Diabetes Care 2007;30:2098-2100

275. Estrada CL, Danielson KK, Drum ML, Lipton RB. Insufficient sleep in young patients with diabetes and their families. Biological Research for Nursing 2012;14:48-54

276. Prince SA, Adamo KB, Hamel ME, Hardt J, Gorber SC, Tremblay M. A comparison of direct versus self-report measures for assessing physical activity in adults: a systematic review. International Journal of Behavioral Nutrition and Physical Activity 2008;5:1-24

277. Pedišić Ž, Dumuid D, S Olds T. Integrating sleep, sedentary behaviour, and physical activity research in the emerging field of time-use epidemiology: definitions, concepts, statistical methods, theoretical framework, and future directions. Kinesiology 2017;49:252-269

278. Johansson MS, Søgaard K, Prescott E, Marott JL, Schnohr P, Holtermann A, Korshøj M. Can we walk away from cardiovascular disease risk or do we have to 'huff and puff'? A cross-sectional compositional accelerometer data analysis among adults and older adults in the Copenhagen City Heart Study. International Journal of Behavioral Nutrition and Physical Activity 2020;17:1-18

279. Aadland E, Andersen LB, Migueles JH, Ortega FB, Kvalheim OM. Interpretation of associations between the accelerometry physical activity spectrum and cardiometabolic health and locomotor skills in two cohorts of children using raw, normalized, log-transformed, or compositional data. Journal of Sports Sciences 2020;38:2708-2719

280. Chastin SF, Palarea-Albaladejo J, Dontje ML, Skelton DA. Combined effects of time spent in physical activity, sedentary behaviors and sleep on obesity and cardio-metabolic health markers: a novel compositional data analysis approach. PloS One 2015;10:e0139984

281. Powell C, Browne LD, Carson BP, Dowd KP, Perry IJ, Kearney PM, Harrington JM, Donnelly AE. Use of compositional data analysis to show estimated changes in cardiometabolic health by reallocating time to light-intensity physical activity in older adults. Sports Medicine 2020;50:205-217

282. McGregor DE, Carson V, Palarea-Albaladejo J, Dall PM, Tremblay MS, Chastin SF. Compositional analysis of the associations between 24-h movement behaviours and health indicators among adults and older adults from the Canadian health measure survey. International Journal of Environmental Research and Public Health 2018;15:1779

283. Talarico R, Janssen I. Compositional associations of time spent in sleep, sedentary behavior and physical activity with obesity measures in children. International Journal of Obesity 2018;42:1508-1514

284. Brage S, Wedderkopp N, Ekelund U, Franks PW, Wareham NJ, Andersen LB, Froberg K. Features of the metabolic syndrome are associated with objectively measured physical activity and fitness in Danish children: the European Youth Heart Study (EYHS). Diabetes Care 2004;27:2141-2148

285. Larisch L-M, Kallings LV, Hagströmer M, Desai M, von Rosen P, Blom V. Associations between 24 h Movement Behavior and Mental Health in Office Workers. International Journal of Environmental Research and Public Health 2020;17:6214

286. Carson V, Tremblay MS, Chaput J-P, Chastin SF. Associations between sleep duration, sedentary time, physical activity, and health indicators among Canadian children and youth using compositional analyses. Applied Physiology, Nutrition, and Metabolism 2016;41:S294-S302

287. Lytle LA, Pasch KE, Farbakhsh K. The relationship between sleep and weight in a sample of adolescents. Obesity 2011;19:324-331

288. Hassan F, Davis MM, Chervin RD. No independent association between insufficient sleep and childhood obesity in the National Survey of Children's Health. Journal of Clinical Sleep Medicine 2011;7:153-157

289. Sivertsen B, Pallesen S, Sand L, Hysing M. Sleep and body mass index in adolescence: results from a large population-based study of Norwegian adolescents aged 16 to 19 years. BMC Pediatrics 2014;14:1-11

290. Monzon A, McDonough R, Meltzer LJ, Patton SR. Sleep and type 1 diabetes in children and adolescents: Proposed theoretical model and clinical implications. Pediatric Diabetes 2019;20:78-85

291. Poitras VJ, Gray CE, Borghese MM, Carson V, Chaput J-P, Janssen I, Katzmarzyk PT, Pate RR, Connor Gorber S, Kho ME. Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth. Applied Physiology, Nutrition, and Metabolism 2016;41:S197-S239

Appendices

Appendix A **Results of outcomes (Glucose, insulin, lactate, glucagon, cortisol) of included studies**

Study, year,	**Outcomes**				
	Glucose	*Insulin*	*Lactate*	*Glucagon*	*Cortisol*
Adolfsson et al., 2012[a]	**DE 0-60 min:** HIIE ↓ MICE ↓ **DE 0-60 min (changes, mmol/L):** HIIE -2.7 ± 4.8 vs MICE -4.1 ± 5.0 **DE 0-60 min (peak, mmol/L):** HIIE 11.4 ± 5.8 vs MICE 11.2 ± 5.0 **DE 0-60 min AUC (mmol/L/min):** HIIE 733 ± 443 vs MICE 873 ± 486	**DE 0-60 min (peak, mU/L):** HIIE 44.0 ± 29.7 vs MICE 36.8 ± 17.1 **DE 0-60 min AUC (mU/L/min):** HIIE 3334 ± 2670 vs MICE 3178 ± 1195	**DE 0-60 min (peak, mmol/L):** HIIE 8.9 ± 3.3 vs MICE 2.6 ± 0.8 **DE 0-60 min AUC (mmol/L/min):** HIIE 456 ± 98.3 vs MICE 212 ± 71.2	**DE 0-60 min (peak, pmol/L):** HIIE 33.8 ± 9.9 vs MICE 35.3 ± 8.6 **DE 0-60 min AUC (pmol/L/min):** HIIE 2596 ± 1161 vs MICE 3468 ± 742	**DE at 60 min (peak, nmol/L):** HIIE 538 ± 222 vs MICE 466 ± 183 **DE 0-60 min AUC (nmol/L/min):** HIIE 32227 ± 9102 vs MICE 36991 ± 13298
Bally et al., 2016[b]	**DE 0-90 min (mmol/L):** HIIE 7.88 ± 0.22 vs MICE 7.29 ± 0.20 ↔; $p = 0.16$ **PE 0-120 min (mmol/L):** HIIE 8.02 ± 0.61 vs MICE 10.09 ± 1.13 ↔; $p = 0.08$ **NP (mmol/L):** HIIE 7.85 ± 0.72 < MICE 8.80 ± 0.64; $p = 0.04$	**DE 0-90 min(pmol/L):** HIIE 150.7 ± 11.5 vs MICE 148.5 ± 15.1; $p = 0.50$ (*ns*) **PE at 120 min (pmol/L):** HIIE 80.4 ± 12.2 vs MICE 102.6 ± 20.8; $p = 0.13$ (*ns*)	**DE 0-90 min**: HIIE 7.3 ± 0.4 > MICE 2.0 ± 1.2; $p < 0.001$	**DE 0-90 min**: HIIE 14.9 ± 0.9 v s MICE 13.3 ± 0.6; $p = 0.21$ (*ns*)	**DE 0-90 min**: HIIE 510.8 ± 35.8 vs MICE 461.5 ± 27.3; $p = 0.28$ (*ns*)
Campbell et al., 2014[b]	**DE 0-45 min (reduction, mmol/L):** HIIE -1.1 ± 1.4 < MICE -5.3 ± 0.4; $p = 0.037$ **PE 0-60 min AUC (mmol/L/min):** HIIE 1604 ± 74 vs MICE 1093 ± 54; $p = 0.112$ (*ns*)	NR	**PE 0-60 min:** HIIE > MICE	NR	**PE at 0 min:** HIIE 1.99 ± 0.26 vs MICE 1.35 ± 0.13 **PE at 60 min:** HIIE 1.60 ± 0.14 vs MICE 1.18 ± 0.17

	NP: HIIE vs MICE; *p* = 0.715(*ns*)				
Dube et al., 2012[b]	**DE 0-60 min (reduction, mmol/L):** HIIE -3.0 ± 2.2 vs MICE -2.5 ± 3.3 **DE 0-30 min (reduction, mmol/L):** HIIE -1.4 ± 1.2 vs MICE -1.7 ± 2.0 **DE 30-60 min (reduction, mmol/L):** HIIE -1.5 ± 1.6 vs MICE -0.8 ± 1.8 **DE 0-60 min (reduction, mmol/L) before dextrose infusion:** HIIE -3.5 ± 1.7 vs MICE -4.9 ± 2.7 **DE at 60 min:** HIIE 6.2 ± 1.7 vs MICE 5.3 ± 0.9 **PE at 30 min:** HIIE 5.9 ± 1.8 vs MICE 5.5 ± 0.9	NR	**DE at 30 min:** HIIE > MICE; *p* < 0.05	NR	NR
Guelfi et al.,	**DE 0-30 min (reduction, mmol/L):** HIIE < MICE; HIIE -2.9 ± 0.8 vs MICE -4.4 ± 1.2; *p* = 0.006 **PE 0-60 min:** HIIE remained stable; *p* = 0.378; MICE continued ↓; *p* = 0.009 **PE 60 min (reduction, mmol/L):** HIIE -3.3 ± 2.6 vs MICE -6.3 ± 1.8**;** *p* = 0.021	**90 min (DE 30 min + PE 60 min):** HIIE vs MICE ↔**;** *p* = 0.677	**DE 0-30 min**: HIIE ↑; MICE ↑ **DE 0-30 min (increase):** HIIE > MICE; *p* = 0.011	**DE 0-30 min**: HIIE vs baseline ↔; MICE vs baseline ↔;	**DE 0-30 min**: HIIE vs baseline ↔; MICE vs baseline ↔;

Hubinger et al., 1985[b]	**DE 0-30 min (mmol/L)**: HIIE ↓ 5.72 ± 0.61 vs MICE ↓ 4.72 ± 1.05	**DE 0-30 min (free insulin):** MICE ↑ vs baseline $p < 0.01$ **PE at 30 min:** MICE vs baseline ↔	**DE 0-30 min:** HIIE ↑ vs baseline MICE ↑ vs baseline	**DE 0-30 min:** MICE ↑ vs baseline $p < 0.01$ **PE at 30 min:** MICE vs baseline ↔	NR
Iscoe et al., 2011[b]	**DE 0-45 min (interstitial absolute reduction, mmol/L):** HIIE -5.0 ± 0.5 vs MICE -5.1 ± 0.7; $p = 0.8$(*ns*) **DE 0-45 min (interstitial relative reduction, mmol/L):** HIIE 50.6 ± 4.2% vs MICE 51.6 ± 4.7%; $p = 0.9$ (*ns*) **DE 0-45 min (plasma reduction, mmol/L):** HIIE -4.4 ± 0.05 vs MICE -5.1 ± 0.6; (*ns)* **NP:** HIIE 2.8 ± 0.44 vs MICE 2.6 ± 0.51	NR	**DE 0-45 min (increase, mmol/L):** HIIE 4.7 ± 0.1 vs MICE 2.8 ± 0.3; $p < 0.01$	NR	**DE 0-45 min (increase, µ/dL):** HIIE 0.07 ± 0.03 vs MICE 0.07 ± 0.02; (*ns)*
Jayawardene et al., 2017[a]	**DE 0-45 min:** HIIE ↑, MICE ↓; $p < 0.001$ **DE at 30 min (mmol/L):** HIIE 11.3 ± 0.5 > MICE 9.7 ± 0.6; $p < 0.001$ **PE at 60 min (mmol/L):** HIIE 11.1 ± 1.3 > MICE 8.9 ± 0.8; $p < 0.001$	**DE 0-45 min (pmol/L):** HIIE 75 ± 11 vs MICE 82.9 ± 9; $p = 0.35$ (*ns*) **PE 0-120 min (pmol/L):** HIIE 74 ± 6 vs MICE 71 ± 8; $p = 0.60$ (*ns*)	**DE at 15 min (increase, mmol/L):** HIIE 6.2 ± 0.4 > MICE 3.0 ± 0.4; $p < 0.001$ **PE at 60 min (reduction, mmol/L):** HIIE > MICE; $p = 0.031$	**DE 0-45 min:** HIIE vs baseline↔; MICE vs baseline ↔	**DE 0-45 min (nmol/L):** HIIE 338 ± 23 vs MICE 272 ± 22; $p < 0.001$ **PE 0-120 min (nmol/L):** HIIE 472 ± 46 vs MICE 328 ± 54; $p < 0.001$
Lee et al., 2020[a]	**NP Mean Glucose:** HIIE 11.6 ± 4.7 vs MICE 13.3 ± 6.6 **NP Mean glucose nadir**: HIIE 8.8 ± 4.8 vs MICE 10.2 ± 5.7	NR	NR	NR	NR

	NP Mean glucose peak: 14.7 ± 4.6 vs 16.5 ± 5.9				
Maran et al., 2010[a]	**DE 0-30 min**: HIIE ↓; MICE ↓ **PE at 120 min**: HIIE (tended) > MICE; (*ns)* **NP AUC (mg/dL/420min):** HIIE 16 ± 3 < MICE 23.3 ± 3; *p* = 0.04 **NP at 3:00 a.m. (mg/dL)**: HIIE 147 ± 17 < MICE 225 ± 31; *p* < 0.05	**150 min (DE 30-min +PE 120-min):** HIIE vs MICE; *(ns)*	**DE 0-30 min (peak, mmol/L):** HIIE 4 ± 0.2 > MICE 1.5 ± 0.2; *p* = 0.002 **150 min AUC (DE 30 min + PE 120 min, mmol/L/150 min):** HIIE 247 ± 22 > MICE 123 ± 13; *p* = 0.002	NR	**150 min (DE 30-min +PE 120-min):** MICE vs HIIE; (*ns)*
Moser et al., 2015[a]	**DE 0-30 min (reduction, mmol/L):** HIIE (A): 1.27 ± 0.96 vs MICE (A) 2.01 ± 1.04**;** *p* = 0.244 (*ns*) HIIE (B): 1.51 ± 0.92 < MICE (B) 3.0 ± 1.54; *p* = 0.024 HIIE (C): 2.91 ± 1.35 vs MICE (C) 3.42 ± 2.34; *p* = 0.573 (*ns*) **NP (CGM):** HIIE (A): 9.94. ± 2.0 vs MICE (A) 8.21 ± 1.39; (*ns)* HIIE (B): 8.77 ± 2.78 vs MICE (B) 9.82 ± 1.67; (*ns)* HIIE (C): 8.55 ± 1.94 vs MICE (C) 9.38 ± 3.27; (*ns)*	NR	**DE 0-30 min (decrease, mmol/L):** HIIE (A): 1.67 ± 0.50 vs MICE (A) 0.96 ± 0.41**;** *p* = 0.006; HIIE (B): 2.08 ± 0.64 vs MICE (B) 1.33 ± 0.48: *p* = 0.004; HIIE (C) 4.93 ± 1.80 vs MICE (C) 4.75 ± 1.53: *p* = 0.418	**DE 0-30 min:** HIIE vs baseline ↔; MICE vs baseline ↔;	**DE 0-30 min:** HIIE slight ↑, *ns*; MICE slight ↑, (*ns)*
Rempel et al., 2018[a,c]	**DE at 45 min (changes, mmol/L):** HIIE (Condition 1) vs MICE 1.1 (0.2-1.6) vs 0.9 (0.0-2.7) HIIE (Condition 2) vs MICE 0.7 (−0.4-3.0) vs 0.9 (0.0-2.7) HIIE	NR	NR	NR	NR

	(Condition 3) vs MICE 1.0 (0.0 - 2.0) vs 0.9 (0.0-2.7)				
Sarnblad et al., 2021[a]	**DE 0-45 min (Reduction, mmol/L)** HIIE -5.1 ± 1.6 vs MICE -5.4 ± 1.8	NR	NR	NR	NR
Scott et al., 2018[b]	**24-hour period (mmol/L):** HIIE 9.0 ± 0.4 vs MICE 9.5 ± 0.5 **Nocturnal period (mmol/L):** HIIE 9.0 ± 0.7 vs MICE 9.3 ± 0.9	NR	NR	NR	NR
Taleb et al., 2016[a]	**DE 60 min, (reduction)** SAP HIIE 1.7 ± 2.2 vs MICE 2.2 ± 2.1; DAP HIIE 1.4 ± 1.5 vs MICE 2.1 ± 2.1 **NP:** SAP HIIE 9.4 ± 2.8 vs MICE 9.1 ± 2.0; DAP HIIE 7.2 ± 1.6 vs MICE 8.1 ± 2.1	**90min (DE 60 min + PE 30min)** SAP HIIE 30.37 ± 21.7 vs MICE 26.65 ± 18.49; DAP HIIE 27.37 ± 18.7 vs MICE 25.51 ± 17.87 (delivery)SAP HIIE 0.32 ± 0.35 vs MICE 0.30 ± 0.33; DAP HIIE 0.44 ± 0.3 vs MICE 0.40 ± 0.36	NR	**90min (DE 60 min + PE 30min) (pg/L):** SAP HIIE 78.3 ± 16.0 vs MICE 81.5 ± 21.3; DAP HIIE 210.8 ± 96.0 vs MICE 210.6 ± 71.4	NR
Zaharieva et al., 2017	**DE at 40 min:** MICE ↓ 5.7 ± 0.4 mmol/L HIIE ↓ 6.8 ± 0.6 mmol/L **DE 0-40 min (reduction):** HIIE < MICE HIIE -0.5 ± 3.0 vs MICE -3.8 ± 1.5; p = 0.001	NR	NR	NR	NR
Zebrowska et al., 2018[a]	**DE at 40 min:** MICE ↓ $p < 0.001$; HIIE ↑ $p < 0.01$ **DE at 40 min:** HIIE 5.43 ± 2.45	**DE at 40 min:** Insulin max MICE 4.1 ± 1.2 vs HIIE	NR	NR	NR

	vs MICE 5.64 ± 2.37 p =0.84 (*ns*) **DE 0-40 min (reduction):** HIIE 35.3% > MICE 25.6%; $p < 0.05$ **NP:** HIIE 5.84 ± 1.44 vs MICE 6.83 ± 3.37 $p < 0.05$ **DE 0-40min (reduction):** HIIE -1.96 ± 0.9 vs MICE -1.42 ± 0.72 **DE 0-40min (reduction):** HIIE vs baseline ↔, MICE vs baseline ↔	5.8 ± 1.3, $p > 0.05$			

HIIE: High-intensity interval exercise; MICE: Moderate intensity continuous exercise; BE: Before exercise; DE: During exercise; PE: Post-exercise; NP: Nocturnal period; CGM: Continuous Glucose Monitoring; AUC: area under curve; MDI: multiple daily injection; CSII: continuous subcutaneous insulin infusion; >: higher; <: lower/smaller; ↑: increase; ↓: decrease; ↔: no difference; ns: not significant; heart rate reserve (HRR); NR: Not Reported; SAP: single-hormone artificial pancreas; DAP: dual-hormone artificial pancreas;

Appendix B **Results of outcomes (Growth hormone, epinephrine, norepinephrine, dopamine, Hypo/hyperglycemia) of included studies**

Study, year,	**Outcomes**				
	Growth Hormone	*Epinephrine*	*Norepinephrine*	*Dopamine*	*Hypoglycemia & Hyperglycemia*
Adolfsson et al., 2012[a,b]	**DE 0-60 min (peak, mU/L):** HIIE 63.2 ± 27 MICE 16.2 ± 10.1 **DE 0-60 min AUC (mU/L/min) :** HIIE 2335 ± 1216 MICE 1882 ± 1196	**DE 0-60 min:** HIIE (eightfold ↑) vs MICE (fivefold ↑) **DE 0-60 min (peak, mmol/L):** HIIE 1.5 ± 1.1 vs MICE 1.0 ± 0.9 **DE 0-60 min AUC (mmol/L/min):** HIIE 62.1 ± 38.3 vs MICE 53.1 ± 37.6	**DE 0-60 min:** HIIE (sevenfold ↑) vs MICE (threefold ↑) **DE 0-60 min (peak,** mmol/L**):** HIIE 14.7 ± 6.9 vs MICE 5.6 ± 2.1 **DE 0-60 min AUC (**mmol/L/min**):** HIIE 650 ± 195 vs MICE 427 ± 141	NR	No hypoglycemia episodes
Bally et al., 2016[c]	**DE 0-90 min:** HIIE 15.6 ± 2.0 > MICE 10.3 ± 1.3; p = 0.02	**DE 0-90 min**: HIIE > MICE; *p* = 0.002	**DE 0-90 min**: HIIE > MICE; *p* < 0.001	NR	**Time spent in hypo/hyperglycemia (NP):** HIIE 20 ± 9 vs MICE 10 ± 6, *p* = 0.52 / HIIE 107 ± 40 vs MICE 106 ± 35, *p* = 0.87
Campbell et al., 2014[c]	MR	NR	NR	NR	**Participants who experienced early-onset / nocturnal hypoglycemia:** HIIE 2 vs MICE 3/ HIIE 6 vs MICE 6 **Time spent in hypo/hyperglycemia (23-h post-exercise; min):** HIIE 223 ± 55 vs MICE 157 ± 59; *p* = 0.808 **/** HIIE 693 ± 140 vs MICE 684 ± 93; *p* = 0.982

Dube et al., 2012[c]	NR	**During test (DE 60 min + PE 30 min):** HIIE (tended) > MICE	**DE at 30 min:** HIIE > MICE; HIIE 7.8 ± 3.2 ↑ vs baseline 3.2 ± 1.0	**DE at 30 min;** HIIE > MICE	**Participants who experienced early-onset (DE 0-60 min / PE 0-60 min) hypoglycemia:** HIIE 4 vs MICE 7 / HIIE 3 vs MICE 7
Guelfi et al., [a]	**DE 0-30 min**: HIIE ↑; $p = 0.022$	**DE 0-30 min**: HIIE ↑; MICE ↑	**DE 0-30 min**: HIIE ↑; MICE ↑ **DE 0-30 min (**increase**)**: HIIE > MICE; $p = 0.001$	NR	**Participants who experienced early-onset hypoglycemia (DE 30 min + PE 60 min):** HIIE 1 vs MICE 2
Hubinger et al., 1985[c]	**DE 0-30 min:** HIIE ↑MICE ↑ $p < 0.01$; HIIE 0.41 nmol/L vs MICE 0.59 $p < 0.05$ **PE at 30 min:** MICE vs baseline ↔	**DE 0-30 min:** HIIE ↑ vs baseline; MICE ↑ vs baseline $p < 0.01$HIIE vs MICE ↔ **PE at 30 min:** MICE vs baseline ↔	**DE 0-30 min:** HIIE ↑ vs baseline MICE ↑ vs baseline $p < 0.01$; HIIE vs MICE ↔ **PE at 30 min:** MICE vs baseline ↔	NR	**Participants who experienced early-onset hypoglycemia:** HIIE: 1 vs MICE:2
Iscoe et al., 2011[c]	**NR**	**DE 0-45 min (increase,pmol/L) :** HIIE 551.7 ± 81.2 vs MICE 571.8 ± 148.9**;** *ns*	**DE 0-45 min (increase, pmol/L):** HIIE 3.50 ± 0.60 vs MICE 2.90 ± 0.85; *ns*	NR	**Participants who experienced early-onset / nocturnal hypoglycemia:** HIIE 3 vs MICE 7 / HIIE 3 vs MICE 5
Jayawardene et al., 2017[a]	**DE 0-45 min (increase, mcg/L):** HIIE 9.2 ± 1.9 vs MICE 7.7 ± 1.8; $p = 0.23$ (*ns*) **PE 0-120 min (increase, mcg/L):** HIIE 4.8 ± 1.2 vs MICE 3.6 ± 0.8; $p = 0.13$ (*ns*)	**DE 0-45 min (increase, pmol/L):** HIIE 777 ± 110 > MICE 498 ± 80; $p = 0.019$	**DE 0-45 min (increase, pmol/L):** HIIE 10024 ± 872 > MICE 7416 ± 686; $p = 0.005$	**DE 0-45 min (increase , pmol/L):** HIIE 491 ± 88 vs MICE 304 ± 59; $p = 0.039$	**AUC of hyperglycamia (DE 0-45 min, min·mmol/L):** HIIE 50 ± 5.0 vs MICE: 30 ± 3; $p = 0.22$ **AUC of hyperglycamia (PE 0-120 min, min·mmol/L):** HIIE 238 ± 18 vs MICE 54 ± 7; $p = 0.011$
Lee et al., 2020[a]	NR	NR	NR	NR	**Percentage time spent in nocturnal hypoglycemia HIIE:** 3.6 ± 11.3 vs MICE 0.0 ± 0.0 $p = 0.75$;

					Percentage time spent in hypoglycemia (24-h period): HIIE 3.5 ± 6.4 vs MICE 0.8 ± 1.4
Maran et al., 2010[a]	**150 min (DE 30-min +PE 120-min):** MICE vs HIIE; (*ns)*	**DE at 30 min (peak, pg/mL):** HIIE 159.6 ± 17 vs MICE 136 ± 14.6; $p = 0.29$ (*ns*)	**DE at 30 min (peak, pg/mL):** HIIE 1016.3 ± 154 vs MICE 680 ± 84.5**;** $p < 0.02$	NR	**Participants who experienced nocturnal hypoglycemia**: HIIE 7 vs MICE 2 $p < 0.05$
Moser et al., 2015[a]	NR	**DE 0-30 min:** HIIE ↑**,** MICE ↑**;** $p = 0.001$	**DE 0-30 min:** HIIE ↑, MICE ↑**;** $p = 0.003$	**DE 0-30 min:** HIIE ↑, MICE ↑**;** $p <$ 0.001	No hypoglycemia episodes
Rempel et al., 2018[a,d]	NR	NR	NR	NR	**Participants who experienced nocturnal hypoglycemia** (Condition 1) 3 vs (Condition 2) 4 vs (Condition 3) 2
Sarnblad et al., 2021[a]	NR	NR	NR	NR	**Participants who experienced early-onset hypoglycemia** (PE 30min): HIIE 1 vs MICE 0
Scott et al., 2018[c]	NR	NR	NR	NR	**Percentage time spent in nocturnal hypo/hyperglycemia (%):** HIIE: 8.0 ± 3.6 vs MICE: 7.9 ± 4.7 / HIIE 35.1 ± 8.7 vs MICE 33.3 ± 9.8 **Percentage time spent in severe hypoglycemia (%):** HIIE: 3.8 ± 2.4 vs MICE: 4.0 ± 2.7

Taleb et al., 2016[a]	NR	NR	NR	NR	**Percentage time spent in early-onset hypoglycemia (DE 60min + PE 30min):** SAP HIIE 19.9 ± 25.7 vs MICE 27.7 ± 29.4; DAP HIIE 2.5 ± 9.9 vs MICE 6.2 ± 17.6 **Participants who experienced early-onset hypoglycemia 90min (DE 60min + PE 30min,)**: SAP HIIE 7 vs MICE 9; DAP HIIE 1 vs MICE 3
Zaharieva et al., 2017	NR	NR	NR	NR	**Percentage time spent in nocturnal hypo/hyperglycemia (%):** HIIE: 3 vs MICE10 / HIIE 24 vs 29;
Zebrowska et al., 2018[a]	NR	NR	NR	NR	**Participants who experienced nocturnal hypoglycemia** MICE (50% patient) > HIIE

[a.] Data are expressed as mean ± standard deviation mean ± standard deviation (SD); [b.] Data are expressed as median (range); [c.] Data are expressed as mean ± standard error of the mean; [d.] Data are expressed as median and percentiles (Q1-Q3); HIIE: High-intensity interval exercise; MICE: Moderate intensity continuous exercise; BE: Before exercise; During exercise: DE; Post-exercise: PE; NP: Nocturnal period; CGM: Continuous Glucose Monitoring; AUC: area under curve; MDI: multiple daily injection; CSII: continuous subcutaneous insulin infusion; >: higher; <: lower/smaller; ↑: increase; ↓: decrease; ↔: no difference; ns: not significant; heart rate reserve (HRR); NR: Not Reported; SAP: single-hormone artificial pancreas; DAP: dual-hormone artificial pancreas

Appendix C **Telephone interview**

Telephone Interview	
1. Assigned number:	Sex: □ M □ F □ Non-Binary
2. Email address:	Phone number:
3. When were you diagnosed with type 1 diabetes (mm/dd/yyyy)? (____/____/____)	
4. What type of insulin treatment are you currently using: □ multiple daily injections (MDI) □ continuous subcutaneous insulin infusion (CSII, also called insulin pump therapy)	
5. Do you use self-monitoring of blood glucose (SMBG)? □ YES □ NO	
6. Have you ever worn a Continuous Glucose Monitor (CGM)? □ YES □ NO	
7. What was your last Hemoglobin A1c (3-month test of blood sugar)? Date(dd/month/yyyy): (____/___/____) Result: _____	
8. Have you been hospitalized for your diabetes in the last 6 months? □ YES □ NO Date(dd/month/yyyy): (___/___/____) where hospitalized:_____ What was the problem? _____	
9. Has a doctor ever said that you have cardiovascular disease □ YES □ NO If yes, further details: _____	
10. Diabetes Complications: Has a doctor ever said that you have: High blood pressure □ YES □ NO Nephropathy □ YES □ NO Retinopathy □ YES □ NO Neuropathy □ YES □ NO	
11. Are you taking any medications currently? □YES □ NO If yes, further details: _____	
12. Do you exercise regularly? □ YES □ NO How many times a week? _____ Duration of each time _____ Type of exercise ____	

Appendix D **Anthropometrics and CVD risk factors**

Anthropometrics and risk factors
1. Assigned number:
2. Sex: □ M □ F □ Non-Binary
3. Date of birth (mm/yyyy): ____/____/_____ Age: _____
4. Dominant hand: □ L □ R
5. Race/Ethnicity: □ Caucasian □ American Indian/Alaska Native/Native Canadian □ Asian □ Native Hawaiian or Other Pacific Islander □ Black or African American □ Other: _____
6. Weight:_____.____kg /lbs (circle kg or lbs)
7. Height: _____.____cm/in (circle cm or in)
8. 1) Percent body fat (%): _____ 2) NIH Waist Circumference (cm): _____
9. Systolic BP (SBP): (1)_____mm Hg (2)_____mm Hg (3)_____mm Hg **Average:**_____mm Hg
10. Diastolic BP (DBP): (1)_____mm Hg (2)_____mm Hg (2)_____mm Hg **Average:**_____mm Hg
11. Resting/Basal Heart Rate (HR): (1)_____bpm (2)_____bpm (2)_____bpm **Average:**_____bpm
13. HbA1c: _____ HDL-C: _____ Total cholesterol: _____. LDL-C:_____ Triglycerides:_____.

Appendix E **Diabetes information**

Diabetes Information
1. Assigned number**:**_____Date of Diagnosis (dd/mm/yyyy)**:**__**/**_____/_____
2. Have you been hospitalized due to hypoglycemia and/or required 3rd party assistance in the past 6 months? □ Y □ N
3. How often do you check your blood sugar?_____times/day; What times of day: _____ Current glucometer (make/model):___
4. What was your last Hemoglobin A1c (3-month test of blood sugar)? Date (dd/month/yyyy):__/___/_____ Result:
5. Your insulin is injected by ☐ pen, ☐syringe or ☐insulin pump ☐ Other: __
6. Your insulin management regimen: ☐ multiple daily injections (MDI), ☐ continuous subcutaneous insulin infusion (CSII, also called insulin pump therapy) ☐ Other: _____
7. **MDI** section: If you use an insulin pump, please fill out the insulin pump section (**Question 8**) instead. 1) **Time of injection units and type of insulin units and type of insulin** _____ _____ _____ _____ 2) Where do you inject? _____ 3) How long do you inject your short acting insulin before a meal?_____
8. Insulin pump section (CSII): If you **do not** have an insulin pump, pleas skip this section to **Question 9**. 1) Brand & model of pump _____ Date on pump(dd/month/yyyy):____/____/ 2) Type of Insulin:_____ 3) Current Basal Rates: a. _____(U/hr) + time (e)_____(U/hr) + time b. _____(U/hr) + time (f)_____(U/hr) + time

c. _____(U/hr) + time (g)_____(U/hr) + time

d. _____(U/hr) + time (h)_____(U/hr) + time

4) Bolus insulin for carbohydrate: ____unit:_____grams of carbohydrate

5) Bolus scale for high blood sugar: 1unit insulin lowers glucose _____mg/dl

6) Target glucose _____ mg/dl

9. Your monitoring:

☐ self-monitoring of blood glucose (SMBG)

☐ real-time Continuous Glucose Monitor (CGM)

☐ SMBG & real-time CGM

10. Diabetes Complications:

Has a doctor ever told that you have:

Heart condition □ Y □ N High cholesterol □ Y □ N

High blood pressure □ Y □ N

Nephropathy (kidney disease) □ Y □N

Retinopathy (eye disease) □ Y □ N

Neuropathy (nerves damage) □ Y □ N

11. History of Low blood sugar reactions:

When you feel low, do you test and record their blood glucose? □ Y □ N

Do you treat with carbohydrates? □ Y □ N

Does the low usually resolve itself within ~15 minutes? □ Y □ N

Do you usually feel (know) when you are low? □ Y □ N

12. Total daily insulin dose (average):_____Units