Prifysgol Abertawe
Swansea University

Investigating the relationship between habitual physical activity and cardiovascular health in healthy and clinical populations

Zoë Alexandra Marshall

BSc (Hons)

Submitted to Swansea University in fulfilment of the requirements for the Degree of Doctor of Philosophy

Swansea University
School of Sport and Exercise Science

2020

Abstract

Physical activity (PA) is beneficial for arterial and autonomic health and, subsequently, cardiovascular disease risk. However, fundamental questions remain regarding the relationship between PA and health, the relative importance of the volume, intensity or composition of PA, and whether this differs in chronic conditions. Therefore, the aim of this thesis was to explore the influence of movement behaviours on key cardiovascular risk factors in healthy populations and those with T1D using novel methods and analysis techniques.

Chapter 4 revealed that, contrary to expectation, the composition of daily movement and sleep behaviours was not associated with arterial stiffness in healthy children, with the reallocation of time between any behaviours not predicting significant change in arterial stiffness. It was hypothesised that this may be related to the measurement duration being insufficient to reflect habitual PA and its health-associated fluctuations. Therefore, a 28-day measurement period was used in **Chapter 5**, which revealed that, whilst there was minimal fluctuation in movement behaviours, PA metrics derived from 28 days were more strongly associated with cardiovascular health markers. Using a similar measurement protocol, children with type I diabetes (T1D) were found to engage in more light and less moderate-to-vigorous physical activity (MVPA) than healthy peers and were characterised by poorer arterial stiffness and autonomic function (**Chapter 6**). Importantly, **Chapter 6** suggested that the intensity of PA was more influential than the volume. Subsequently, **Chapter 7** supported this contention, revealing that the reallocation of time from any behaviour to MVPA was the most potent stimulus to cardiovascular health in T1D.

Overall, this thesis demonstrates that the composition and the relative importance of the volume and intensity of PA must be considered when investigating the relationship with health. The findings highlight key targets for future interventions seeking to enhance the cardiovascular function of youth, especially in T1D.

Declarations and Statements

DECLARATION

This work has not previously been accepted in substance for any degree and is not being concurrently submitted in candidature for any degree.

Signed .....

Date .....11/02/21.....

STATEMENT 1

This thesis is the result of my own investigations, except where otherwise stated. Where correction services have been used, the extent and nature of the correction is clearly marked in a footnote(s).

Other sources are acknowledged by footnotes giving explicit references. A bibliography is appended.

Signed .....

Date ..... 11/02/21.....

STATEMENT 2

I hereby give consent for my thesis, if accepted, to be available for photocopying and for inter-library loan, and for the title and summary to be made available to outside organisations.

Signed .....

Date ..... 11/02/21.....

Table of Contents

Acknowledgements

Firstly I would like to give a huge thank you to Dr Melitta McNarry and Dr Kelly Mackintosh for taking a chance on giving me this opportunity and the support throughout the past four years, without your support, mentorship and guidance I would not have got to this point. I would also like to thank Professor Michael Lewis and Dr Libby Ellins for not only providing the equipment that made this research possible, but also for the support and guidance throughout this process.

A very large thank you also goes to my family, Peter, Fiona, Matt, Luke, Lottie, Tank and Lily, and my better half, Adam. This endeavour would not have been possible without your incredible support, so thank you for believing that I could achieve this, even when I did not, and for being there when I needed that extra push and encouragement. I would also like to thank all of the amazing people in the A-STEM research office for being there to discuss ideas and problems, and for the much needed breaks to go a little crazy at 4pm.

A final thanks to those that volunteered to take part in the current research, the parents and families of the young people that took part and the paediatric diabetes teams in Swansea and Cardiff, all of whom made this thesis possible.

List of Tables

List of Figures

Abbreviations and Symbols

1-ß	Statistical Power
AGE	Advanced glycosylation end product
AIx	Augmentation index
ALR	Additive log-ratio
ANOVA	Analysis of variance
ANS	Autonomic nervous system
AP	Augmentation pressure
aPWV	Aortic pulse wave velocity
BMI	Body mass index
BMIz	Body mass index z-score
BrachD	Brachial artery distensibility
BP	Blood pressure
BPM	Beats per minute
CAN	Cardiac autonomic neuropathy
CGM	Continuous glucose monitoring
CI	Confidence interval
CLR	Cumulative log-ratio
CM	Centimetres
CO_2	Carbon dioxide
CRF	Cardiorespiratory fitness
CV	Coefficient of variation
CVD	Cardiovascular disease
DAN	Diabetic autonomic neuropathy
º	Degrees
DLW	Doubly labelled water
ECG	Electrocardiogram
EE	Energy expenditure
ENMO	Euclidian Norm Minus One
$ExCO_2$	Excess carbon dioxide method
FMD	Flow mediated dilation
GET	Gas exchange threshold
IBI	Inter-beat-interval

ICC	Intraclass correlation coefficient
IGF	Insulin-like growth factor
IL-6	Interleukin-6
ILR	Isometric log ratio
IPAQ	International physical activity questionnaire
HbA1c	Glycated haemoglobin
HDL-c	High density lipoprotein
HF	High frequency
HR	Heart rate
HRV	Heart rate variability
Hz	Hertz
KG	Kilograms
LDL-c	Low density lipoprotein
LF	Low frequency
$L \cdot min^{-1}$	Litres per minute
LMM	Linear mixed models
LPA	Light physical activity
MANOVA	Multivariate analysis of variance
MAP	Mean arterial pressure
MDT	Multi-disciplinary team
MET	Metabolic equivalent
Mg	Milligravity-based acceleration units
Min	Minute
$ML \cdot kg^{-1} \cdot min^{-1}$	Millilitres per kilogram per minute
$ML \cdot kg^{-b} \cdot min^{-1}$	Millilitres per kilogram (to the power of the logarithmic exponent) per minute
$Min \cdot day^{-1}$	Minutes per day
mm	Millimetre
mmHg	Millimetre of mercury
MMP	Matrix metalloproteinase
MO	Maturity offset
MPA	Moderate physical activity
MRI	Magnetic resonance phase contrast imaging
$M \cdot sec^{-1}$	Metres per second

MVPA	Moderate to vigorous physical activity
MVPAb	Bouted moderate-to-vigorous physical activity
MX	Most active X minutes/time
O_2	Oxygen
N	Sample size
NCDs	Non-communicable diseases
NICE	The National Institute for Health and Care Excellence
NN	Normal intervals between heart beats
NHS	National health service
NO	Nitric oxide
P	Significance
PKC	Protein kinase C
PHV	Peak height velocity
PP	Pulse pressure
PWA	Pulse wave analysis
aPWV	Aortic pulse wave velocity
PWV	Pulse wave velocity
r^2	Strength of correlation or fit of model
RSA	Respiratory sinus arrythmia
s	Seconds
SD	Standard deviation
SD1	Standard deviation of normal intervals perpendicular to the line of the Poincaré plot
SD2	Standard deviation of normal intervals on the line of the Poincaré plot
SDNN	Standard deviation of normal intervals
SDRR	Standard deviation of inter-beat intervals over a 24-hour duration
SEM	Standard error of the mean
SpO_2	Oxygen saturation
ST	Sedentary time
SVM	Signal vector magnitude
SWC	Smallest worthwhile change
SWC%	Percentage smallest worthwhile change
RMSSD	Root mean square of successive RR intervals
RPM	Revolutions per minute

RR	Difference between RR peaks on the QRS
T1D	Type 1 diabetes
T2D	Type 2 diabetes
Total-c	Total cholesterol
TSP	Total spectral power
VE/CO_2	Ventilatory equivalent of carbon dioxide
VE/O_2	Ventilatory equivalent of oxygen
VEQ	Ventilatory Equivalent Method
$\dot{V}CO_2$	Carbon dioxide production
VLF	Very low frequency
$\dot{V}O_2$	Aerobic capacity
$\dot{V}O_{2peak}$	Peak aerobic capacity
VPA	Vigorous physical activity
UK	United Kingdom
W	Watts
$W \cdot min^{-1}$	Watts per minute
WHO	World Health Organisation
Yrs	Years

Scientific Output and Public Engagement

Publication

Marshall, Z.A., Mackintosh, K.A., Lewis, M.J., Ellins, E.A., McNarry, M.A. *Associations of Physical Activity Metrics with Indicators of Cardiovascular Function and Control in Children with and without Type 1 Diabetes.* 2020. Pediatric Diabetes.

Conferences

Poster Presentation at 1st Pan Wales Sports and Exercise Conference. *Investigating the Influence of Physical Activity on Metabolic Control and Cardiac Risk in Children and Adolescents with Type 1 Diabetes Mellitus*. Swansea UK, April 2017.

Oral Presentation at the 2nd Pan Wales Sports and Exercise Conference. *Habitual Physical Activity and its Role in Cardiovascular Health in Youth with Type 1 Diabetes*. Bangor UK, May 2018.

Oral Presentation at the 3rd Pan Wales Sports and Exercise Conference. *Sedentary time, Physical activity and Cardiovascular disease.* Cardiff UK, May 2019.

Public Engagement

Research Engagement and Feedback Sessions with Participating Schools. Swansea UK.

Chapter 1

Introduction

Chapter 1: Introduction

Cardiovascular disease (CVD) is the most prevalent cause of mortality worldwide, accounting for 17.8 million, or 31% of, deaths globally in 2017 (Virani et al., 2020). CVD is an umbrella term for numerous myocardial and vascular conditions, including hypertension, atherosclerosis, stroke and coronary heart disease (Virani, et al., 2020). Pivotally, 80% of these CVD conditions are proposed to be preventable with appropriate lifestyle modifications, particularly regarding physical activity, with the key time for intervention suggested to be childhood given that the pathophysiological processes underpinning these diseases are now well recognised to manifest during this period (Berenson, 2002). Indeed, early intervention, and thus prevention, may be key to reducing the incidence of CVD in later life (Parsons et al., 2016).

Arterial stiffening, a measure of artery wall rigidity (Shirwany &Zou, 2010), combined with cardiac autonomic activity, an indication of cardiac control (Palatini &Julius, 2009), can provide a holistic insight to cardiovascular health and identify premature risks of CVD (Adji, O'Rourke, & Namasivayam, 2011; Thayer, Yamamoto, & Brosschot, 2010). Arterial stiffness is a fundamental structural function of arteries, required to compensate for the significant pressure changes in large and peripheral arteries caused by ejection pressure and systolic pulse waves (Greenwald, 2007). With increasing age, arteries become stiffer, losing the ability to vasodilate and vasoconstrict in response to the pressure variations associated with each pulse wave (Greenwald, 2007). Thus, the ability to effectively compensate for changes in pressure decreases, resulting in hypertension and atherosclerosis, and potentially causing trauma to pressure-sensitive organs (Greenwald, 2007). Similarly, cardiac autonomic activity naturally declines with age, potentially leading to neuropathy and dysregulation of the parasympathetic-sympathetic balance, with subsequent diastolic decline and increased risk of heart failure (Parashar, Amir, Pakhare, Rathi, & Chaudhary, 2016). It is also important to note the interdependence of these responses (Mäki-Petäjä et al., 2016); autonomic activity is a key factor in blood pressure and vascular resistance responses as it influences smooth muscle tone, one of the major determinants of arterial stiffness (Mäki-Petäjä, et al., 2016).

Children with chronic conditions, including those characterised by systemic inflammation (Davis &Kaliner, 1983; Roman et al., 2005b) or metabolic dysfunction (Chessa et al., 2002; Liatis et al., 2011; Shah et al., 2015), show significant premature increases and decreases in stiffening and autonomic function, respectively. Specifically, in children with type 1 diabetes (T1D), characterised by decline in ability to produce endogenous insulin and possible extremes in blood glucose, premature progression of these indices has been demonstrated as early as two years post diagnosis and is associated with both short- and long-term complications (M. Jaiswal et al., 2013; Shah, et al., 2015). Specifically, for children with T1D, chronic hyperglycaemia has been hypothesised to result in decreases in nitric oxide (NO) bioavailability, thereby promoting premature endothelial dysfunction (Urbina et al., 2019). Similarly, prolonged periods of high blood glucose can cause premature declines in autonomic function and, in the long-term, can be associated with a significantly increased risk of diabetic autonomic neuropathy (DAN; Vinik, Maser, Mitchell, & Freeman, 2003). Consequently, children with T1D are at a two-fold increased risk of developing CVD later in life, compared to non-diabetic peers (de-Ferranti et al., 2014).

There are numerous factors that can influence vascular and autonomic health in those with T1D, especially considering the early associated cardiovascular risk. Indeed, key risk factors of CVD include age (Dhingra &Vasan, 2012), genetics (Knowles &Ashley, 2018), inflammation (Willerson &Ridker, 2004), extremes in blood glucose (Conget &Giménez, 2009), adiposity (Juonala et al., 2011), cardiorespiratory fitness (CRF; Myers et al., 2015) and numerous lifestyle influences (Prasad &Das, 2009; Rippe, 2019). Specifically, the lifestyle influences of inactivity and sedentary time have been independently associated with deleterious effects on cardiovascular health in children (Raitakari et al., 1994), adults (Ford &Caspersen, 2019; Prasad &Das, 2009) and those with conditions such as T1D (Aman et al., 2009; Czenczek-Lewandowska, Leszczak, Weres, et al., 2019; de Lima et al., 2017; Michaliszyn &Faulkner, 2010).

A major lifestyle factor for CVD is physical inactivity, defined as accruing less than the recommended volumes of moderate-to-vigorous physical activity (MVPA) per day for children and adults, respectively (Chief Medical Officers, 2019). In England, 53% of children and 21% of adults (National Health Service Digital, 2020) are deemed

physically inactive and are therefore likely to gain lesser health benefits associated with physical activity. Physical inactivity is a modern pandemic, estimated to cost the UK economy and national health service (NHS) £7.4 billion each year (Public Health England, 2014). Long-term physical inactivity has been found to significantly increase the risk of non-communicable diseases (NCD), including CVD, type 2 diabetes, and cancer (Lee et al., 2012), in addition to promoting poor mental health (Harris, 2018) and a reduction in life expectancy (Lee, et al., 2012). Indeed, physical inactivity is the 4th leading risk factor for all-cause mortality, accounting for approximately 6% of deaths globally annually (WHO, 2010a).

In addition to inactivity, sedentary time has been identified as a key lifestyle factor that influences cardiovascular health, with sedentary time associated with negative health impacts, independent of physical activity (Borodulin, Karki, Laatikainen, Peltonen, & Luoto, 2015; Carson et al., 2014; G. N. Healy et al., 2008; Koster et al., 2012). Specifically, total sedentary time has been linked to insulin resistance (Carson, et al., 2014), an unfavourable lipid profile (G. N. Healy, et al., 2008), inflammation (Warren et al., 2010; Wilmot et al., 2012), a poor mental health and a poor health-related quality of life (Teychenne et al., 2019). Subsequently, these impaired outcomes are associated with unfavourable changes in artery compliance (Ananey et al., 2015; Haapala et al., 2016; Laurent et al., 2011) and sympathetic dominance in the long-term (Thayer, et al., 2010; Veijalainen et al., 2019). Consequently, an increased time spent sedentary results in significant increases in the risk of developing obesity (Heinonen et al., 2013) and cardiometabolic diseases (Saunders, Chaput, & Tremblay, 2014). Therefore, as there is an increasing amount of time spent being sedentary, irrespective of population, a greater understanding of the variation in, and effects of, this time are warranted to inform future interventions.

Whilst meeting the physical activity guidelines is associated with health-associated benefits and a decreased risk of CVD, previous research may have underestimated physical activity volumes and intensities (Canning et al., 2014; Shephard &Vuillemin, 2003; Watkinson et al., 2010). Specifically, self-report questionnaires, the most commonly employed measure of physical activity for large-scale studies, have been found to misrepresent actual behaviours (Hagstromer, Ainsworth, Oja, & Sjostrom, 2010; Shephard &Vuillemin, 2003; Silsbury, Goldsmith, & Rushton, 2015), with

individuals found to both under and overestimate physical activity and sedentary time (Besson, Brage, Jakes, Ekelund, & Wareham, 2010; Hagstromer, et al., 2010; Sallis &Saelens, 2000). Moreover, these measures do not provide insight regarding behavioural variation and its effect on health. In contrast, accelerometer-based measures of physical activity provide more reliable and representative insight to movement behaviours, allowing a more accurate exploration of the dose-response relationships between physical activity and health (Cain, Sallis, Conway, Dyck, & Calhoon, 2013; Lee &Shiroma, 2014). The use of such measures has therefore substantially improved our understanding of the effect of physical activity on health and how physical activity can be used in a preventative manner to reduce risk of NCDs, especially CVD (Lachat et al., 2013).

Nonetheless, whilst accelerometer-based methods have improved our understanding of how physical activity influences health, until recently, measurement periods have been limited to relatively short durations, most commonly seven days (Barreira et al., 2015; Cain, et al., 2013; Matthews, Hagströmer, Pober, & Bowles, 2012; Sasaki et al., 2018; Trost, Pate, Freedson, Sallis, & Taylor, 2000), thereby limiting the understanding of habitual physical activity and its fluctuations beyond this duration. It is also pertinent to note that, whilst measurements are nominally seven days, in reality, conclusions regarding the relationship between physical activity and health are being drawn on as little as three days with eight hours of wear-time. However, advances in accelerometry now support measurement durations of significantly longer than seven days (Hills, Mokhtar, & Byrne, 2014). These advances may facilitate potential insights to behavioural variation and provide a more accurate and reliable representation of physical activity for health.

In addition to being derived from a relatively small window of time, our current understanding of the influence of physical activity is also predominantly based on a single movement behaviour in isolation. Specifically, the vast majority of research has focused solely on MVPA, a behaviour that typically makes up only 4% of a 24-hour day (Chastin, Palarea-Albaladejo, Dontje, & Skelton, 2015). This focus is further compounded by a reliance on conventional statistics, which typically assume independence of the remaining movement behaviours within a specified time period (Pearson, 1896), potentially leading to spurious associations with health outcomes

(Chastin, et al., 2015). In order to account for the co-dependency and constrained nature of daily movement and sleep behaviours, it is essential to consider each behaviour relative to the others. Furthermore, it is increasingly recognised that reducing rich accelerometer data to simplistic metrics describing the time spent in different intensities, derived from potentially flawed cut-points and acceleration thresholds, is also likely to affect our interpretation of the relationship between physical activity and health. Consequently, novel metrics to describe the entire physical activity profile have recently been proposed in the form of the intensity gradient and average acceleration, which provide greater insights into how physical activity is accrued. These recent advances in the field of physical activity and health highlight that fundamental questions remain to be addressed, not least of which is the true importance of physical activity for health and whether it is the volume, intensity or overall composition that is more important and should therefore be the target of future interventions (Chastin, et al., 2015).

Therefore, the aim of this thesis was to explore the influence of physical activity and time spent sedentary on key cardiovascular risk factors across the age spectrum and according to disease status using novel methods and analysis techniques.

1.1 Experimental study aims

Study 1 (Chapter 4):
To explore the relative effects of daily physical activity, sedentary time and sleep on markers of arterial stiffness and adiposity, in addition to the effects of reallocating time between movement behaviours in children and adolescents.

Study 2 (Chapter 5):
To determine the influence of T1D on the accumulation of physical activity and whether volume or intensity of physical activity has a greater influence on cardiovascular health for children with T1D.

Study 3 (Chapter 6):
To determine the influence of measurement duration on physical activity metrics and their relationship with cardiovascular measures across two distinct populations, and to provide recommendations for optimal recording durations, for both children and adults.

Study 4 (Chapter 7):
To employ compositional analyses to explore the associations of daily movement behaviours with markers of cardiovascular health in children in T1D and a non-diabetic control group, in addition to exploring if movement composition fluctuated across 28 days.

Chapter 2

Literature Review

Chapter 2: Literature Review

Physical activity is well established to positively influence cardiovascular health to some extent in all populations, which is worrying given that in healthy populations only 47% of children and 67% adults in the UK meet the currently recommended physical activity guidelines (National Health Service Digital, 2020). Furthermore, the numbers of individuals meeting these guidelines in chronic conditions is typically lower potentially exacerbating disease severity (Barker et al., 2019). In contrast, sedentariness is increasing with the rise of sedentary travel, occupations and multimedia use (Dunstan, Thorp, & Healy, 2011; Saunders, et al., 2014; Telford et al., 2013). The negative effects of sedentary time on cardiovascular health is equivocal, potentially as a result of the difference effects of behaviours that make up this time (Dunstan, et al., 2011; Owen, Healy, Matthews, & Dunstan, 2010) and inappropriate statistical models which fail to account for co-dependency (Chastin, et al., 2015; Dumuid et al., 2018; Stefelová et al., 2018). Consequently, a more in-depth exploration of habitual physical activity and movement behaviours is necessary to better understand the influences of physical activity on cardiovascular health.

2.1 Physical Activity

Physical activity is defined as any movement produced by skeletal muscles requiring expenditure of energy above the resting state (Caspersen, Powell, & Christenson, 1985). Whereas, exercise, a sub-component of physical activity, is 'planned, structured, and repetitive bodily movement to improve or maintain one, or more, components of physical fitness' (Caspersen, et al., 1985). Measures of physical activity encompass all movement including strucutured exercise, sporadic physical activity and time spent being sedentary, which encompasses any activity during which less than 1.5 metabolic equivalents (METs) is expended, in either a seated or reclined position (Sedentary Behaviour Research Network, 2012). Indeed, in adults, it is generally accepted that 1 MET is equivalent to the amount of energy expended whilst the body is resting, with < 3 METs, ≥ 3-≤ 6 METs and ≥ 6 METs associated with light physical activity (LPA), moderate physical activity (MPA), vigorous physical activity (VPA), respectively (Trost, Loprinzi, Moore, & Pfeiffer, 2011). However, there remains considerable contention regarding the appropriate MET-thresholds to

represent different intensities of physical activity in children (Mendes Mde et al., 2018; Saint-Maurice, Kim, Welk, & Gaesser, 2016). Children and adolescent's resting energy expenditure (EE) has been found to range from 1.2 to 1.8 METs (Harrell et al., 2005). Consequently, it has been suggested that the MET value to distinguish sedentary time from LPA is increased from 1.5 to 2 METs in children (Butte et al., 2018; Saint-Maurice, et al., 2016). Nonetheless, the Compendium of Physical Activity suggests the thresholds of children's LPA, MPA and VPA can be represented by 2, 4 and 7 METs, respectively (Butte, et al., 2018; Harrell, et al., 2005). Whilst METs provide an estimation of EE associated with physical activity, the reliance of many MET calculations on standardised resting metabolic rates (RMRs) is unlikely to be suitable for all participants in each age group, especially for those with clinical conditions (Byrne, Hills, Hunter, Weinsier, & Schutz, 2005; Mendes Mde, et al., 2018). Specifically, Butte et al. (2018) demonstrated that for the same activity the associated EE for specific activities, such as hiking or skipping can increase by 0.5 METs between the age of 6-18 yrs. Indeed, RMRs are demonstrated to differ further between children, adolescents and adults (Harrell, et al., 2005), with the resting rate for those with clinical conditions varying further due to the increased metabolic demands of chronic conditions, such as cystic fibrosis (Vaisman, Pencharz, Corey, Canny, & Hahn, 1987). The implications of differing RMRs between population and the standardisation of METs associated with activities may therefore over or underestimate the true EE associated with these activities.

2.1.1 Benefits of Physical Activity

Physical activity has been associated with numerous physiological and psychosocial health benefits, irrespective of population. Specifically, adults are recommended to accrue a minimum of 150 minutes of MPA or 75 minutes of VPA each week to achieve the associated health benefits and reduce the risk of all cause mortality, cardiovascular and metabolic diseases (Chief Medical Officers, 2019). In comparison, children and adolescents in the UK, aged 5-18 years, are recommended to accrue a minimum 60 minutes of MVPA per day across the week to attain the equivalent health-associated benefits (Chief Medical Officers, 2019).

The physiological benefits, regardless of population or health status, associated with regular physical activity include improvements in bone mineral density, vascular reactivity and endothelial function, decreases in fat:muscle ratio and low density lipoprotein:high density liprotein ratio (LDL-c:HDL-s), possible improvements in triglycerides and total cholesterol (total-c) and increases in insulin sensitivity, and aerobic capacity (Eijsvogels, George, & Thompson, 2016; Janssen &Leblanc, 2010). These benefits have been found to translate to improved cardiovascular health in both the short- and long-term, with a decreased risk of cardiovascular disease (CVD) risk factors, potentially explained, at least in part, by the prevention of age-related arterial stiffness, endothelial dysfunction and autonomic decline (Laursen et al., 2015). Conversely, numerous negative health consequences have been reported to be associated with being insufficiently active, with over 5 million deaths a year worldwide attributed to inactivity (Blair, 2009; Larouche, 2014). Concerningly, large proportions of children and adults in the UK have been identified as inactive (British Heart Foundation, 2017; Sport England, 2018) and are therefore at an increased risk of metabolic syndrome, type 2 diabetes (T2D), CVD and all-cause mortality (Blair, 2009; British Heart Foundation, 2017).

2.2 Cardiovascular health

Cardiovascular diseases are the most significant single cause of mortality worldwide, which may be exacerbated by lifestyle influences such as physical inactivity (Hamer, O'Donovan, & Murphy, 2017; Raitakari, et al., 1994). The likelihood of developing CVD is predicted using a range of different cardiovascular risk factors. Risk factors employed in research and clinical environments to give an estimation of present and future risk include measures of adiposity (Juonala, et al., 2011), serum lipids (Arsenault, Boekholdt, & Kastelein, 2011), blood pressure (Magnussen &Smith, 2016) and lifestyle and environmental influences (Brotman, Golden, & Wittstein, 2007; Dimmeler, 2011). However, more structural and functional measures of cardiovascular health can give a more in-depth understanding of the potential risk to CVD (Palatini &Julius, 2009; Shirwany &Zou, 2010). Specifically, measures of arterial health and cardiac autonomic control can provide the current functional state of the vascular and autonomic systems gaining greater insight as to the mechanisms underlying progression towards CVD.

2.2.1 Arterial stiffness

2.2.1.1 Artery Function

An artery's elastic properties are fundamental to the maintenance of, and response to changes in, blood pressure (BP) and the ventricular ejection pressure from the heart. Indeed, these properties allow for the regulation of blood flow in the peripheral and micro- vasculature, protecting pressure sensitive organs, including the kidneys, eyes and brain, from damage or barotrauma (Greenwald, 2007). The elasticity and structural integrity of the arteries are a result of structural proteins, namely elastin and collagen, and smooth muscle tone, with arteries reducing in contractibility the more peripheral they are from the heart (Greenwald, 2007). Large arteries differ in structure, with different ratios of elastin and collagen fibres depending on the demands for the compensation of pressure. Specifically, large central arteries, including the aorta, have a high proportion of elastin fibres to equalise the ventricular ejection, propelling and regulating blood flow (Thijssen, Carter, & Green, 2016). Conversely, peripheral arteries in musculature have a higher ratio of collagen fibres and, thus, a reduced elasticity (Thijssen, et al., 2016). In healthy populations, arteries gradually lose elasticity across the lifespan (Greenwald, 2007), however, lifestyle (Tanaka &Safar, 2019), genetics (Laurent, Boutouyrie, & Lacolley, 2005), autoimmune and inflammatory conditions (Roman et al., 2005a) can lead to premature increases in arterial stiffness and subsequent increases in risk of adverse cardiovascular events.

2.2.1.2 Arterial Stiffening

Arteriosclerosis reflects a reduction in arterial compliance ability which is the ability of the arteries to expand and contract in response to the cardiac cycle (Zieman, Melenovsky, & Kass, 2005). Multiple structural and functional factors are suggested to regulate the stiffness of arteries, including degradation of elastin fibres, increased collagen burden, calcification of vascular smooth muscle cells, reduced muscle tone, the cross-linking of structural fibres, modified matrix interactions, and increased inflammatory markers disrupting vascular structure and function (Greenwald, 2007; Zieman, et al., 2005).

Arterial compliance is related to the structure of arterial conduits which comprise of three layers (the intima, media and adventia) that respond to short-term changes in blood pressure (Zieman, Melenovsky, & Kass, 2005). Regulation of arterial compliance is predominantly a function of the medial layer, which consists largely of elastin layers, collagen fibres and vascular smooth muscle cells (Zieman et al., 2005). Vascular smooth muscle cells are sensitive to numerous vasoactive mediators, resulting in the regulation and modification of atrial compliance through changes in the distribution of stress between collagen and elastin fibres within the vessel walls (Lyle & Raaz, 2017; Zieman et al., 2005). Smooth muscle tone (SMT), the state of partial constriction when no extrinsic nor intrinsic factors act on large artery compliance, has been found to be influenced by a number of factors. Indeed, the sympathetic innervation found in smooth muscle, and the catecholamine production associated with the sympathetic system (Zieman et al., 2005), is activated by the baroreflex response to changes in pressure in large arteries (Shahoud, Sanvictores, & Aeddula, 2020). Therefore, consistently increased blood pressure would result in prolonged sympathetic activation and increases SMT, thereby decreasing arterial compliance. Additionally, endothelial-derived mediators, including nitric oxide, endothelin-1, and c-type natriuretic peptides, can also alter SMT and therefore regulation of arterial compliance (Zieman et al., 2005).

In the long-term, large arteries respond to differing pressure loads by undergoing growth and the remodelling of lumen diameter and wall thickness, thereby altering and reducing compliance of these arteries (Lyle & Raaz, 2017). Specifically, remodelling occurs as a result of a range of mechanisms, with the most commonly proposed processes including artery calcification, changes in intima-media thickness and impaired flow mediated dilation (Lyle & Raaz, 2017). These mechanisms can be influenced both mechanically and hormonally, in particular by haemodynamic forces and hormone regulation including angiotensin II, salt and glucose (Lyle & Raaz, 2017; Zieman et al., 2005). Furthermore, the mechanisms of compliance in large arteries can be influenced by excess levels of glucose in the blood, prevalent in condition such as diabetes mellitus, triggering adverse changes that can lead to premature arterial stiffening and less favourable compensation to pressure.

The overall consequence of this reduced contractibility is poor arterial compliance and BP compensation, resulting in an increase in systolic pressure and a decrease in diastolic pressure (Hamilton, Lockhart, Quinn, & McVeigh, 2007; Zieman, et al., 2005). The long-term effects of large artery stiffening are possible reductions or changes in the timing of arterial wave reflections, causing a reduction in coronary perfusion during diastole, increases in ventricular afterload, and the loss of protection from pressure changes in the microcirculation (Cheung, 2010; Hamilton, et al., 2007). Subsequently, these effects can cause an increased sheering pressure and fatigue and thus damage to artery walls, promoting atherosclerosis, and an increased pressure in the microvasculature, with potential barotrauma to the pressure sensitive organs (Hamilton, et al., 2007). The result of these detrimental haemodynamic and structural changes in the circulatory system is an increase in hypertension, risk of atherosclerotic rupture and progression towards CVD (Cecelja &Chowienczyk, 2012). Arterial stiffness assessment is therefore suggested to be a powerful prognostic tool with potential future clinical relevance (Adji, et al., 2011).

2.2.1.3 Assessing Arterial Stiffness

Arterial stiffness can be assessed through both invasive and non-invasive techniques. The use of angiographic catheterisation provides a very accurate assessment of the extent of stiffening (Adji, et al., 2011). However, due to the invasive nature and extremely high level of training required for this technique, it is rarely utilised in research. Consequently, the most common techniques used in research are non-invasive and typically involve the use of echo, ultrasound, pressure sensitive probes or pressure cuffs (Rhee, Lee, & Park, 2008). More specifically, these assessments include brachial artery distensibility (BrachD), flow mediated dilation (FMD), pulse wave velocity (PWV) and analysis (PWA), and ultrasound (Adji, et al., 2011; Hamilton, et al., 2007; Rhee, et al., 2008). While each of these non-invasive assessments are reliable and validated in specific populations, they assess different structural and functional attributes, limiting inter-study comparisons.

Perhaps one of the most commonly used non-invasive techniques is PWV, measured with the use of pressure sensors or cuffs (Hamilton, et al., 2007). PWV gives a reliable estimate of stiffness in a specific artery by measuring the pulse wave at two points of

an arterial section, giving the time interval, and therefore velocity, of the pulse wave (Hamilton, et al., 2007). An elevated PWV, above the normal age-specific range, is indicative of the presence of stiffening as the pulse wave would travel at a faster rate due to the increased rigidity of the measured artery (Parikh, Hollingsworth, Kunadian, Blamire, & MacGowan, 2016). Interpretation of this PWV result should be made in combination with the mean arterial pressure (MAP) during the assessment, as the circumferential pressure can alter the extent of stiffening and possibly skew the PWV results obtained (Reference Values for Arterial Stiffness Collaboration, 2010). This technique requires limited training, provides an easily interpretable output and is a relatively quick assessment, thereby reducing patient burden. The gold standard of central PWV measurement is aortic pulse wave velocity (aPWV) due to the extensive data available on the pathophysiology and outcomes of premature stiffening at this site (Wilkinson et al., 2019). However, due to the lack of insight in variations in different regions and the possible influence of other arterial properties, aPWV is not clinically recognised (Wilkinson, et al., 2019).

Another method used to assess arterial function in research is PWA, a technique which has the potential to be a valuable tool as an indirect measure of both central and peripheral stiffening through the assessment of ventricular ejection wave reflections (Stoner, Young, & Fryer, 2012). Specifically, augmentation index (AIx), calculated as the difference between the initial ejection and the peripheral reflection peaks, or augmentation pressure (AP), as a percentage of pulse pressure (PP), indicates stiffening with the loss of pulse wave reflections (Lowe, Harrison, El-Aklouk, Ruygrok, & Al-Jumaily, 2009; Stoner, et al., 2012). On visualisation of the waveform, a healthy peripheral artery should show a peak for the initial ejection of blood from the heart, with a secondary ‘half’ peak on the downward arm of the wave form (Figure 2.1). Peripheral arteries where significant stiffening is present will show the same initial peak but there would be little to no reflection peak, with the downward arm declining steeply (Figure 2.1; Lowe, et al., 2009; O'Rourke, Pauca, & Jiang, 2001).

2.2.1.4 Influences on Arterial Health and Premature Arterial Stiffening

Arterial stiffness in children, according to aPWV, typically increases with age, with such increases suggested to be a result of the continued development of structural

properties of the arterial walls (Glukhova, Frid, & Koteliansky, 1991; Greenwald, 2007). Specifically, these changes have been attributed to the thickening of intimal and

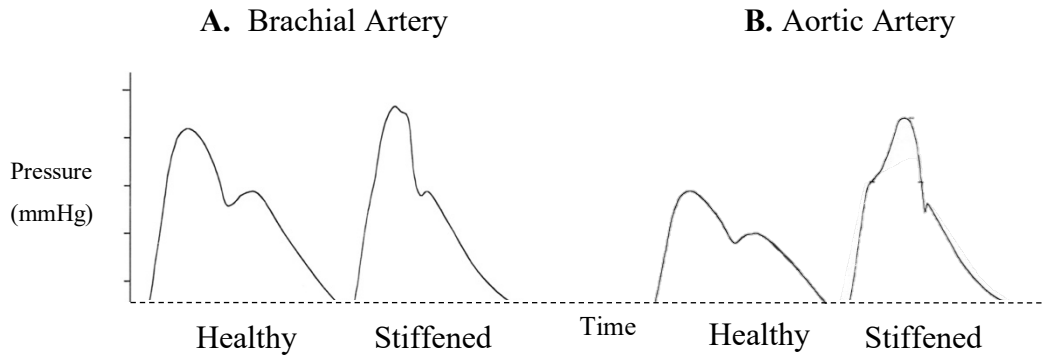


Figure 2.1. Representative example of systolic pressure waveforms of healthy and stiffened arteries assessed at the brachial artery and aortic artery, providing a depiction of relatively normal compliance and the presence of stiffening (Oliver &Webb, 2003).

medial arterial layers from birth (Glukhova, et al., 1991), in addition to an increasing collagen to elastin fibre ratio (Cheung, 2010). Premature increases in arterial stiffening are well recognised to result in an increased risk of cardiovascular disease, due to the unfavourable haemodynamic changes and subsequent burden on the circulatory system that they are associated with (Zieman, et al., 2005). The pathophysiology of premature arteriosclerosis is suggested to result from multiple mechanisms, in particular, a lack of nitric oxide (NO) bioavailability, a decrease of elastin and increase of collagen production (Johnson, Baugh, Wilson, & Burns, 2001), promotion of elastin breakdown via pro-inflammatory cytokines (Lakatta &Levy, 2003), and an increase in mechanical sheering stress due to increases in BP (Zieman, et al., 2005). Commonly suggested causative factors for these mechanisms are systemic inflammation (Park &Lakatta, 2012), high levels of low density lipoproteins (LDL-c) and triglycerides (Wilkinson &Cockcroft, 2007), hypertension (Tanaka &Safar, 2019), prolonged hyperglycaemia (blood glucose generally greater than 7 mmol·l-1; Greenwald, 2007; Schofield, Ho, & Soran, 2019), sex, and genetic traits associated with non-Caucasian ethnicity (Zieman, et al., 2005).

Systemic inflammation and prolonged hyperglycaemia result in increased levels of pro-inflammatory cytokines, including, but not limited to, matrix metalloproteinases (MMPs) and interlukin-6 (IL-6), and poor NO bioavailability, both of which are may result in a lower ratio of elastin to collagen in the vascular wall (Zieman, et al., 2005). Systemic inflammation can be attributed to chronic inflammatory conditions (Roman, et al., 2005a), as well as a poor lifestyle, resulting in an undesirable lipid profile and an increased risk of obesity (Safar, Czernichow, & Blacher, 2006). Hyperglycaemia can also be attributed to poor lifestyle choices (Tanaka &Safar, 2019) and to conditions such as diabetes mellitus, irrespective of type (Prenner &Chirinos, 2015). Finally, hypertension can both be causative of, and consequential to, premature arterial stiffening, with a consistently elevated BP increasing mechanical stress on walls of the arteries (Safar et al., 2018). This process promotes the breakdown of elastin due to the subsequent inflammatory response and can damage the endothelium, stimulating atherosclerosis. Consequently, arterial stiffening occurs and the lumen of arteries can narrow, further elevating circumferential pressure and advancing hypertension (Zieman, et al., 2005).

Those with chronic conditions, such as T1D, show premature increases in arterial stiffening, most often as a result of prolonged hyperglycaemia (Prenner &Chirinos, 2015). This is supported by evidence in both children and adults that indicates those with prolonged hyperglycaemia, often indicated by an elevated glycated haemoglobin (HbA1c), demonstrate higher measures of central and peripheral stiffening (Noh, Kim, Seo, & Kim, 2016; Obermannova, Petruzelkova, Sulakova, & Sumnik, 2017; Perchard &Amin, 2015). Moreover, disease duration has been demonstrated to modulate the relationship of HbA1c with arterial aging (Urbina, et al., 2019), with adults with a disease duration of > 10 years presenting with a higher aPWV compared to those with shorter disease durations (Vastagh et al., 2010). Similar results have also been reported in children (Wadwa et al., 2010). Indeed, for children with T1D, premature arterial stiffening has been demonstrated from as early as two years post diagnosis, when compared to non-diabetic peers (Shah, et al., 2015). Arterial stiffening in this population results in earlier wave reflections, represented by increases in AIx, in addition to increases in aPWV (Haller et al., 2004). Consequently, these premature changes in paediatric diabetes have been associated with an increased risk of disease-

related complications (Theilade, Lajer, Persson, Joergensen, & Rossing, 2013), a decline in autonomic function (Liatis, et al., 2011), and a significantly increased risk of developing atherosclerosis and CVD in later life (Shah, et al., 2015; Snell-Bergeon &Nadeau, 2012).

2.2.2 Physical Activity and Arterial Health

An inverse association between physical activity and arterial stiffness has been demonstrated for all popualtions (Ananey, et al., 2015; Endes et al., 2016; Sakuragi et al., 2009), suggested to result from the anti-inflammatory nature of physical activity and the promotion of nitric oxide bioavailability (Lessiani et al., 2016). All intensities of physical activity have been reported to slow the progression of arterial stiffness in adults, with the strongest correlation demonstrated between MVPA and central stiffness (Ahmadi-Abhari et al., 2017; Ananey, et al., 2015). Specifically, MVPA is most likely to be most beneficial, as higher intensities of movement and exercise are associated with reducing oxidative stress and enhancing autonomic regulation of smooth muscle tone. Subsequently, such improvements may lead to the prevention of age-related stiffening (Bruno et al., 2012; Seals, Walker, Pierce, & Lesniewski, 2009). The beneficial relationship between MVPA and arterial health has been further supported by the absence of age-related increases in central stiffness in active adults compared to their less physically active peers (Jakovljevic, 2018; Park, Park, Lim, & Park, 2017; Tanaka, DeSouza, & Seals, 1998). In constrast to MVPA, whilst light-intensity physical activity (LPA) has been found to reduce arterial stiffening, a greater volume of LPA than MVPA was required to achieve a significant improvement, with a larger effect of increases in LPA evident in individuals classed as “unfit” (Gando et al., 2010). The more significant effect in the unfit may due, at least in part, to a potentially less favourable arterial stiffeness, thus there may have been a greater capacity for change in this group despite the same intensity of physical activity. Additionall, cardiorespiratory fitness (CRF) is proposed to have a concomitant but independent effect on the mechanisms associated with a more favourable arterial stiffening profile (Mundwiler et al., 2017). Specifically, a high CRF can improve the functional and structural capabilities of large arteries (Peng, Haldar, Deshpande, Irani, & Kass, 2003), an effect resulting in improvements in central stiffening and suggested to be mostly indepdendent of MVPA (Williams, 2001). However, those who accrue

high volumes of MVPA could be postualted to be more likely to have a higher CRF (Mundwiler, et al., 2017).

In children and adolescents, MVPA has been negatively associated with measures of arterial stiffness, with higher physical activity levels associated with more favourable age-related central stiffening (Edwards et al., 2012; Sakuragi, et al., 2009). A lower risk of premature peripheral and central stiffening has been found in children who accrued higher volumes of MVPA (>60 minutes), compared to more inactive peers (<60 minutes of MVPA; Nettlefold, McKay, Naylor, Bredin, & Warburton, 2019). Furthermore, research has demonstrated that LPA has little influence on decreasing periperal stiffening in either healthy or high risk paediatric groups, including those classified as overweight or obese, however, increases in MVPA and meeting recommeneded volumes of this behaviour have been shown to be effective (Hawkins et al., 2014; Nettlefold, et al., 2019). The lack of association of LPA with age-related stiffening in children contrasts the effects of LPA in adults, indicating that a higher intensity of movement is necessary to achieve change for this population. Low intensities of physical activity may be less strongly associated with arterial stiffening in children due to the inadepquate shearing stress associated with this intensity of movement (Veijalainen et al., 2016). Indeed, previous research has highlighted that a certain threshold of sheering stress, achieved with higher intensity physical activity, may be necessary to promote increases in arterial compliance through promotion of nitric oxide bioavailability and in the longer term a reduction in oxidative stress (Ashor, Lara, Siervo, Celis-Morales, & Mathers, 2014). Furthermore, the differing effects of physical activity between children and adults may also be explained, at least in part, by the development of the parasympathetic nervous system (Mäki-Petäjä, et al., 2016). Specifically, the development of this system acts on smooth muscle tone a factor in arterial compliance, therefore possibly influencing the strength of the association of physical activity and arterial stiffness between children and adults (Lacolley, Regnault, Segers, & Laurent, 2017)

2.2.3 Autonomic Function

2.2.3.1 Autonomic Nervous System

The autonomic nervous system (ANS) is a network of nerves responsible for the regulation of muscles and glands, independent of conscious control, including in the pulmonary, cardiovascular, gastrointestinal, urinal and reproductive systems (Vinik, et al., 2003). The ANS is divided into two main arms, the sympathetic and the parasympathetic systems (Bankenahally, ST6 Anaesthesia, Krovvidi, & Consultant Neuroanaesthetist, 2019). The parasympathetic system is responsible for maintaining homeostasis and the rest, digest and repair state of the body, while the sympathetic system is responsible for the stress response and the fight or flight state (Vinik, et al., 2003). The ANS plays a major role in regulating the cardiovascular system, controlling heart rate (HR), BP, and regulating vagus nerve activity in response to stimuli (Vinik &Ziegler, 2007). The vagus nerve is a vital component of the parasympathetic system which exerts continuous parasympathetic activity on the sinoatrial node, the internal pacemaker of the heart (Bankenahally &Krovvidi, 2019). Increased vagus nerve activity, or increased vagal tone, results in a reduction in HR and vasodilation of blood vessels in the heart, as well as the lungs and gastrointestinal system. Sympathetic activity acts on the vagus nerve, reducing vagal tone and thereby allowing HR to increase and blood vessels to constrict (Bankenahally &Krovvidi, 2019). Therefore, the parasympathetic and sympathetic systems act in an antagonistic but complementary nature to provide balance, regulate HR and BP at rest, and in response to stimuli (Hägglund et al., 2012). Indeed, a healthy cardiovascular function and reduced risk of CVD is reliant on the balance between these two arms of the ANS (Hägglund, et al., 2012; Vinik &Ziegler, 2007).

2.2.3.2 Influences on Autonomic Function

Age and sex have been found to impact autonomic function in both children and adults (Abhishekh et al., 2013; Jensen-Urstad et al., 1997; Moodithaya &Avadhany, 2012). During early childhood, the indicators of parasympathetic function increase, regardless of sex, indicating a progressive development of the autonomic system during this time (Silvetti, Drago, & Ragonese, 2001). Moving into adolescence, indices of parasympathetic nervous activity stabilise, irrespective of sex, however a progressive decrease in resting HR can be observed in both sexes possibly due to an

increase in stroke volume (SV) mediated by increases in left ventricular mass (Armstrong &Welsman, 2019; Obert et al., 2005). Specifically, pubertal and post-pubertal boys have a greater progressive decrease in resting HR resulting in a consistently lower resting HR compared to girls, despite girls maturing at an earlier age (Gąsior et al., 2015; Silvetti, et al., 2001). Therefore, studies not accounting for maturity, and relying solely on decimal or biological age, should be interpreted with caution. Moreover, the sex-related differences in progression of decline in resting HR have been attributed to the differences in autonomic function, with boys found to have higher indicators of cardiac autonomic control than girls (Gąsior, et al., 2015). Moreover, research has found an association between age and declines in cardiac autonomic function in adults, with a progressive decline throughout adulthood and a subsequent increased risk of postural hypertension (Mancia &Grassi, 2014), arrhythmia (Coumel, 1993) and progression towards CVD (Thayer, et al., 2010). Therefore, dysfunction in the cardiac ANS is associated with a decreased longevity and survival for older adults (Zulfiqar, Jurivich, Gao, & Singer, 2010).

Environmental and lifestyle factors (Brotman, et al., 2007; Hu, Lamers, de Geus, & Penninx, 2017; Jarczok et al., 2013; Skrapari et al., 2007), in addition to age (Ingall, McLeod, & O'Brien, 1990), genetics (Skrapari, et al., 2007) and medical conditions (Mirakhur &Walshaw, 2003; Nolan et al., 1998; Vinik, et al., 2003), have been shown to have long-term effects on cardiac function and balance. Specifically, higher levels of physical activity and sports participation have been associated with a lower resting HR, suggesting an increased parasympathetic activity, in addition to improved indicators of cardiac activity (respiratory sinus arrhythmia and pre-ejection period; Hu, et al., 2017). In contrast, medical conditions, such as hypertension (Mancia &Grassi, 2014), metabolic conditions (Vinik, et al., 2003), obesity (Skrapari, et al., 2007) and CVD (Thayer, et al., 2010), can also cause negative changes and premature dysregulation in the balance of the ANS, most commonly resulting from damage to the autonomic neurons, known as autonomic neuropathy (Vinik, et al., 2003). Neuropathy can be a result of chronic hyperglycaemia occurring as a symptom for those with diabetes mellitus, which can then progress to diabetic autonomic neuropathy (Vinik, et al., 2003).

2.2.3.3 Heart Rate Variability

Autonomic activity is most typically assessed non-invasively by measuring the autonomic response to a stimulus. A typical method of non-invasive assessment is an electrocardiogram (ECG) recording to obtain indicators of cardiac activity, including resting HR, respiratory sinus arrhythmia, the pre-ejection period (Hu, et al., 2017) and the variability of RR intervals (Acharya, Joseph, Kannathal, Lim, & Suri, 2006). All of these measures are well utilised to give an estimation of autonomic activity, however, a well-employed measure in research, and suggested to be potentially clinically valid in early diagnosis of neuropathy in many populations, is heart rate variability (HRV; Acharya, et al., 2006; Chessa, et al., 2002). HRV is based on the variation between consecutive RR intervals during sinus rhythm, giving an estimation of how the parasympathetic/sympathetic balance impacts the sinoatrial nerve and its control of the heart rhythm (Butler, Yamamoto, & Hughson, 1994; European Society of cardiology, 1996; Vinik, et al., 2003). Subsequently, RR intervals can be analysed with the application of time and frequency domain methods, in addition to non-linear techniques (Tarvainen, Niskanen, Lipponen, Ranta-Aho, & Karjalainen, 2014).

Good ANS function has been suggested to result in higher time, frequency and non-linear HRV indices, indicating that the ANS and sinoatrial nerve respond well to environmental stimuli (European Society of cardiology, 1996). In contrast, reduced HRV measures suggest an impairment in the ability of the ANS and sinoatrial nerve to respond to internal and external stimuli (Butler, et al., 1994). Indeed, a reduced HRV has been hypothesised to independently predict mortality in both healthy (Zulfiqar, et al., 2010) and clinical populations, such as CVD (Colhoun, Francis, Rubens, Underwood, & Fuller, 2001; Stein &Reddy, 2005), and T1D (Astrup et al., 2006), independent of modifiable cardiac risk factors (Astrup, et al., 2006; Mirakhur &Walshaw, 2003; Stein &Reddy, 2005). In addition, a reduction in time domain HRV indices has been closely attributed to an increased arterial stiffening, often indicated by an elevated pulse pressure, and exacerbated by hyperglycaemia (M. Jaiswal, et al., 2013; Routledge, Campbell, McFetridge-Durdle, & Bacon, 2010). Despite the associations of decline in HRV, for children decreases must be interrpreted with caution, as HRV indices has been found to naturally decrease during maturation, indicating the development of this system as opposed to impairment (Gąsior, et al., 2015; Silvetti, et al., 2001). Specifically, maturation-related decreases in resting HR

have been attributed to time domain measures and the HF band which are reported to demonstrate the greatest decrease during the process of maturation (Gąsior, et al., 2015). Furthermore, sex-related differences have been demonstrated in the decrease of both time domain measures and HF band attributed to the difference in resting HR between boys and girls (Gąsior, et al., 2015). Specifically, the higher resting HR typically found in girls results in lower standardised HRV indices compared to boys (Silvetti, et al., 2001), highlighting the need to HR normalisation when assessing HRV (Gąsior, et al., 2015).

While a healthy population may show a natural decline in autonomic function, chronic conditions such as T1D are associated with premature declines in the ANS (Vinik, et al., 2003). Indeed, it is common for diabetic patients to be characterised by poor autonomic function, represented by a reduced HRV. Impairment in this system has been linked to a possible increased risk in cardiovascular morbidity and other adverse outcomes at a later stage in life (Astrup, et al., 2006). Furthermore, prolonged periods of hyperglycaemia are suggested to have a negative impact on the function of the ANS, possibly leading to autonomic damage (Chen, Lee, Chiu, & Jeng, 2008). This negative effect is thought to occur as a result of a reduction in NO availability, a decrease in vascular function, hyperosmolarity, and an increase in oxidative stress during hyperglycaemia. The resulting damage to ANS can manifest as an altered vascular structure and subsequent increases in arterial stiffness, as well as possible progression towards neuropathy (Chen, et al., 2008). Specifically, in a paediatric diabetic population, progression toward neuropathy is suggested to be represented by a decreased standard deviation of RR intervals (SDNN) and root mean square of successive differences (RMSSD), associated with a prematurely increased central and peripheral stiffening (M. Jaiswal, et al., 2013).

2.2.4 Physical Activity and Autonomic Function

The relationship between HRV and physical activity has been postulated to be similar to that of physical activity and arterial stiffness, with both time and frequency domains increased in active compared to sedentary adults (Gutin et al., 2005; Jarczok, et al., 2013; Rennie et al., 2003). Indeed, CRF and MVPA have both been found to be strongly and indepdendently correlated to an elevated HRV and subsequently a

possible decrease in risk of CVD (Rennie, et al., 2003; Routledge, et al., 2010; Yamamoto, Hughson, & Peterson, 1991). Thus indicating that both arterial stiffening and autonomic function may share common pathways both improved by being physically activity and maintaining or improving CRF in adults. Furthermore, evidence in adults suggests that age is associated with HRV, independent of physical activity levels, as indicated by comparable rates of decline in autonomic function for both active and sedentary adults (Davy, DeSouza, Jones, & Seals, 1998).

In children, accruing greater volumes of MVPA has been associated with an elevated HRV (Nagai, Hamada, Kimura, & Moritani, 2004), improved cardiac autonomic modulation (Nagai, et al., 2004), vascular health (Nettlefold, et al., 2019) and a decreased risk of CVD (Ekelund et al., 2019). Specifically, MVPA, but not VPA alone, has been associated with HRV indices of vagal tone, possibly indicating that there may be an intensity threshold where higher intensities may be associated with limited additional benefits (Oliveira, Barker, Wilkinson, Abbott, & Williams, 2017). However, caution is required whern interpreting these findings as the lack of assocation between autonomic function and VPA could be a result of variation in methodologies between studies, such as long epoch lengths and sampling frequencies of physical activity, which may underestimate the VPA undertaken by children (Sanders, Cliff, & Lonsdale, 2014). The lack of association of VPA and HRV indices could also be due to the sample investigated accruing less VPA in comparison to MPA, however this differences is not able to be explored as MVPA is presented as a combination of MPA and VPA. The benefits of MVPA for HRV are further supported by increases in parasympathetic activity as indicated by an elevated RMSSD and HF at rest in those meeting physical activity guidelines compared to those who do not (Cayres et al., 2015). Research has also shown the relationship between autonomic function and physical activity in children to be mediated by maturation (da Silva, Pereira, Cardoso, Moore, & Nakamura, 2014). Specifically, no association has been reported between physical activity of any intensity and HRV in pre-pubertal children, while pubertal and post-pubertal adolescents demonstrate a strong postive assocation (da Silva, et al., 2014). Possible reasons for the differing associations according to maturity status are the continuing development of this system during pre-adolescence, as demonstrated by progressive increases in indices indicative of parasympathetic activity, independent of sex (Silvetti, et al., 2001). However, in circa- and post-

pubertal adolescents the progressive increases in HRV typically stabilise and difference in indices of parasympathetic activity become sexually dimorphic with lower HRV indices observed in girls compared to boys (Gąsior, et al., 2015). Thus, the differing effects of MVPA on HRV according to maturity status may be attributed to the development of the parasympathetic nervous system. Indeed, parasympathetic development in prepubertal children may act more significantly than MVPA or the system could be too immature for MVPA to have an effect.

2.2.5 Physical Activity, Cardiovascular Health and Type 1 Diabetes

In clinical populations, and especially chronic conditions including T1D, physical activity is often recommended as part of clinical management to maintain functional capacity, quality of life and reduce the risk of long-term complications or comorbidities, such as CVD (Philpott, Houghton, & Luke, 2018). T1D is an autoimmune disorder characterised by chronic hyperinsulinemia and a reliance on exogenous insulin to maintain blood glucose homeostasis due to minimal or non-existent insulin production in-vivo. This limited insulin production results from immuno-inflammatory T-cell-mediated destruction of beta islet cells in the pancreas and subsequent inability of muscle and hepatic cells to efficiently uptake glucose (American Diabetes Association, 2010; Robertson, Adolfsson, Scheiner, Hanas, & Riddell, 2009). While T1D predominantly presents during childhood or adolescence, it can present at any age depending on the extent of autoimmune degradation of beta islet cells and the residual insulin production (American Diabetes Association, 2010; Snell-Bergeon & Nadeau, 2012). Given that there is currently no cure for T1D, effective management, which revolves around three key elements (insulin, diet and physical activity), is vital and must be tailored to each patient (NICE, 2015). Metabolic or glycaemic control is maintained through the application of exogenous insulin via various methods.

Insulin therapy by exogenous insulin can be categorised based on whether the time action profile is short- or long-acting. Short-acting insulin acts quickly with a short-action duration mimicking the insulin response to glucose absorbed from ingested food or drink, whereas longer-acting insulin has a slower onset and a longer duration of action, replicating the endogenous basal insulin released throughout the day (NICE,

2020). Application of exogenous insulin is most typically applied through either multiple daily injections or insulin pump therapy, involving continuous insulin absorption (NICE, 2020). While insulin therapy is essential for those with T1D, adverse effects can be associated with the process, with the primary negative effect being hypoglycaemia (NICE, 2020). Glycaemic control on a day-to-day basis is monitored with the use of a blood glucose monitor, which is supplemented by the measurement of the percentage of HbA1c and lipid profile to determine long-term control (NICE, 2015). Strict glycaemic control via insulin therapy has been associated with improvements in insulin sensitivity (Kaul, Apostolopoulou, & Roden, 2015); poor insulin sensitivity, or insulin resistance, is suggested to occur as a consequence of increases in adipose tissue, dehydration and hyperglycaemia, as well as in response to the physiological changes associated with puberty (Odegaard & Chawla, 2021). Furthermore, the insulin counter-regulatory hormones (glucagon, adrenaline, cortisol and growth hormone) released in response to hypoglycaemia, have also been proposed to promote insulin resistance in those with T1D (Nishimura et al., 2011).

The primary consequence of a reduced insulin production is hyperglycaemia due to a reduced glucose uptake and an increased glucose output by the liver, through glycogenolysis and glucogenesis, exacerbated by irregularly high glucagon concentrations in plasma (Greenbaum, 2002). Specifically, glucagon is often abnormally increased as a result of a reduced glucose permeability of alpha islet cells in the pancreas due to insufficient insulin. Consequently, glucagon production is upregulated, mimicking the effect of low blood glucose levels. Additionally, the metabolic disruption caused by a decreased level of insulin and high glucagon is further confounded by the excess promotion of lipolysis and a suppression of triglyceride synthesis, resulting in disproportionate lipid levels in the blood (Stanfield, 2012). A consequence of the over utilisation of lipids in metabolism, in particular fatty acids, can be an over-production of ketones and ketosis (Stanfield, 2012), in addition to impairing adenosine triphosphate (ATP) synthesis in muscle cells (Kaul et al., 2015). Furthermore, the lack of insulin can result in disproportionate protein catabolism due to the inhibition of protein synthesis, thereby causing muscle weakness, interfering with tissue repair and retardation of a child's normal growth (Herbert & Sreekumaran Nair, 2010). Subsequently, the metabolic disruption associated with the condition can negatively influence exercise tolerance, thereby

possibly discouraging those with the condition to engage in physical activity due to the additional effort necessary to achieve the same activity levels as non-diabetic peers (Colberg, Laan, Dassau, & Kerr, 2015).

Physical activity for those with T1D has been found to aid in the maintenance of glycaemic control by improving insulin receptor sensitivity in skeletal muscles and the liver, thereby increasing insulin sensitivity and reducing the risk of glycaemic extremes (Chimen et al., 2012). Indeed, minimising chronic hyperglycaemia is evidenced to slow premature increases in arterial stiffness due to improvements in nitric oxide bioavailability, thereby reducing long-term risk of hypertension, atherosclerosis and CVD (Snell-Bergeon &Nadeau, 2012). In addition to its role in regulating blood glucose, the anti-inflammatory nature of physical activity may also slow the progression of beta cell degradation in newly diagnosed T1D adults (Lascar et al., 2013), which could promote prolonged endogenous insulin production. This is highly important as prolonging endogenous insulin production may decrease the likelihood of extremes in blood glucose, thereby significantly reducing complications such as neuropathy, retinopathy and damage to blood vessels (Lascar, et al., 2013). However, the influence of physical activity on progression of beta cell degradation in child-onset T1D has yet to be elucidated.

The current adult and child recommendations for physical activity in T1D are the same as the general population (Chimen, et al., 2012). However, in general, adults, children and adolescents with T1D have been found to accrue significantly less MVPA when compared to non-diabetic peers, irrespective of glycaemic control (de Lima, et al., 2017). Failure to meet the recommended volume of physical activity for this population (Chief Medical Officers, 2019) is associated with an increased insulin resistance, an increased necessity for exogenous insulin and significant risk of long-term complications, including hypertension, DAN and all-cause mortality (Valerio et al., 2007). Furthermore, these negative effects in chronic conditions, and general populations, can be compounded by an increased time spent sedentary (Thivel et al., 2018). Reasons for accruing less MVPA are complex and typically include anxiety around hypoglycaemia, a lack of knowledge of how to compensate for different activities, and a reported fear of losing control of their diabetes (Brazeau, Rabasa-Lhoret, Strychar, & Mircescu, 2008). While de Lima et al (2017) found children with

T1D engaged in significantly less MVPA, they did however, have significantly higher levels of LPA, indicating that children with this condition are not necessarily inactive, but engage in physical activity at a lower intensity. Although less is known regarding the benefits of lower intensities of physical activity in T1D, the current understanding indicates that all physical activity, irrespective of intensity, may enhance health (Haapala, et al., 2016; Stone, Rowlands, Middlebrooke, Jawis, & Eston, 2009).

Whilst all intensities of physical activities have the potential to be beneficial for health, not all intensities of physical activity, nor patterns of accrual, are equal for metabolic control and risk of cardiovascular complications for children with T1D (Edmunds, Roche, & Stratton, 2010). Specifically, Edmunds et al. (2010) found that despite diabetic children accruing 60 minutes of MVPA per day, this did not result in a more favourable glycaemic control, CRF or adiposity than those who accrued MVPA in shorter bouts. The lack of favourable influence for children with T1D is proposed to be a consequence of time in MVPA being accrued in short bouts as opposed to sustained periods at a given intensity (Edmunds, et al., 2010). Subsequently, shorter bouts of moderate-to-vigorous physical activity may be insufficient to influence insulin sensitivity and glycaemic control (Colberg et al., 2016; Landt, Campaigne, James, & Sperling, 1985). However, the lack of association between MVPA and glycaemic control reported by Edmunds et al. (2010) could also be a consequence of participants in this study being characterised by relatively good glycaemic control, therefore the influence of physical activity may differ in those with poorer control but further research is required to elucidate this (NICE, 2015). Research has however proposed sporadic high-intensity bouts of exercise to have an acute stabilising effect on blood glucose, thereby reducing the risk of extremes in glycaemic variability (Yardley et al., 2013). Consequently, more habitual participation in VPA may exert a greater influence on glycaemic control and cardiovascular health than MPA for children with T1D, with shorter bouts of VPA alone possibly providing similar benefits to sustained bouts of MVPA. However, the independent influence of VPA for children with T1D remains to be elucidated, as research predominantly combines moderate and vigorous physical activities and does not explore the whole intensity spectrum (Rowlands et al., 2018), thereby precluding the elucidation of the effect of individual intensities on health.

2.2.6 Maturation, Growth and Cardiovascular Health

Puberty is a period during which a child progresses towards the attainment of adulthood and involves substantial physiological, developmental and neurological changes that affect linear growth, body composition and mental functioning (Coupal et al., 2019). In addition to significant growth in height, noticeable changes in sexual maturation occur, with development to the genitals and the breasts, as well as changes in the bone, renal, immune and cardiovascular systems (Rogol & Roemmich, 2002). The pubertal process is controlled by the hypothalamic pituitary gonadal (HPG) axis, with the hypothalamus releasing gonadotropin releasing hormone (GnRH) to stimulate the anterior pituitary gland to release follicle-stimulating hormone and luteinising hormone (Loomba-Albrecht & Styne, 2012). Whilst the cause of the onset of HPG axis maturation remains contentious, one suggestion is that puberty is initiated by an increase in the production and release of FSH and LH, thereby stimulating the sex organs to produce the sex hormones: oestrogen, progesterone and testosterone. Commencement of the production and release of sex hormones initiates changes in linear growth and body composition (Breehl & Caban, 2020; Loomba-Albrecht & Styne, 2012).

Significant increases in growth during the pubertal period, known as the pubertal growth spurt, are a result of a multifaceted interaction between sex hormones, growth hormone and insulin-like growth factor 1 (IGF-1). Specifically, the increases in testosterone, which is converted to oestradiol in girls, causes a rise in growth hormone production and release from the pituitary gland, subsequently stimulating a rise in IGF-1 (Breehl & Caban, 2020; Loomba-Albrecht & Styne, 2012). The pubertal process is also associated with rapid weight gain through sex-specific muscle development and deposition of fat, with approximately half of adult body weight being gained during this time (Rogol, Clark, & Roemmich, 2020).

Female and male sex hormones have been suggested to modulate large artery stiffness (Marlatt et al., 2013). Evidence indicates androgens, in particular testosterone, have a protective effect on the cardiovascular system and influence cardiovascular homeostasis (Coupal et al., 2019; Lyrio dos Santos, Bragança da Silva, Faustino Ribeiro Jr, & Stefanon, 2014). Furthermore, sex hormones are thought to be involved in the acute control of vascular function, specifically regarding the vascular smooth

muscle (Nettleship, Jones, Channer, & Jones, 2009; Traish, Guay, Feeley, & Saad, 2009). Indeed, oestrogen, progesterone and testosterone promote endothelium-dependent mechanisms of vascular dilation and prevent mechanisms of vascular smooth muscle contraction (Maranon & Reckelhoff, 2013). Furthermore, increases in oestrogen, thyroid, and growth hormones, as well as insulin and IGF-1, during puberty promote vasodilation and decrease blood volume, possibly intensified by increases in progesterone, found to suppress catecholamine release and sympathetic outflow (Coupal et al., 2019). Interactions between pubertal hormones are important to understand as whilst growth hormone is a vasodilator it has also been found to promote insulin resistance (Palmeiro et al., 2012) while, in contrast, IGF-1 acts in a similar manner but enhances insulin sensitivity (Kelsey & Zeitler, 2016). The action of growth hormone has as such been intimated as a possible cause of the considerable decrease in insulin sensitivity that occurs during puberty (Kelsey & Zeitler, 2016). In addition to vascular health, puberty is also associated with significant changes in autonomic function and regulation of the cardiovascular system, as demonstrated by decreases in markers of vagal tone, increases in endothelial function and blood pressure post puberty (Deda, Sochett, & Mahmud, 2015; Tanaka et al., 2000). Subsequently, upregulation of pubertal hormones has been indicated to potentially increase susceptibility to cardiovascular autonomic dysfunction (Coupal et al., 2019).

Finally, adolescence is a period of psycho-social and behavioural change that may be consequential to the hormonal and neurological changes occurring during the maturational process. In particular, the maturational process is associated with changes in sleep and fatigue, mood swings, changes to social behaviour and increases in cognitive development (Coupal et al., 2019). Furthermore, this behavioural change is reflected in the volume of physical activity and sedentary time, with sedentary time and physical activity found to increase and decrease, respectively, with increasing maturity (Farooq et al., 2018).

2.3 Sedentary Time

Sedentary time is distinctly different from inactivity, which is defined as levels of activity that do not meet the recommended guidelines for physical activity (Sedentary Behaviour Research Network, 2012). While the terms sedentary behaviour and

inactivity have been, and are still often, used interchangeably this distinction is important as a person could be classed as both active and sedentary, thereby meeting physical activity guidelines, but also spending a large proportion of their time sedentary, and vice-versa (Sedentary Behaviour Research Network, 2012).

The trend of increasing sedentary time across the world in all populations (Colley et al., 2011; Health and Social Care Information Centre, 2008; Matthews et al., 2008) is attributed to the rise of sedentary modalities of travel and sedentary employments, as a result of advancements in technology and multimedia use (Colley, et al., 2011; Health and Social Care Information Centre, 2008; Matthews, et al., 2008). Time spent in sedentary pursuits has been closely associated with health, independent of physical activity, including, but not limited to a range of health markers including, adiposity, insulin resistance, triglycerides and predictors of CVD (Borodulin, et al., 2015; Carson, et al., 2014; G. N. Healy, et al., 2008; Koster, et al., 2012). These deleterous physiological effects are subsequently linked to decreases in aerobic capacity, muscular hypotrophy, promotion of triglycerides and LDL-c in the lipid profile, increased inflammatory markers, and endothelial dysfunction (Warren, et al., 2010; Wilmot, et al., 2012).

2.3.1 Sedentary Time in Children and Adolescents and Cardiovascular health

In the paediatric population, sedentary time is an increasingly worrying issue, with children found to spend approximately 40-60% of waking hours in sedentary pursuits (Saunders, et al., 2014). Furthermore, a negative correlation between age and the breaks in sedentary time has been demonstrated in the general paediatric population (Carson &Janssen, 2011; Saunders, et al., 2014). However, total sedentary time has been found to remain relatively consistent, suggesting sedentary time is accrued in more prolonged bouts with age (Carson &Janssen, 2011; Saunders, et al., 2014). Prolonged sedentary time, defined as an extended period sedentary with no interruptions (Tremblay et al., 2017), includes multimedia use and has been independently correlated with risk factors of both cardiovascular and metabolic conditions, with the most significant relationship found in obese children and adolescents (Carson &Janssen, 2011). Interestingly, many of the negative effects associated with prolonged sitting time accrued through multimedia use have not been

demonstrated when compared to prolonged sitting associated with reading or during school time (Saunders, et al., 2014). Consequently, the concomitant behaviours of multimedia use, such as little posture change for prolonged periods, few breaks and high calorie intake, may be the cause of the observed negative effects (Saunders, et al., 2014). Specifically, a period of greater than 15 minutes of sedentary time has been independently associated with a greater body mass index (BMI), waist circumference, and a more unfavourable lipid profile (Wijndaele et al., 2019). Furthermore, these prolonged periods of sedentary time in children and adolescents have also been associated with premature adverse changes in vascular markers of central stiffness, aPWV and AIx, indicating an increased risk towards CVD in later life (Haapala, et al., 2016; Horta et al., 2015).

The proposed mechanisms by which chronic prolonged periods of sedentary time may promote impairment in vascular health are long-term decreases in stroke volume, as a result of increases in resting HR, linked to negative changes in sheering rate and antegrade blood flow (Thosar, Bielko, Mather, Johnston, & Wallace, 2015; Thosar, Johnson, Johnston, & Wallace, 2012). Subsequently, these changes are attributed to a decrease in NO bioavailability causing the promotion of negative structural adaptations in large and peripheral arteries, with an imbalance between collagen and elastin thereby promoting premature stiffening (Thosar, et al., 2015). Furthermore, time spent sedentary has been associated with increases in inflammation, an unfavourable lipid profile and negative changes in insulin resistance (Sardinha et al., 2008), found to act in a deleterious manner on arterial health (Zieman, et al., 2005). Whilst the mechanisms associated with prolonged sedentary time are proposed to elicit change in arterial stiffening measure, contradictory evidence is also presented that time spent sedentary in children has little to no adverse effect on arterial compliance (Haapala, et al., 2016). Inter-study differences in the association of sedentary time with arterial health may be a consequence of differences in maturity of the participants in each study, as well as differing durations and frequencies of sedentary bouts observed.

In the paediatric literature, sedentary time has been weakly associated with arterial measures in post-pubertal adolescent (Fujiwara et al., 2018), but no associations were present in samples of pre-pubertal and pubertal children (Haapala, et al., 2016; Haapala et al., 2017; Nettlefold, McKay, Naylor, Bredin, & Warburton, 2012; Veijalainen, et

al., 2016). The differences in association of time in this behaviour may therefore be due to the development of arterial health between pre-puberty and post-puberty, but also a consequence of possible changes in the behaviours that make up the total time spent sedentary. Indeed, pre-pubertal children have been reported to spend less time sedentary using multimedia, in comparison to pubertal and post-pubertal (Saunders, et al., 2014). Moreover, progressing into adolescence has been associated with a significant reduction in the regularity of breaks in sedentary time, further attributed to significant increases in multimedia use (Carson, et al., 2014; Saunders, et al., 2014). Therefore, the differences in concomitant behaviours associated with multimedia use may be the cause of the more significant negative changes in arterial health observed with sedentary time in more mature populations (Saunders, et al., 2014). Whilst maturation may contribute to differences in the association between sedentary time and arterial health, it is pertinent to note that the studies on which the understanding is based use a range of methods to quantify arterial compliance and sedentary time, likely further confounding this relationship (Königstein, Klenk, Appenzeller-Herzog, Hinrichs, & Schmidt-Trucksäss, 2020). Further research is therefore required to elucidate the relationship between sedentary time and arterial health in youth.

Evidence regarding the specific influence of sedentary time on autonomic function in childhood is limited (Oliveira, Barker, & Williams, 2017), but the current evidence indicates sedentary time to be independently associated with deleterious changes in cardiac autonomic regulation (Veijalainen, et al., 2019). Specifically, sedentary time is negatively associated with HRV indices representative of parasympathetic activation, RMSSD and high frequency (HF), accounting for physical activity, CRF, and maturity offset (Veijalainen, et al., 2019). The negative association of sedentary time with HRV implies time in this behaviour acts in a deleterious manner on vagal tone, postulated to be attributed to prolonged sympathetic activation resulting in increases in resting HR, BP and a decreased stroke volume (Hughson &Shoemaker, 2015). Moreover, the negative influence of sedentary time was further corroborated by Farah et al. (2020), who found increased recreational sedentary time to act in a deleterious manner on parasympathetic activity in adolescents. However, contrary findings in adolescents suggest device-based assessment of sedentary time was not independently associated with parasympathetic activation (Oliveira, Barker, & Williams, 2017). Such discrepancies may be a consequence of methodological

differences in quantifying time spent sedentary (i.e. subjective versus accelerometer-based), despite all studies using short-term HRV to estimate cardiac autonomic modulation (Oliveira, Barker, & Williams, 2017). In particular, two of the three studies supporting the negative effects of sedentary time quantified time spent sedentary using questionnaires, which, despite being validated, have been indicated to underestimate actual time in this behaviour (Dollman et al., 2009). In comparison, Veijalaninen et al. (2019) and Oliveira et al. (2017), employed HR and accelerometry, and accelerometry respectively, to quantify sedentary time. Whilst there are limitations associated with accelerometer-based quantification of sedentary time, as those without inclinometers may misclassify time between sedentary time and LPA, the more objective understanding of this time is still likely be more reliable than questionnaires (Byrom, Stratton, Mc Carthy, & Muehlhausen, 2016). Taken together, the true extent of the relationship between sedentary time and vagal tone remains to be fully established.

2.3.2 Sedentary Time in children with Type 1 Diabetes

In chronic disease, specifically T1D, the burden of the condition is often found to lead to increased periods of sedentary time, with diabetic children found to have significantly less breaks in this time when compared to non-diabetic peers (Czenczek-Lewandowska, Leszczak, Weres, et al., 2019). Prolonged periods of sedentary time for those with T1D have been linked to increases in insulin resistance, long-term dyslipidaemia and declines in CRF (Michaliszyn &Faulkner, 2010). Furthermore, screen time, > 3 hours per day independent of total sedentary time for children with T1D, have been significantly associated with increases in HbA1c and the serum lipids, triglycerides and LDL-c (Li et al., 2015b). Subsequently, many of the negative effects of sedentary time may be attributed to the concomitant behaviours associated with sedentary behaviours, such as screen time (Saunders, et al., 2014). Furthermore, the increase in HbA1c, more unfavourable lipid profile and insulin resistance associated with prolonged time in these behaviours, are subsequently linked to an increased likelihood of glycaemic extremes (Greenbaum, 2002; Nadeau et al., 2010). A persistently elevated blood glucose, in addition to an unfavourable lipid profile, have been linked to premature increases in arterial stiffening (Obermannova, et al., 2017; Shah, et al., 2015; Urbina, et al., 2019) and autonomic decline (M Jaiswal et al., 2013; Vinik, et al., 2003). However, no studies have explored the direct association between

sedentary time, arterial stiffness and autonomic function in a paediatric diabetic population. Given the independent negative health associations of prolonged sedentary time in otherwise-healthy children, more research is necessary to explore these interactions in the paediatric T1D population with the aim of identifying meaningful relationships and targets for intervention.

2.3.3 Guidelines for Time Spent Sedentary

The most recent UK physical activity guidelines for health in children and adults include recommendations for all ages to reduce and break up extended periods of sedentary time with light to moderate physical activity, with the aim to reduce, or offset, the negative effects associated with this time (Chief Medical Officers, 2019). However, there is no guide as to the necessary frequency of breaks or at what duration LPA should be performed to offset the negative associations of sedentary time (Chief Medical Officers, 2019). This part of the guideline has not changed since the previous recommendations, likely due to the lack of conclusive evidence with regards to offsetting the negative effects of sedentary time. Indeed, whilst the evidence is clear that reducing and breaking up prolonged periods of sedentary time is beneficial (Benatti &Ried-Larsen, 2015; Keadle, Conroy, Buman, Dunstan, & Matthews, 2017), what is less clear is how frequent and the duration of interruptions in this time required to reduce these negative associations (Benatti &Ried-Larsen, 2015).

The current understanding of breaking up sedentary time in adults indicates that as frequency of breaks in this time increases, concomitant decreases, independent of total sedentary time and MVPA, are demonstrated in of a range of cardiometabolic risk factors, including decreases in systolic and diastolic BP (Carson, et al., 2014), waist circumference (Carson, et al., 2014; G. Healy et al., 2008), triglycerides (G. Healy, et al., 2008; Henson et al., 2013), and increases in glucose tolerance and high density lipoprotein (HDL-c; G. Healy, et al., 2008; Henson, et al., 2013). However, in children, whilst the number of breaks in sedentary time per day was not associated with any cardiometabolic risk factor, a longer duration of daily breaks in this time were linked to a decreased risk of adiposity and a higher diastolic BP (Bailey, Charman, Ploetz, Savory, & Kerr, 2016). The differences according to daily breaks in sedentary time could be indicative of the effects associated with a decreased total sedentary time or

possibly an increased physical activity, highlighting the need to explore the relative effects of sedentary time and physical activity relative to movement behaviours in a day (Chastin, et al., 2015) Whilst the majority of evidence supports that sedentary time has a negative effect on cardiometabolic health, the differing findings with regards to interrupting this time between children and adults indicates possible differences in patterns of accumulation for sedentary time. Indeed, children have been proposed to accumulate sedentary time in bouts of a shorter duration compared to adults and subsequently may break up this time more frequently (Altenburg et al., 2015). In addition to breaking up prolonged periods of sedentary time evidence has also indicated that reducing time in this behaviour can slow the accrual of associated negative health effects in both children and adults (Keadle, et al., 2017). Meeting the physical activity guidelines, or above, is suggested to ameliorate the negative effects of extended periods of sedentary time (Alves et al., 2016; Wilmot, et al., 2012). However, many studies have refuted this suggestion and found that the deleterious associations of sedentary time remain independent of physical activity (Chaput et al., 2012; Koster, et al., 2012; Thorp, Owen, Neuhaus, & Dunstan, 2011). Therefore, the effects of both behaviours may be distinct and highlights that more evidence is needed to elucidate how sedentary and active behaviours interact, within the confines of each day.

2.4 Accumulation of physical activity and sedentary time

Current research suggests that the manner in which sedentary time and physical activity are accumulated per day influences health (Bailey, et al., 2016; Boerema, van Velsen, Vollenbroek, & Hermens, 2020; Vasankari et al., 2017). Specifically, different patterns of accumulation, which add up to the same total volume of time spent in each movement behaviour per day, may have different effects on indicators of health (Hnatiuk, Lamb, Ridgers, Salmon, & Hesketh, 2019; Porter, Matthews, Salvo, & Kohl, 2017). As such, investigating the total time in isolation would not reveal such patterns or effects. For example, the manner of accumulation of total physical activity and sedentary time may significantly differ between individuals who are identified as similarly active and sedentary but show significant differences in frequency and duration of active and sedentary bouts (Figure 2.2). Consequently, despite

accumulating similar volumes of physical activity and sedentary time, the health association of these patterns of accumulation may differ.

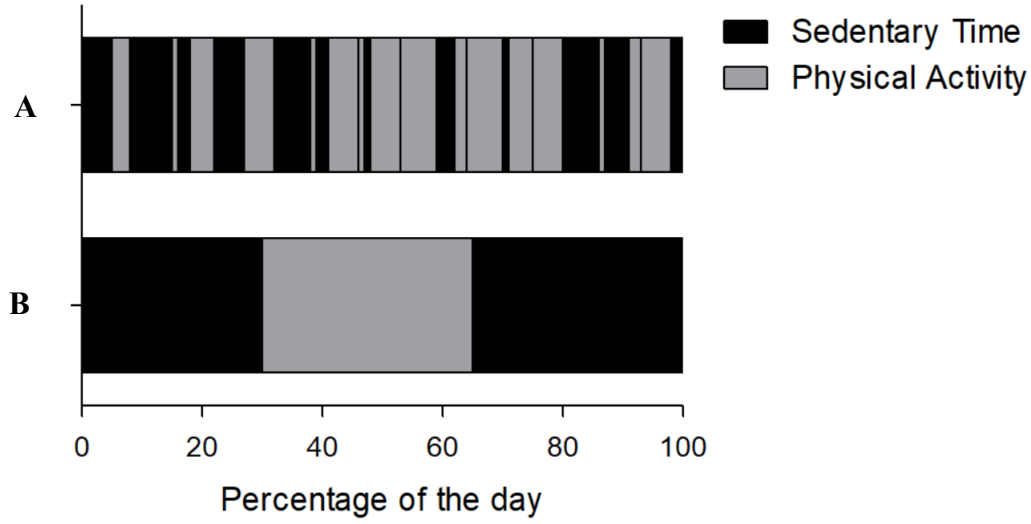


Figure 2.2.. An example demonstrating distinct patterns of physical activity and sedentary time accumulation between individuals A and B.

The accumulation of physical activity is further complicated by the potential tendency to compensate for a lack of, or excessive, physical activity, by accruing more or less, respectively in the following days or periods (Gay, Buchner, Smith, & He, 2017). Specifically, the theory of physical activity compensation, or the ActivityStat hypothesis, proposes that physical activity fluctuates around a mean and therefore remains relatively constant over time (Rowland, 1998). The ActivityStat is postulated to impact accumulation and subsequent health effects, both positive and negative (Gomersall, Rowlands, English, Maher, & Olds, 2013b), and is hypothesised to be a factor in the effectiveness of physical activity for adults and children (Gray, Murphy, Gallagher, & Simpson, 2018; Ridgers, Timperio, Cerin, & Salmon, 2014). Research has found children who engage in 10 additional minutes of LPA and MVPA, demonstrated a concomitant reduction of 5 and 25 minutes, respectively, the following day, with a similar effect observed for sedentary time (Ridgers, et al., 2014). Moreover, Wilkin et al (2006) found little difference in overall physical activity levels, despite large differences in school-based activities and active travel to and from school. Conversely, Dale et al. (2000) reported a minimal increase in additional physical activity, despite restriction of school-based activities in primary school children.

Whilst in adults there is less evidence to support or refute the hypothesis, the existing studies suggest a similar lack of consensus with regard to the compensation effect in physical activity (Lynch, Corbin, & Sidman, 2009; Nooijen et al., 2018). As such, the current understanding of the compensation effect remains equivocal, not least as it is predominantly based on cross-sectional studies (Gomersall, et al., 2013b). Whilst these cross-sectional studies are important to advance our understanding of possible associations (Gomersall, et al., 2013b), the observational nature of these studies precludes conclusions from being drawn regarding the cause and effect of the associations observed (Baggett et al., 2010; Frémeaux et al., 2011; Goodman, Mackett, & Paskins, 2011; Lynch, et al., 2009; Rowlands, Pilgrim, & Eston, 2009; Wickel &Eisenmann, 2007; Wilkin, et al., 2006). Furthermore, these studies only explored the effect in physical activity, with the other movement behaviours in a day that can influence physical activity not accounted for. Subsequently, evidence surrounding the existence of a compensation effect in children and adults remains unclear.

2.4.1 Compensation Effect in Physical Activity

Whilst a compensation effect is a possible influence on how physical activity is accumulated, physical activity can be further influenced by numerous factors, including the type of day (Kristensen et al., 2008; Matthews, Ainsworth, Thompson, & Bassett, 2002), season (Atkin, Sharp, Harrison, Brage, & Van Sluijs, 2016; O'Connell, Griffiths, & Clemes, 2014), random incidents (Rowlands et al., 2015), the Hawthorne effect (Bravata et al., 2007), and the natural fluctuations of physical activity behaviour (Shang, Duan, Huang, & Brehm, 2018). As a consequence of variance associated with accumulation of physical activity, differences in patterns of accumulation between populations have been observed. Specifically, children have been found to accrue physical activity in more high-intensity, sporadic bursts throughout the day (Janssen &Leblanc, 2010), but the overall the pattern is likely predictable especially during school time, due to daily and weekly routines. Conversely, adults accumulate physical activity in longer, structured periods of lower intensities, often in a less predictable manner (Livingstone, Robson, Wallace, & McKinley, 2003). Taken together, these differences in physical activity accumulation highlight the need to account for behavioural variation when quantifying habitual

physical activity, while acknowledgement of such variation is an important consideration to identify targets for intervention.

2.4.2 Physical Activity and Sedentary Time Composition

When considering the behaviours of accumulation and compensation, the constraints of the 24-hour period and how this time is made up need to be considered. Specifically, the finite 1,440 minutes within a day are spent in one of four major behaviours: sleep, sedentary time, LPA or MVPA (Stefelová, et al., 2018). As these behaviours create a ratio within the day, a change in one of these components leads to a change in one, or more, of the others (Stefelová, et al., 2018). For example, if time spent in MVPA is to increase, this would necessitate a decrease in sleep, sedentary time and/or LPA, in order for the total day to remain at 1,440 minutes. An understanding of how physical activity behaviours and sleep interact is an important consideration, especially when exploring the association between physical activity and health. Furthermore, when exploring this association, traditional statistics, such as linear regression, assume independence between all covariates (Pearson, 1896). However, the co-dependent nature of movement behaviours within a day violates this assumption of independence, highlighting the need for compositional analyses which can account for this dependence (Chastin, et al., 2015).

Compositional analyses have recently been applied to physical activity data in order to explore how these compositions of time relate to health, in addition to the prediction of change in health outcome, depending on a change in ratios of physical activity behaviours (Chastin, et al., 2015). Interestingly, research with the compositional technique has demonstrated that while MVPA often makes up the smallest proportion of the day, small changes in this behaviour can have significant impacts on various health outcomes (Chastin, et al., 2015). Specifically, research has shown that substituting 10 minutes of MVPA with any other behaviour for children and adolescents resulted in the greatest deleterious effect on cardiometabolic and obesity risk (Carson, Tremblay, Chaput, & Chastin, 2016). Conversely, substituting time from sedentary to VPA was found to have the greatest positive change in cardiometabolic measures, reducing the risk of obesity and cardiometabolic complications later in life (Stefelová, et al., 2018). In adults, the greatest positive effects on health were observed

with the reallocation of time from sedentary to MVPA, reducing cardiometabolic risk and identifying a key target for intervention (Chastin, et al., 2015). However, whilst predictive modelling can give insights as to possible influence of change, limitations to the interpretation of these findings must be acknowledged. Specifically, the predictive changes observed are based on the average composition of the population, therefore, the changes observed may not be generalisable. Furthermore, predictive modelling gives no indication as to whether the predictive changes may be acute or chronic, or the duration of change in behaviour necessary to achieve such a change.

Whilst recent studies employing compositional analyses have revealed valuable insights regarding the effect of the movement composition, in addition to the relative effects of individual movement behaviours, these studies are based on a single seven days of accelerometer-based monitoring (Carson, et al., 2016; Chastin, et al., 2015; Stefelová, et al., 2018). Specifically, seven days of monitoring have been proposed to be insufficient to account for behavioural variation in physical activity (Bergman, 2018; Shephard, 2017), thereby possibly under- or over- estimating habitual physical activity and movement behaviours within these compositions. Subsequently, the associations between habitual movement behaviours and health outcomes remain to be fully elucidated. Therefore, the use accelerometer derived physical activity derived from longer measurement durations could not only provide a potentially more reliable understanding of the movement composition, but could also provide insight as to possible variation in the movement compositions over time. Indeed, the compensation effect in physical activity and the fluctuations associated with this behaviour (Gomersall, et al., 2013b; Shang, et al., 2018) would therefore result in concomitant changes in sedentary time, LPA and sleep due to the bounded nature of this data. Moreover, this analysis technique has only been used in a limited range of populations, such as healthy children and adolescents (Carson, et al., 2016; Stefelová, et al., 2018), adults (Chastin, et al., 2015; Dumuid, et al., 2018) and those at risk of T2D (Swindell et al., 2020); further exploration of the movement composition is therefore warranted in other populations. Indeed, compositional analysis could further our understanding of physical activity compositions in and between different populations, with a reduced likelihood of anomalous correlations and less influence of outliers (Chastin, et al., 2015; Stefelová, et al., 2018). Moreover, such a technique would be highly valuable

when devising interventions as the ability to predict health outcomes can suggest specific changes to give a greater effect on health outcomes (Chastin, et al., 2015).

2.5 Physical Activity and Sedentary Time Monitoring

Fundamental to addressing the issue of inactivity and gaining a greater understanding of how physical activity and sedentary time influence health, is the ability to accurately quantify and interpret physical activity and sedentary time across the lifespan. The accurate assessment of physical activity is imperative to understand how physical activity, such as the volume and intensity, is an independent predictor of risk for cardiovacular disease, in both general and clincial populations (Andersen et al., 2006; Borodulin, et al., 2015; Chastin, et al., 2015). Moreover, an accurate representation of physical activity and sedentary time is critical to subsequently inform future interventions seeking to reduce the risk of long-term health conditions. However, physical activity and sedentary time, irrespective of the population, are inherently hard to quantify. It is not only important to consider the behavioural variation within and between populations, but to understand the challenges associated with obtaining an accurate reflection of true habitual movement patterns (Rowlands, et al., 2018).

2.5.1 Subjective Measures of Physical Activity and Sedentary Time

Subjective measures, such as self-report questionnaires, which are low cost and relatively easily implemented for large scale studies (Besson, et al., 2010), are the most widely available method of quantifying physical activity and sedentary time. Consequently, subjective, population-based, data has previously been utilised to inform guidelines regarding the volume, and intensity, of physical activity necessary to attain health-associated benefits (Chief Medical Officers, 2019; Haskell et al., 2007; Office of Disease Prevention and Health Promotion, 2008). There are numerous validated physical activity questionnaires (Helmerhorst, Brage, Warren, Besson, & Ekelund, 2012; Hidding, Chinapaw, van Poppel, Mokkink, & Altenburg, 2018; Silsbury, et al., 2015), with one of the most widely utilised being the international physical activity questionnaire (IPAQ; Craig et al., 2003). Questionnaires of this type ask individuals to recall activities over a specific period of time to provide an overview of the perceived time spent in each intensity of physical activity (Craig, et al., 2003; Sirard &Pate, 2001). The IPAQ, and, indeed, equivalent measures, have been

demonstrated to provide an insight into physical activity and sedentary time, with good repeatability but questionable validity in comparison to more objective measures (Craig, et al., 2003). Furthermore, subjective measures of this type have been found to underestimate physical activity and sedentary time due to recall bias (Besson, et al., 2010). Therefore, earlier physical activity guidelines may have underestimated the volume of physical activity required to attain health-associated benefits.

2.5.2 Accelerometers

Subjective measures for quantifying physical activity and sedentary time are valuable for large-scale population studies, however, to achieve a more in-depth representation of movement behaviours objective measures are needed. Objective, or accelerometer-based, measures of physical activity are now widely used in research, to quantify bodily movement (Karas et al., 2019). Accelerometers provide the opportunity to accurately and reliably monitor habitual physical activity, in addition to obtaining information about bout duration, intensity, frequency, and volume, for up to 35 days, depending on the specific model and recording resolution (Hills, et al., 2014). Modern accelerometers are able to record movement acceleration in three axes at ≥ 100 Hz (Cain, et al., 2013), and have therefore substantially evolved from early uni-axial accelerometers that commonly utilised 60s epochs (Brage, Wedderkopp, Bo Andersen, & Froberg, 2003). The use of accelerometery, however, can be costly and labour intensive in large scale population studies, due to the number of devices necessary (Lee &Shiroma, 2014). Furthermore, accelerometery can only be used to estimate EE and the intensity of physical activity, as whole body movement is not quantified and no context of movement is obtained (Cain, et al., 2013).

Recent advances in accelerometer design have led to an increasing focus on the optimal placement for accelerometers. Hip-worn accelerometers are well validated and suggested to be reliable for use in children (Rowlands et al., 2014) and adults (Montoye, Pivarnik, Mudd, Biswas, & Pfeiffer, 2016), providing a good estimation of physical activity, sedentary time and EE (Lynch et al., 2019). However, hip-mounted monitors have been found to underestimate physical activity due to the lack of account for upper limb movement, in addition to the inconvenient accelerometer placement resulting in a lower compliance in comparison to wrist-worn devices (Fairclough et

al., 2016; McLellan, Arthur, & Buchan, 2018). Conversely, wrist-worn accelerometers are increasingly utilised due to their associated compliance, as well as demonstrating greater accuracy in estimating free-living activity (Fairclough, et al., 2016; McLellan, et al., 2018; Scott et al., 2017). However, wrist-worn devices have been found to be less accurate at predicting EE, compared to devices worn on the hip, and cannot distinguish between inactivity and sedentary time (Kerr et al., 2017). Furthermore, wrist-worn devices have been shown to underestimate certain activities, such as cycling (Lynch, et al., 2019). Whilst it would seem intuitive to increase accuracy through multiple placements, Mackintosh et al. (2016) found that there was no significant improvement in accuracy with additional accelerometers. Moreover, there was no significant difference in EE prediction, irrespective of placement (Mackintosh, et al., 2016). Therefore, accelerometer placement is likely to be influenced by device type and a compromise in terms of compliance.

2.5.3 Accelerometer Monitoring Criteria

Given that wear compliance is essential to gain an accurate measure of physical activity and sedentary time accumulated over the monitoring period, various wear-time criteria have been established (Mattocks et al., 2008). Wear-time criteria within a 24-hour period is defined as the duration of time the accelerometer must be worn per day to be included within the analysis. Conversely, non-wear criteria is defined as the duration over which the device was removed (Choi, Liu, Matthews, & Buchowski, 2011). The number of hours necessary to represent a valid day has been highly contested in literature (Choi, et al., 2011); any wear-time less than the full 24-hours would result in a loss of insight as to actual physical activity behaviour. The minimum number of hours proposed to date as valid for waking hours monitoring, excluding sleep, is eight hours (Troiano, McClain, Brychta, & Chen, 2014). However, for 24-hour monitoring, 13 – 16 hours are suggested to be necessary (Herrmann, Barreira, Kang, & Ainsworth, 2013; Matthews, et al., 2012). Furthermore, weekly or overall recording criteria are defined as the number of days with valid hourly wear-time, for the whole monitoring period to be classed as acceptable and included in analyses. Currently, there is no consensus regarding the minimum number of days required in order to provide reliable data, with research ranging from three to seven days (Trost, 2007; Trost, et al., 2000), with a longer duration suggested to yield an improved

representation of habitual behaviour. The generally accepted criteria, irrespective of population, is a minimum of two weekdays and one weekend day, due to the contrasting situational influences associated with the different periods (Trost, et al., 2000). However, such minimal criterion is suggested to be most suitable in active individuals whose physical activity patterns tend to be more predictable (Rowlands, et al., 2018). Children move in short burst of higher-intensities, but in the longer term accumulate physical activity in a more routine manner, while adult's movement tends to be more structured, but accumulated in a more sporadic and varied manner (Loprinzi &Cardinal, 2011; Loprinzi, Lee, & Cardinal, 2014; Rowlands, et al., 2018). Such differences in accumulation patterns highlights the importance to monitor physical activity for a sufficient duration in order to obtain an accurate insight of habitual behaviours and patterns. Given that previous research has demonstrated significant differences in the time spent in physical activity intensities per day according to wear-time criteria selected (Herrmann, Barreira, Kang, & Ainsworth, 2014), selecting appropriate wear-time criteria is of paramount importance and can considerably alter the interpretation of data.

The duration of physical activity monitoring using accelerometery is also associated with considerable debate in the literature, with seven days being the most commonly utilised period and shown to be reliable in both children (Barreira, et al., 2015; Cain, et al., 2013; Trost, et al., 2000) and adults (Matthews, et al., 2012; Sasaki, et al., 2018). However, a recent review suggests that this period may be insufficient, and that a longer duration may be necessary to reliably and accurately characterise intra- and inter-individual variation in habitual physical activity (Rowland, 1998). Previously, longer durations of recording were not possible due to accelerometer limitations, such as limited battery life and storage capabilities. However, accelerometers are now capable of recording for more than 30 days at acceptable sampling frequencies, which may thereby enhance the understanding of habitual physical activity, but also enables the identification of meaningful trends and cycles in physical activity. That said, it is imperative to ensure the duration of wear is considered carefully to maximise meaningful data and provide a reliable indication of physical activity levels, but not over burden participants.

2.5.4 Accelerometery Data and Movement Behaviour Metrics

Whilst recording duration, and frequency, are vitally important, the ability to accurately calculate volume of time spent in each movement behaviour, as well as the manner in which it was accumulated, is of equal importance. To achieve accurate classifications of the time spent in physical activity, sedentary time and sleep during a day, the accelerometer data obtained must be processed and analysed according to a range of processing decisions (Migueles et al., 2017). Accelerometer data is typically processed by device software into specified common sample or epoch durations (e.g. 1s, 5s, 15s and 60s; Orme et al., 2014). Some accelerometers have in-built processing to compress movement acceleration into 'counts' of activity, which is then also averaged to a chosen epoch. However, compressing data in this way may result in an underestimation of physical activity or sedentary time accrued and presents further issues for inter-study comparability, due to the different modes of compartmentalising the initial data, before any further analysis (Hildebrand, Hansen, van Hees, & Ekelund, 2017). However, the use of acceleration in its raw state, prior to significant processing, is a relatively recent development that can overcome issues of inter-study and accelerometer comparison (Rowlands, 2018). Specifically, raw acceleration data is the omni-directional gravitational equivalents of movement, produced from the acceleration signal output extracted from tri-axial accelerometers (de Almeida-Mendes et al., 2018). When using raw accelerometry data, a greater understanding of the analysis techniques is required to produce meaningful outputs in terms of movement behaviours. However, this may be balanced by the improved comparability in output between accelerometers, resulting in the need for only population specific thresholds, as opposed to population and accelerometer specific thresholds (Migueles et al., 2019).

The magnitude of movement, and the associated EE, is quantified with the use of thresholds or 'cut-points', thereby allowing researchers to distinguish time spent sedentary and in LPA, MPA and VPA (Trost, et al., 2011). Specific thresholds have been created for different populations (Evenson, Catellier, Gill, Ondrak, & McMurray, 2008; Watson, Carlson, Carroll, & Fulton, 2014), accelerometers (Loprinzi &Cardinal, 2011; Lynch, et al., 2019; Phillips, Parfitt, & Rowlands, 2013; Trost, et al., 2011) and accelerometer placements (Fairclough, et al., 2016; McLellan, et al., 2018; Scott, et al., 2017). However, the use of different thresholds between studies can limit inter-

study comparison and subsequent interpretations, as the use of different thresholds can change the quantification of movement behaviours, in addition to whether a participant meets physical activity guidelines (Trost, et al., 2011). Subsequently, acknowledging the limitations of such thresholds, recent advances have been made to develop non-threshold based metrics of physical activity to gain a more in-depth insight as to the accumulation of physical activity in terms of both volume and intensity. Specifically, the negative curvilinear relationship of time and movement intensity can be natural logged creating a log-linear relationship. The gradient, or 'intensity gradient', of this relationship can then be obtained to give an indication of the movement intensity accrued over a given monitoring period and provide a representation of the full intensity profile (Rowlands, et al., 2018). A steeper intensity gradient is associated with engaging in lower intensities of movement, while a more shallow gradient is indicative of achieving a greater range of intensities (Rowlands, et al., 2018). Moreover, the volume of physical activity can be represented by averaging acceleration data over a given period (Rowlands, 2018). Therefore, these metrics, when used for the full 24-hour period, give a good representation of overall intensity distribution and total movement. Whilst these metrics have been criticised as being more difficult to interpret with regards to physical activity guidelines, Rowlands et al. (2019) proposed the most active X minutes over time or (MX) metrics, which translate these data-driven metrics to be more meaningful for physical activity guidelines and public health. An example of the translation of these metrics is the M60, representing the most active 60 minutes of the day, indicative of the children's physical activity guidelines and could be used compare between and within groups (Rowlands, et al., 2019).

Presenting the full physical activity profile, alongside total volume, enables greater insight of how physical activity is accumulated, providing a consistent and accurate estimation of the physical activity accrued, in addition to facilitating the explanation of intra- and inter-individual variation (Rowlands, et al., 2018). Current studies employing these more data-driven metrics to explore the effects of the physical activity profile on adiposity, CRF (Buchan, McLellan, Donnelly, & Arthur, 2019; Fairclough, Taylor, Rowlands, Boddy, & Noonan, 2019) and physical function (Rowlands, et al., 2018), reveal the effects of physical activity intensity, independent of total volume. However, these studies so far have only explored the influences of volume and

intensity in otherwise healthy children (Buchan, et al., 2019; Fairclough, et al., 2019; Rowlands, et al., 2018) and adults with T2D (Rowlands, et al., 2018). Furthermore, the current studies derived these data-driven metrics from seven day accelerometer recordings, therefore the behavioural variation accounted for over this period may be limited. However, employing a longer duration of accelerometer-monitoring would likely encompass more behavioural variation, supporting understanding of the capabilities of these metrics to reveal variation in intensity and volume of physical activity across this duration (Bergman, 2018). Additionally, while T2D and T1D can result in similar complications, the aetiology and pathophysiology of these conditions vary significantly (American Diabetes Association, 2010), therefore additional studies are needed to explore the use of these metrics in populations such as T1D.

2.6 Summary and Conclusion

The present literature review has summarised the current understanding of the influences of physical activity and sedentary time on arterial and autonomic health, in both paediatric and adult populations. This review highlights the equivocal evidence as to the influence of the full range of movement intensity on arterial stiffening and autonomic function, in addition to the effects of sedentary time in children and adolescents. Furthermore, this chapter sought to review current and developing practice for utilising accelerometer-based measurement durations and movement behaviour analysis techniques.

Physical activity is proposed to act in a preventative manner on the risk of CVD, acting in a positive manner to prevent premature arterial and autonomic ill-health. However, despite this approximately half of children and adults are not consistently meeting physical activity guidelines. Evidence of the effects of accruing a lesser volume and intensity than the physical activity guidelines for cardiovascular health are equivocal in children. Moreover, the paediatric population, in particular adolescents, are becoming increasingly sedentary in prolonged periods, attributed to increases in multimedia and screen use. Whilst there is a lack of consensus as to the effects of total sedentary time, breaking up prolonged periods and reducing this time has been found to be beneficial and may prevent premature progression in arterial stiffening and autonomic decline. Taken together, improving the understanding of these behaviours,

and variation in this time could be key to elucidate how to prevent negative changes towards CVD in various populations. Therefore, a better quantification of movement behaviours, by representing the full physical activity profile and exploring habitual fluctuations, could be key to understanding the stimulus for change necessary to influence cardiovascular health. Moreover, analysing these behaviours relative to the remaining daily behaviours may provide a more appropriate understanding of the effects of these behaviours and identify key interventional targets.

Subsequently, the primary aim of this thesis was to better understand the influences of physical activity and sedentary time on arterial and autonomic health, exploring how fluctuations and compositions of movement behaviour, as well as the physical activity profile influences these associations.

Chapter 3

Methodology

Chapter 3: Methodology

Data collection was conducted in outpatient departments and schools in South Wales and the Swansea University Applied Sports, Technology, Exercise and Medicine (A-STEM) Research Laboratories. All investigations were cross-sectional in nature, with all experimental procedures approved prior to any recruitment or data collection by the relevant NHS (16/NE/0082 – Chapters 5 and 7) or institutional ethical committees (2018-0.65 – Chapter 4, 2018-101 – Chapter 6, 2018-043 – Chapters 6 and 7).

3.1 Participants

All participants took part in the research willingly and were fully informed of the investigation prior to volunteering and taking part. The general exclusion criteria for all studies were any condition that would prevent the participant completing the requirements of each study, any congenital heart condition that could abnormally influence the assessment of autonomic or vascular stiffness, anyone deemed not suitable for the study by the multi-disciplinary team (MDT; Chapters 5 and 7) or health professionals present, or anyone who did not pass the pre-screening questionnaire (Appendix B). Participants were screened prior to recruitment either by the relevant multi-disciplinary team or a pre-screening process (Appendix B). Pre-screening was conducted to ensure eligibility to take part according to the general exclusion criteria, to notify of any pre-existing conditions and ensure the safety of participants. All participants were asked to refrain from consuming stimulants (e.g. caffeine) or alcohol, as well as from performing strenuous activity, for 12-hours prior to the assessment, in addition to not eating a large meal two-hours prior.

3.2 Recruitment

Participants were recruited in person or by recruitment advertisements. All participants and parents/guardians, where appropriate, were provided with the respective information sheets (Appendix A) and were fully informed of what was involved in each study. School assemblies were used to inform year groups of study information, and give an additional opportunity to ask questions prior to recruitment (Appendix A). Written informed consent was obtained from participants aged 16 years and over, with written informed parental/guardian consent and written informed assent obtained for those under 16 years (Appendix C).

3.3 Experimental Procedure

3.3.1 Age and anthropometrics

Decimal age for all participants was calculated to the nearest 0.1 years as the difference between date of birth and assessment date. All anthropometric measurements were taken in line with the standards set by the International Society for the Advancement of Kinanthropometry (Stewart, Marfell-Jones, Olds, & Ridder, 2011), with measures obtained at the commencement of data collection. Standing height was measured to the nearest 0.1 cm using the available calibrated stadiometer in outpatients clinics, a potable stadiometer (Seca 213, Seca GmbH, Hamburg, Germany), or a calibrated Holtain stadiometer (Holtain Ltd, Crymych, Pembrokeshire, Wales). For all measurements, the participant was asked to stand with their back against the stadiometer, heels touching the back, feet together with good posture and chin parallel to the floor. Sitting height, obtained to calculate the ratio of the torso to leg length for estimation of maturity stage, was measured to the nearest 0.1 cm for all participants aged 16 years and younger. A specialist sitting height stadiometer (Harpenden Sitting Height Table model 607VR, Holtain Ltd, Crymych, Pembrokeshire, Wales) was utilised, with participants asked to sit with good posture, legs at 90 degrees and chin parallel to the floor. For field-based measurements of torso height in Chapter 4, a portable stadiometer (Seca 213, Seca GmbH, Hamburg, Germany) was used, with the participant sitting on the base of the stadiometer, with good posture and chin parallel to the floor. For all participants, body mass was obtained to the nearest 0.01 kg on calibrated electronic scales (Seca 899, Seca GmbH, Hamburg, Germany). All participants were measured without shoes and with any heavy clothing or items in pockets removed. Body mass index (BMI) was calculated for all participants as height (in metres) squared, divided by body mass.

3.3.2 Maturity Offset

It is important to account for the influence of maturation due to the significant difference between chronological and biological age (Iuliano-Burns, Mirwald, & Bailey, 2001). Maturity status can be assessed using biological age, skeletal age, secondary sex characteristics or somatic growth (Mirwald, Baxter-Jones, Bailey, & Beunen, 2002). However, each is method associated with certain limitations with

regard to their implementation and interpretation. Indeed, whilst skeletal age is typically considered the gold standard assessment of maturational stage, it is costly and requires highly specialised equipment and training, and exposes participants to unnecessary radiation (Beunen, 1989; Mirwald et al., 2002). Furthermore, assessing pubertal stage according to secondary sex characteristics does not give an indication of tempo and is considered intrusive by many parents and participants. Finally, calculating the age at peak height velocity (PHV) and time from this necessitates repeated measurements throughout the maturational process and is therefore unsuitable for cross-sectional studies (Beunen, 1989; Mirwald et al., 2002). However, the use of predictive equations based on age of PHV data and the differential regional growth of the limbs and torso can provide a non-invasive indication of maturation status (Malina & Bouchard, 1991). There are a number of predictive methods now available but earlier methods used predicted adult stature, based on average height between parents, and then calculated maturity from this (Mirwald et al., 2002). In contrast, more recent maturity offset equations use age and differences between the anthropometric measures of height, sitting height and leg length, to estimate time from PHV (Mirwald et al., 2002). Maturity was indirectly estimated according to the maturity offset equations developed by Mirwald et al. (2002). The equations (see Equations 1 and 2) predict the time in years a child is from their PHV, to the nearest 0.1 years. Pubertal status categories were defined as pre-pubertal if a child was more than minus one year from PHV, pubertal if between minus one and plus one year of PHV, and post-pubertal if greater than one year post PHV (Mirwald, et al., 2002).

Equation 1.

$$\text{Boys Maturity Offset} = -9.236 + 0.0002708(\text{leg length} \times \text{sitting height}) - 0.001663\ (\text{age} \times \text{leg length}) + 0.007216\ (\text{age} \times \text{sitting height}) + 0.02292\ (\text{weight} \div \text{height})$$

Equation 2.

$$\text{Girls Maturity Offset} = -9.376 + 0.0001882\ (\text{leg} \times \text{sitting height}) + 0.0022\ (\text{age} \times \text{leg length}) + 0.005841\ (\text{age} \times \text{sitting height}) - 0.002658\ (\text{age} \times \text{weight}) + 0.07693\ (\text{weight} \div \text{height})$$

The maturity offset was originally validated in child and adolescent populations by the Mirwald et al. (2002) and, more recently, by Koziel and Malina (2018), however no data regarding repeatability is available. These maturity offset equations have been reported to have an r^2 according to age at PHV of 0.91 and 0.92 for girls and boys, respectively, and associated with a standard error of ± 0.592 years (Kozieł & Malina, 2018; Mirwald, et al., 2002), a degree of error which could result in a misclassification of pubertal stage. Furthermore, it has been shown that the equations are more limited in their application to early and late maturers, with the standard error likely to be greater the further the estimated maturity offset is from the mean (Kozieł &Malina, 2018). Thus, non-typical maturers are at an increased likelihood of misclassification of maturity status. However, these limitations were considered to be offset by the practical advantages of the simplicity of the measures required to estimate maturity from PHV, feasibility and the non-invasive nature in comparison to gold standard techniques, such as biological age.

3.3.3 Arterial Stiffness

Arterial stiffness was assessed to investigate the current state of the arteries and how this contributes to long-term risk of cardiovascular disease. The gold standard in research for evaluating central arterial stiffness is currently the assessment of central pulse wave velocity (PWV; Van Bortel et al., 2012). In these studies, central stiffness was evaluated utilising an oscillometric device (Vicorder, Skidmore Medical, Bristol, UK), a specialised blood pressure cuff, a partial inflatable sensor and a secured laptop with the corresponding Vicorder software (Skidmore Medical, Bristol, UK). This method was chosen over others, such as flow mediated dilation (FMD), applanation tonometry, ultrasound and magnetic resonance phase contrast imaging (MRI; Van Bortel et al., 2002; Van Bortel, et al., 2012), due to the ease of use and practicality in laboratory and field-based settings, in addition to the relatively low cost and simple training required (Parikh, et al., 2016; Van Bortel, et al., 2002). Strict adherence to the measurement conditions and protocol were maintained throughout all studies to ensure reliability and repeatability of the results (Laurent et al., 2006). The Vicorder device has been shown to be valid for use in children and adolescents (Kracht et al., 2011), with good agreement with applanation tonometry using SphygmoCor, a well-established mode of assessing arterial stiffness, and good inter- and intra-operator

repeatability (Kracht, et al., 2011). Additionally, this device has been validated for use in normotensive adults by Müller et al. (2013).

3.3.3.1 Pulse Wave Analysis (PWA)

Indirect central stiffness was assessed by pulse wave analysis (PWA) obtaining multiple parameters including: pulse pressure (PP), augmentation pressure (AP), an indicator of systemic arterial stiffness, and augmentation index (AIx), an indicator of arterial compliance (Stoner, et al., 2012). Assessment of arterial stiffness in this manner is an established technique, commonly employed in various populations including children, adolescents and adults (Ananey, et al., 2015; Caviezel et al., 2018; Mitchell et al., 2004; Mocnik, Nikolic, & Marcun, 2018). These studies have shown that AIx increases with age during childhood and adolescence but slows in adults, while AP increases progressively with age from childhood to older adulthood (Mitchell, et al., 2004; Stoner, et al., 2012). Therefore, the combination of AIx and AP give a holistic indication of artery compliance with the potential to highlight pre-symptomatic CVD risk. However, it is important to consider sex, height and HR when interpreting AIx, as women and shorter individuals typically demonstrate an elevated AIx (Fantin, Mattocks, Bulpitt, Banya, & Rajkumar, 2018; Mitchell, et al., 2004). Specifically, an inverse relationship is present between AIx and HR, therefore for all PWV assessments a resting period was used to ensure a resting HR (Wilkinson et al., 2000).

Assessment of indirect central stiffness was performed at the brachial artery in the supine position, with the participant asked to remain still and to refrain from talking for the duration of the assessment, as recommended by the Arterial Stiffness Task Force III (Van Bortel, et al., 2002). An initial blood pressure was performed utilising an oscilliometric device (Vicorder, Skidmore Medical, Bristol, UK) followed immediately by the assessment, with the cuff over the brachial artery (D.E.Hokanson Inc, Bellevue, WA, USA) inflating to the previously obtained diastolic pressure. After a stable aortic waveform was obtained, the series of waveforms were captured after a minimum of four-recorded heartbeats. A further two waveform series were captured over a period of three - five minutes. The measures obtained during the process are presented in Figure 3.1. Pulse pressure was calculated as the difference between

systolic and diastolic pressures, AP as the difference between the second and first systolic peaks, and AIx as the difference between peaks one and two on the systolic waveform (Figure 3.1), presented as a percentage of pulse pressure (Equation 3; Stoner, et al., 2012).

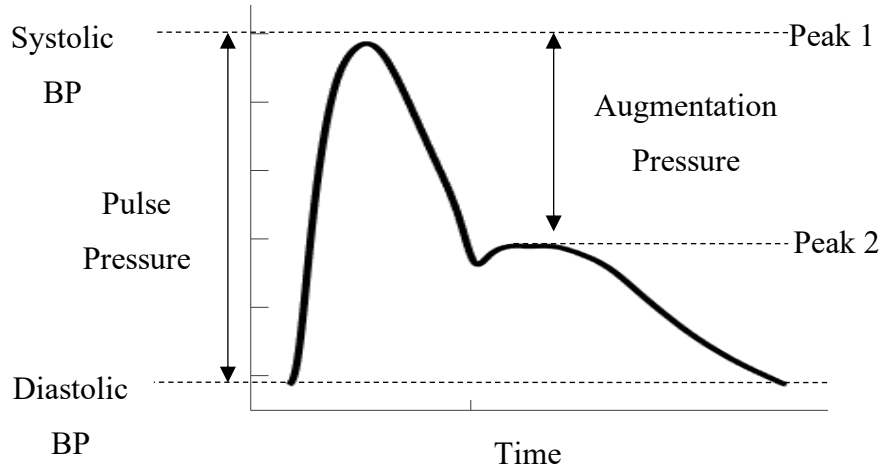


Figure 3.1.. Example of systolic waveform assessed at the brachial artery, providing visual identification of systolic, diastolic, pulse and augmentation pressures.

Equation 3.

$$AIx = \frac{Augmentation\ pressure}{Pulse\ pressure} \times 100$$

3.3.3.2 Pulse wave velocity

Aortic pulse wave velocity (aPWV) was attained as a measure of central stiffness, an independent indicator of CVD risk (Van Bortel, et al., 2012). The gold standard for obtaining aPWV is MRI to detect the arrival of pulse waves, however, the Vicorder (Skidmore Medical, Bristol, UK) has been reported to perform comparatively (Parikh, et al., 2016). Indeed, aPWV derived using a Vicorder has been validated in youth (Collins, Somes, & Alpert, 2008; Im, Lee, Shim, Lee, & Lee, 2007; Kracht, et al., 2011; Reusz et al., 2010) and adults (Ananey, et al., 2015; Caviezel, et al., 2018; Müller, et al., 2013).

The assessment of aPWV was performed in a quiet and temperate room, with the participant in the supine position and the head and shoulders elevated at 30^{o} to ensure the muscles over the carotid were relaxed, and after resting for a minimum of five minutes (Thurn et al., 2019; Wilkinson, et al., 2019). BP cuffs (D.E.Hokanson Inc, Bellevue, WA, USA) were applied at the femoral and carotid arteries to record the arrival of pulse waves. A brachial cuff was placed over the femoral artery on the upper right thigh as close as possible to the groin, with a partial neck cuff placed over the right carotid artery (Müller, et al., 2013). The participant was asked to remain still and refrain from talking the duration of the test. The distance between the suprasternal notch and the femoral cuff via the umbilicus was measured to the nearest 0.1 cm (Kracht, et al., 2011; Wilkinson, et al., 2019), using a measuring tape to inform the path travelled by the pulse wave. This technique was chosen over a direct measurement from suprasternal notch to femoral recording site to more accurately describe the path of the arterial tree, in line with previous recommendations (Kracht, et al., 2011). The cuffs were inflated to approximately 60 mmHg (Müller, et al., 2013), then the carotid and femoral waveform series were recorded in real time simultaneously for a minimum of 10 heart beats, with the automatic identification of the maximum systolic upstroke on each pulse wave utilised to determine transit time by cross correlation (Thurn, et al., 2019). Carotid to femoral measurement was repeated in triplicate, with aPWV calculated (Equation 4) for each test and the means retained for further analysis. Finally, mean arterial pressure (MAP), important when interpreting central stiffness, was obtained and calculated for each participant (Equation 5; Müller, et al., 2013).

Equation 4.

$$aPWV(m \cdot sec^{-1}) = \frac{(Suprasternal\ notch\ to\ umbilicus) + (umbilicus\ to\ femoral\ site) - (suprasternal\ notch\ to\ cardotid\ site)(m)}{Transit\ time\ (s)}$$

Equation 5.

$$MAP\ (mmHg) = diastolic\ pressure + (0.33 \times (systolic\ pressure - diastolic\ pressure))$$

3.3.4 Autonomic Nervous Function

Heart rate variability (HRV), an indirect measure of autonomic function, was chosen due to its non-invasive nature, simplicity to obtain and its well-documented use for evaluating the control of the cardiovascular system (Acharya, et al., 2006; Pumprla, Howorka, Groves, Chester, & Nolan, 2002; Sammito &Bockelmann, 2016). This measure has been well utilised in both child and adult populations, with HRV suggested to be a valuable and sensitive tool for detecting pre-clinical symptoms and indicating risk of CVD in child (Chessa, et al., 2002), adult (European Society of cardiology, 1996), and clinical populations (Nolan, et al., 1998; Vinik, et al., 2003). The current gold standard to obtain beat-to-beat cardiac intervals, necessary for extraction of HRV, in short term recordings outside of the clinical setting is a Holter ECG, recording at a frequency of > 1000 Hz (Sammito &Bockelmann, 2016). A 24-hour ambulatory recording can be utilised for HRV analysis and an assessment of autonomic function (Kleiger, Stein, & Bigger, 2005). However, in the present thesis a shorter recording comprising of 15 minutes rest, followed by five minutes of regulated breathing, was identified as appropriate and subsequently employed to obtain a resting estimation of autonomic control (Shaffer &Ginsberg, 2017). Importantly, the same protocol was utilised for all participants to avoid the confounding influence of recording duration and measurement conditions on resting HRV (Shaffer &Ginsberg, 2017).

For the ECG recording, participants were asked to lie in the supine position for 15 minutes whilst breathing spontaneously, which was followed by five minutes breathing at a pace of six breaths per minute (Williams &Lopes, 2002), then a final minute of spontaneous breathing. Ventilatory control was employed as respiratory frequency can significantly influence HRV, due to the effect of respiratory sinus arrhythmia (RSA; Grossman, Karemaker, & Wieling, 1991; Grossman &Taylor, 2007). Indeed, controlling the pace of breathing, at six inspiration-expiration cycles, ensures a consistent representation of resting autonomic function and vagal tone (Williams &Lopes, 2002). During the protocol, participants underwent Holter ECG monitoring, obtained with the use of a three-lead Reynolds CF Holter Recorder (Spacelabs Medical Ltd, Hertford, UK) producing 12-bit resolution ECG data at a sampling rate of 1,024 Hz. The Holter recorder was chosen for its high sampling rate which is optimal to obtain high resolution, digitised ECG recordings, minimising error

associated with determining the R-Wave, and is in line with recommendations (Berntson et al., 1997; European Society of cardiology, 1996). Prior to the recording, three electrodes were positioned on the anterior of the torso, at the manubrium of the sternum, and the V5 and V5R positions. Accurate placing of each electrode was ensured by testing each channel prior to recording, with application preceded by gently abrading and cleaning the site with an alcohol wipe.

ECG recordings were extracted and processed using the Reynolds Pathfinder ECG analysis system (Spacelabs Medical Ltd, Hertford, UK). The pathfinder system classified QRS cycles as either normal or aberrant, and normal cardiac intervals (RR) were identified and extracted with the use of the Reynolds Research Tools software (Spacelabs Medical Ltd, Hertford, UK). The subsequent RR intervals were visually inspected for any obvious outliers or artefacts, which were deleted if present (D'Silva, Davies, Emery, & Lewis, 2014). The processed data was detrended using the 'Smoothn priors' high pass filter with Lamdba set at 500, and analysed using Kubios HRV analysis software 2.0 (Biomedical Signal and Medical Imaging Analysis Group, Department of Applied Physics, University of Kuopio, Finland). HRV variables were quantified in line with the European Society of Cardiology Task Force guidelines (European Society of cardiology, 1996). The time domain indices are derived from the temporal differences in consecutive RR intervals (European Society of cardiology, 1996). Multiple indices of HRV can be derived from the analysis of the time domain to give an indication of overall autonomic, parasympathetic and/or sympathetic activity, with varying accuracy depending on the length of recording (European Society of cardiology, 1996). For longer recordings, typically 24-hours, the standard deviation of normal to normal intervals (SDNN) is suggested to give an indication of overall autonomic activity and the contribution of the sympathetic system to HRV (European Society of cardiology, 1996). However, shorter recordings are also widely employed and hypothesised to give a good estimation of short-term HRV power. Whilst a minimum of five minutes is suggested to be required, shorter periods of as little as 10-seconds have also been proposed (Salahuddin, Cho, Jeong, & Kim, 2007). For these shorter recordings with paced breathing, SDNN has been recommended to give a representation of parasympathetic contribution (Shaffer, McCraty, & Zerr, 2014), similarly the root mean square of successive RR intervals (RMSSD) is

advocated to better denote vagal tone and to be more influenced by parasympathetic activity (European Society of cardiology, 1996).

Spectral estimation by the Welch's method and autoregressive modelling were used to quantify the component rhythms of HRV in each of the different frequency bands: very low frequency (VLF; 0.00-0.04 Hz), low frequency (LF; 0.04-0.15 Hz), high frequency (HF; 0.15-0.5 Hz) and total spectral power (TSP; 0.04-0.5 Hz; European Society of cardiology, 1996; Ori, Monir, Weiss, Sayhouni, & Singer, 1992). Each frequency band is suggested to indicate the contribution of various branches of the ANS. The VLF has been indicated to be a representation of the heart's intrinsic function and to reflect a significant parasympathetic contribution (Shaffer, et al., 2014; Taylor, Carr, Myers, & Eckberg, 1998), but sympathetic activity has also been proposed to modulate this band due to physical activity and thermoregulatory stress (Kember, Fenton, Armour, & Kalyaniwalla, 2001; Kember, Fenton, Collier, & Armour, 2000). However, it is pertinent to note the physiological basis of the VLF band is unclear in literature, and this representation can only be derived from recordings of greater than five minutes (Shaffer, et al., 2014). The presence of low power in this band has been associated with an increased inflammation (Papaioannou, Pneumatikos, & Maglaveras, 2013), in addition to an elevated risk of arrhythmic mortality (Bigger et al., 1992). At rest, LF power has been proposed to be associated with both the sympathetic and parasympathetic systems, and has been suggested to best reflect baroreflex activity as opposed to cardiac sympathetic influence (European Society of cardiology, 1996; Shaffer, et al., 2014). Conversely, the HF band has been reported to represent parasympathetic activity, as opposed to vagal tone, and to be influenced by RSA (Grossman &Taylor, 2007). Low power in the HF band has been found to be highly correlated with RMSSD (Kleiger, et al., 2005), associated with a stressed state and may be linked to an increased mortality (Thayer, et al., 2010). The ratio between LF and HF has previously been advocated as a tool to estimate the contributions of the parasympathetic and sympathetic nervous systems, based on a 24-hour recording (Shaffer, et al., 2014). A low ratio was suggested to give an indication of parasympathetic control and vice versa (Shaffer, et al., 2014). However, the ratio and what it actually represents has been greatly contested due to the non-linear nature of parasympathetic and sympathetic interactions, in addition to the influence of RSA (Billman, 2013).

The aperiodicity of HR was explored with the use of non-linear measures, taking into account the unpredictability and the complex regulation of HRV (Stein &Reddy, 2005). Specifically, the Poincaré plot, a graph of successive RR intervals plotted against the previous interval, was utilised to derive three non-linear indices. Specifically, the standard deviation of intervals perpendicular to the line (SD1), the standard deviation of intervals on the line (SD2) and the ratio of these two indices (SD2/SD1; Shaffer &Ginsberg, 2017). The SD1 is proposed to represent short-term HRV, similar to RMSSD, in addition to prediction of power in TSP, HF and LF (Shaffer &Ginsberg, 2017). The SD2 has been associated with baroreflex activity and LF power and suggested to reflect both short- and long-term variability (Brennan, Palaniswami, & Kamen, 2002). Conditions such as diabetes have been demonstrated to show a decrease in non-linear indices, in addition to negative changes observed in time and frequency domains (Stein &Reddy, 2005). However, specific conditions, such as post-myocardial infarction, have been evidenced to increase these measures and are subsequently associated with an increased mortality (Stein &Reddy, 2005). Consequently, interpretations of non-linear indices must be made with caution and considering relevant reference values.

3.3.5 Metabolic Function

Long-term glycaemic control in children with T1D is typically evaluated by assessing blood levels of glycated haemoglobin (HbA1c), a vital and valid tool for clinicians in assessing glycaemic control over a period of six weeks (Consensus Committee of HbA1c Standardardisation, 2007; Nathan et al., 2008). Additionally, this tool is valuable for providing an insight to an individual's long-term risk of developing CVD (Cavero-Redondo, Peleteiro, Álvarez-Bueno, Rodriguez-Artalejo, & Martínez-Vizcaíno, 2017). However, a limitation of HbA1c is that it is an average over a period of time and does not reflect potentially significant short-term fluctuations or extremes in blood glucose levels. Therefore, HbA1c may falsely suggest good glycaemic control. More temporally accurate but costly measures, such as continuous glucose monitoring (CGM) or interstitial fluid monitoring (flash monitoring), can give more insight and greater resolution with regard to these fluctuations (Evans, 2016) but these methods were unavailable to be used as part of these studies.

Lipoprotein metabolism is typically assessed by obtaining plasma lipid and lipoprotein levels to determine the lipid profile, including total cholesterol (total-c), low density lipoprotein (LDL), high density lipoprotein (HDL) and LDL:HDL (Arsenault, et al., 2011). The lipid profile is most commonly assessed using a fasted blood sample in order to obtain the pre-prandial lipoprotein levels (Langsted, Freiberg, & Nordestgaard, 2008). However, this is not always possible in an outpatient clinic setting and research has demonstrated that non-fasted samples are reliable and accurate for lipid parameters (Langsted, et al., 2008; Nordestgaard, 2017). Therefore, non-fasting lipid measures were included in Chapters 5 and 7, with age-related changes considered as a covariate (Guy et al., 2009). Dyslipidaemia has been demonstrated to be a key factor in the long-term risk of developing CVD (Miller, 2009), in particular elevated levels of LDL, and total-c. Indeed, the lipid profile is considered a useful and easily obtainable tool for assessing metabolic control. The latest blood test results were accessed by the primary researcher with permission from the clinical lead in each research site (Chapters 5 and 7), with the collected data anonymised once recorded. The lipid profile parameters collected and recorded were total-c, LDL, and HDL.

3.3.6 Aerobic Capacity

Cardiorespiratory fitness (CRF) has been closely linked to the risk of CVD, with an increased fitness associated with a lower incidence of CVD and, indeed, improved survival of CVD (Al-Mallah, Sakr, & Al-Qunaibet, 2018). Thus, aerobic capacity as a measure of CRF was included to assess the risk of CVD in adults and how fitness interacts with physical activity and objective measures of CVD risk. The gold standard to obtain aerobic capacity ($\dot{V}O_2$) as a measure of cardiorespiratory fitness is to assess a participant while completing whole-body exercise, such as on a treadmill (American Thoracic Society, 2003). However, to ensure consistency across studies and the given age range, the use of a lower body exercise was chosen. A maximal effort is the preferred method of representing CRF in all populations (Åstrand, 1952; Robinson, 1938), however 20-30% of children do not reach a plateau in $\dot{V}O_2$ (Barker, Williams, Jones, & Armstrong, 2011), subsequently, in-validating the criteria used to determine a maximal effort in adults (Armstrong, Welsman, & Winsley, 1996). Therefore, whilst a maximal effort may have been achieved, cardiorespiratory fitness in Chapter 6 was

represented as a peak effort ($\dot{V}O_{2peak}$), obtained for both children and adults to ensure consistency between groups.

The assessment of $\dot{V}O_{2peak}$ was conducted with the use of an electronically braked cycle ergometer (Lode Excalibur sport, Groningen, Netherlands), a stationary metabolic cart (Vyntus CPX gas analyser, Carefusion-Jaeger, Höchberg, Germany), a reusable silicon face mask (7450 V2 Series Reusable Mask with Carefusion Mask Adapter and headgear, Hans Rudolph inc, Kansas, United States) and SentrySuite software (Vyaire Medical Inc, Chineham, UK). The Lode Excalibur Sport has been employed previously to assess $\dot{V}O_{2peak}$ in this manner with adults and children (Church et al., 2008; Earnest, Blair, & Church, 2010), and has shown acceptable reliability (Earnest, Wharton, Church, & Lucia, 2005). The Vyntus CPX is a well-validated device, commonly used in research to assess $\dot{V}O_2$ (De Jeu, Schot, Groepenhoff, & Ninaber, 2018; Groepenhoff, de Jeu, & Schot, 2017). However, low reliability and reproducibility for volume of inspired and expired air in breath-by-breath measurements using the Vyntus CPX has been noted, with a relatively high standard error of measurement (SEM) of greater than 19 $ml \cdot min^{-1}$ and intra class coefficients of 0.70-0.80 (Kantaras, 2018). Therefore, to minimise error and moderate any issues of reliability, prior to each test an automated gas calibration using gases of known concentration, then an automatic turbine volume calibration for each turbine were performed. Any differences in gas transit or volume offset were subsequently accounted for allowing for accurate gas and volume analysis for each test performed.

3.3.6.1 Incremental ramp test and measurement of gas exchange parameters

An incremental ramp test to voluntary exhaustion was employed to determine $\dot{V}O_{2peak}$, a test that was developed and demonstrated to be valid by Whipp and colleagues (1981). Additionally, gas exchange variables were collected for each incremental test, measured as inspired and expired air obtained on a breath-by-breath basis, utilising the stationary metabolic cart and sterilised reusable silicon face mask, with a low dead-space, and a calibrated turbine. Prior to the beginning of the warm-up, the handlebar height and seat height were adjusted for each participant, then the participant was allowed a two-to-three minute familiarisation period. A warm-up was then performed for three minutes at 10 W, followed by the ramp test increasing by 30 $W \cdot min^{-1}$ for

adults and those > 13 years, with 15 $W \cdot min^{-1}$ used for those < 13 years (Whipp, et al., 1981). At all times during the familiarisation, warm-up and test, the participant was asked to remain seated and to maintain a cadence of 50-70 rpm, with the test terminated when the participant could not maintain a pedalling rate of 50 rpm. Upon test cessation, the participant completed at least a five-minute cool down on the cycle ergometer, followed by a 10-minute monitoring period to ensure all participants were safe to leave. For the duration of the testing period, the participant was monitored using a HR monitor (Suunto Ambit 3 multi-sport watch, Suunto Oy, Vantaa, Finland and Suunto move sense heart rate belt, Suunto Oy, Vantaa, Finland), and a wrist worn pulse oximeter (SpO_2; Nonin WristOx2 3150, Nonin Medical Inc, Minnesota, USA) to monitor oxygen saturation. The safety termination criteria for the test were set as the participant showing irregular breathing, changes in pallor or signs of distress, an oxygen saturation ($Sp0_2$) ≤ 95% in the healthy population (American Thoracic Society, 2003), or the participant choosing to terminate the test.

3.3.6.2 Determination of peak aerobic capacity and gas exchange threshold

$\dot{V}O_{2peak}$ ($l \cdot min^{-1}$) was identified as the highest 15s rolling average of $\dot{V}O_2$ from the 5s averaged data. The gas exchange threshold (GET) was determined by three common methods: the Ventilatory Equivalent Method (VEQ Method), Excess CO_2 method ($ExCO_2$), and the V-slope method, the results of which were averaged (Gaskill et al., 2001). The VEQ was determined as the point of the first rise in the ventilatory equivalent of O_2 (VE/O_2) with no simultaneous rise in the ventilatory equivalent in CO_2 (VE/CO2; Gaskill, et al., 2001; Reinhard, Muller, & Schmulling, 1979). The $ExCO_2$ was determined as the point at which CO_2 begins to increase excessively from a steady state or ($\dot{V}CO_2/\dot{V}O_2$ - $\dot{V}CO_2$). The V-slope method used the point at which carbon dioxide production ($\dot{V}CO_2$) increased disproportionately to $\dot{V}O_2$ (Beaver, Wasserman, & Whipp, 1986). For these methods, the first 60 seconds of the ramp, and all data following the respiratory compensation point were excluded. This combined method of determining GET has been found to be a valid and reliable method in healthy individuals of varying fitness (Gaskill, et al., 2001). All $\dot{V}O_{2peak}$ and GET calculations were completed by the primary researcher to maintain consistency and reduce error.

3.3.6.3 Relative and allometric scaling for body mass

Absolute $\dot{V}O_{2peak}$ is influenced by numerous factors, such as body size, limiting inter-participant comparisons and highlighting the need to account for such differences. Therefore, to improve comparisons between individuals, two techniques to account for body mass were used. Specifically, the effect of body mass on $\dot{V}O_{2peak}$ was accounted for using ratio ($ml \cdot kg^{-1} \cdot min^{-1}$) and allometric scaling ($ml \cdot kg^{-b} \cdot min^{-1}$), calculated according to Equations 6 and 7. Ratio scaling is a commonly used method to express $\dot{V}O_{2peak}$ in relation to total body mass (Åstrand, 1952). However, such a method has been proposed to penalise more mature and heavier individuals, bringing the applicability of this method into question (Armstong &McNarry, 2016). A possible means of improving ratio scaling and to limit the penalisation of certain individuals, is to scale according to fat free mass, however, this measure was not obtained making this infeasible. Allometric scaling is a method which removes the linear assumption between $\dot{V}O_{2peak}$ and body mass, by scaling body mass to a sample-specific logarithmic exponent and has been deemed to give a more robust and sound representation of relative efficiency of oxygen transport (Nevill, Bate, & Holder, 2005). Indeed, studies comparing ratio and allometric scaling methods report that allometric scaling provides a more appropriate estimate of relative $\dot{V}O_{2max}$ in paediatric populations (Chamari et al., 2005), and anaerobic power indices according to sex (Hazir &Kosar, 2007). Consequently, allometric scaling has been previously employed in research to enable more appropriate comparisons between populations characterised by divergent body sizes (Cunha et al., 2016; McNarry, Mackintosh, & Stoedefalke, 2014).

Equation 6.

$$Ratio\ Scaled\ \dot{V}O_{2peak} = \frac{\dot{V}O_{2peak}\ (L \cdot min^{-1}) \times 1000}{body\ mass}$$

Equation 7.

$$Allometric\ Scaled\ \dot{V}O_{2peak} = \frac{\dot{V}O_{2peak}\ (L \cdot min^{-1}) \times 1000}{bodymass^{b}}$$

$$where\ b = the\ scaling\ coefficient\ derived\ from\ log - linear\ regression$$

3.3.7 Physical Activity and Sedentary Time

A measure of accelerometer-based physical activity and sedentary time was obtained for all participants, across all studies. The gold standard for evaluating physical activity is doubly labelled water (DLW), which assesses EE resulting from bodily movement (Caspersen, et al., 1985). However, DLW is costly, impractical outside of a laboratory setting and has ethical considerations, especially when employed in a paediatric population (Plasqui &Westerterp, 2007). Therefore, tri-axial wrist-worn accelerometery, shown to give good precision in comparison to DLW (White, Westgate, Wareham, & Brage, 2016), was chosen to objectively measure physical activity and sedentary time for all studies, on account of the feasibility and availability of equipment.

3.3.7.1 Hip-worn accelerometry

A hip-located tri-axal accelerometer (ActiGraph GT9X, ActiGraph, Pensacola, Florida, USA), worn on the right hip with an elasticated strap, was employed for Chapter 4 to obtain a 7-day recording (Chapter 4). The hip-worn accelerometer has been deemed reliable to obtain a representative measure of movement behaviours in children when validated against another reliable and well-validated accelerometer (Hänggi, Phillips, & Rowlands, 2013). Participants were provided with the accelerometer along with a paper-based wear-time diary to record wake up time, sleep time, sleep quality, removal times and reason for removal. The accelerometer was initialised utilising ActiLife v6.13.4 software (ActiLife, ActiGraph, Pensacola, Florida, USA) at 100 Hz, with details of height, mass, handedness, position worn, and the start time of recording set as midnight the day after the testing session. Accelerometers were collected at the end of each recording and the raw data was then downloaded utilising the ActiLife 6 software in 1s epochs. These files were then processed to 15s epochs using the ActiLife package, necessary for the use of Evenson physical activity cut points (Evenson, et al., 2008) to be applied, deemed to give the most reliable and valid representation of physical activities in this population (Evenson, et al., 2008). Specifically, these cut-points have been validated by Trost et al. (2011) by comparing against four other sets of paediatric thresholds, with Evenson cut points deemed the most suitable in children to classify physical activity across the whole intensity spectrum. Non wear-time criteria for hip-worn accelerometry was

defined as > 20 minutes of consecutive zeros, while device wear-time was set as ≥ 10 hours per day on a minimum of any three days (Fairclough, et al., 2016; Trost, et al., 2000).

3.3.7.2 Wrist-located accelerometry

A wrist worn tri-axial accelerometer (GENEActiv, Activinsights Ltd, Cambridgeshire, UK) was utilised to obtain a seven day (Chapter 5) and 28 day (Chapters 6 and 7), 24 hours per day, recording of physical activity at a sampling frequency of 20 Hz. The wrist worn GENEActiv accelerometer has been well-validated and demonstrated as reliable when compared to other validated accelerometers (Esliger et al., 2011). Additionally, these monitors have been validated for use in both adult and paediatric populations (Phillips, et al., 2013; Powell, Carson, Dowd, & Donnelly, 2017). The accelerometer was given to each participant at the end of their testing session, along with a wear time diary to record wake up time, sleep time, sleep quality, removal times and reason for removal. The accelerometers were initialised with the use of the GENEActiv PC Software version 3.2 (GENEActiv, Activinsights Ltd, Cambridgeshire, UK), with details of recording frequency, height, mass, handedness, position worn, and start time of recording. The accelerometers were collected following the monitoring period and the raw acceleration data was then downloaded in .bin format using the GENEActiv PC Software. These files were processed with the use of R (http://cran.r-project.org) and the GGIR package (version 1.9-1) to convert triaxial acceleration to omnidirectional acceleration using the Euclidian Norm Minus One (ENMO) method (Hurter et al., 2018). The omnidirectional data was then reduced to 60s epochs and expressed in milligravity-based acceleration units (*mg*). Raw acceleration cut-points to specify intensity of activity and time spent within each intensity were then applied. Acceleration cut-points for activity intensity were identified utilising device-specific predictive equations developed for children and adults (Equations 8 and 9; Hildebrand, van Hees, Hansen, & Ekelund, 2014). Specifically, the regression equations for the prediction of intensity (METs) from wrist-worn GENEActivs were rearranged and solved for each intensity using an average resting $\dot{V}O_2$ for 1 MET, 3.5 and 6.0 $ml \cdot kg^{-1} \cdot min^{-1}$ for adults (Jetté, Sidney, & Blümchen, 1990) and children (Butte, et al., 2018), respectively. The equations were solved for 1.5, 3, and 6 METs for adults (Mendes Mde, et al., 2018; Nelson et al.,

2007; Office of Disease Prevention and Health Promotion, 2008) and 2, 4 and 7 METs for children (Harrell, et al., 2005; Saint-Maurice, et al., 2016), representing the thresholds of light, moderate and vigorous activities, respectively.

Equation 8.

$$\dot{V}O_2\ (ml \cdot kg^{-1} \cdot min^{-1}) = 0.0323 \cdot\ mg + 7.49g$$
$$= ((\mathcal{X}\ METs\ \times\ 3.5\ ml \cdot kg^{-1} \cdot min^{-1}) - 7.49)/0.0323$$

Equation 9.

$$\dot{V}O_2\ (ml \cdot kg^{-1} \cdot min^{-1}) = 0.0357 \cdot\ mg + 11.16g$$
$$= ((\mathcal{X}\ METs\ \times\ 6.0\ ml \cdot kg^{-1} \cdot min^{-1}) - 11.16)/0.0357$$

Minimum device wear time was set as > 16 hours for a minimum of three days per week, including two weekdays and one weekend day. Non-wear time was defined as ≥ 60 minutes of consecutive zeros with a tolerance of two minutes at 0 to < 50 *mg* (Colley, Connor Gorber, & Tremblay, 2010; Van Hees, Gorzelniak, Dean León, et al., 2013). Thresholds for tolerance of activity bouts was set as 10 minutes of consecutive 5s epochs, where 80% was ≥ 100 *mg*, while sedentary bouts were set as ≥ 30 minutes of consecutive 5s epochs of ≤ 50 mg (Van Hees, Gorzelniak, Dean León, et al., 2013). Sleep was classified based on the Hees et al. (2015) nocturnal sleep algorithm as no arm angle change > 5^{o} for ≥ 5 minutes.

3.3.7.3 Intensity gradient and average acceleration

In addition to traditional physical activity metrics quantifying the volume of time spent in each physical activity intensity, less restricted metrics of average acceleration and intensity gradient were included to provide further insight to the pattern of physical activity accrual. Raw acceleration was averaged over a 24-hour period to obtain the average acceleration, a measure of the overall volume of movement per day (Rowlands, et al., 2018). Moreover, intensity gradient was also derived as a metric of physical activity intensity distribution averaged per day. Intensity distribution was determined by dividing intensity into successive 25 *mg* segments, from 0 – 4,000 *mg*, then identifying the time spent in each segment to produce a negative curvilinear relationship. This relationship was then transformed to a linear relationship by taking the natural log of each variable, with the mid-point of each successive 25 *mg* bin (i.e.

12.5 *mg*) plotted against the time per segment, with a line of best fit producing an always negative linear association. Gradient, intercept and r^2 values were then obtained from the linear model, with the gradient and intercept a representation of activity distribution and r^2 an indication of the goodness of fit (Rowlands, et al., 2018). A higher intercept and a more negative gradient were associated with a steeper line, indicating less time accumulated at mid-to-high physical activity intensities. Conversely, a lower intercept and a less negative gradient, shown by a more shallow line was related to achieving a greater range of intensities across the intensity spectrum (Rowlands, et al., 2018).

3.4 Statistical Analysis

The SPSS software package (IBM SPSS Statistics for Macintosh, Version 22.0, Plymouth, UK) was used to perform standard statistical analyses for all experimental Chapters. Significance for all analyses was set as $p < 0.05$, with data expressed as mean ± SD unless stated otherwise. Additionally, data were tested for normality using Shapiro-Wilks to determine the suitability of statistical methods. Differences between those excluded and included, in addition to between groups, were assessed with the use of independent t-tests (Chapter 5), a one-way ANOVA, a multivariate ANOVA with Bonferroni corrections (Chapters 4, 6, 7), or a repeated measures ANOVA with Bonferroni corrections (Chapter 6), with the t or f values, and the corresponding p-values, reported.

3.4.1 Linear Mixed Models

Linear mixed modelling (LMM) was utilised to explore associations and differences, and were chosen over more conventional linear models as this form of modelling can take into account variation due to differing environments produced by numerous factors (Jiang, 2007), such as sex, age and disease status. Moreover, LMMs have been widely used in physical activity research, in particular to explore the relationships between physical activity metrics and health outcomes (Buchan, et al., 2019; Fairclough, et al., 2019). Initial unadjusted models were employed, with further models adjusted for potential covariates of age, sex, BMI, maturation and group (Chapters 5 and 6). Beta values, 95% confidence intervals and p values were retained

from each iteration to indicate association, direction of effect, fit of the model and significance of each model.

3.4.2 Reliability Analysis

Reliability analyses were completed in Chapter 6 to explore if the consistency and reliability of physical activity metrics varied with increasing measurement duration, with analysis based on previous studies exploring variation in physical activity metrics (Barreira et al., 2016; Barreira, et al., 2015; Jaeschke, Steinbrecher, Jeran, Konigorski, & Pischon, 2018), in addition to studies exploring repeated measurements in an exercise context (Atkinson &Nevill, 1998; Runacres, Bezodis, Mackintosh, & McNarry, 2019). The coefficient of variation (CV) was included to investigate the absolute consistency and reliability of each physical activity metric over increasing monitoring durations, with the CV of each physical activity metric, for increasing monitoring durations, calculated according to equation 10 (Eliasziw, Young, Woodbury, & Fryday-Field, 1994). Intraclass coefficient (ICC) analysis was employed to determined relative reliability of metrics between monitoring durations. The ICCs and the subsequent 95% confidence intervals (CI) were produced employing SPSS software package to obtain the mean squared values from an ANOVA of repeated measures, with indices for CIs back-transformed from the log-transformed dataset (Eliasziw, et al., 1994; Runacres, et al., 2019). Currently there is limited consensus as to the thresholds for identifying reliability of metrics for three repeated measures, subsequently based on previous repeated measure reliability studies, thresholds considered suitable for two repeated measures were employed (Runacres, et al., 2019; Simperingham, Cronin, Pearson, & Ross, 2019). Therefore, according to the reliability thresholds proposed by Hopkins et al. (2009), physical activity metrics were deemed highly reliable if the CV $\leq$ 10% and the ICC $\geq$ 0.75, with moderate reliability identified when either the CV > 10% and the ICC > 0.75 or the CV < 10% and the ICC < 0.75, and as unacceptably reliable if the CV $\geq$ 10% and the ICC $\leq$ 0.75 (Hopkins, et al., 2009; Runacres, et al., 2019). These reliability thresholds were subsequently applied to determine if physical activity metrics fluctuated between weeks over the 28-day monitoring period, giving an indication of behavioural variation. Specifically, if physical activity metrics were found to be highly reliable, metrics showed less variation, however, if reliability was deemed moderate or unacceptable, more

significant variation was likely present in physical activity behaviours. In addition to the CV and ICC, calculations of the standard error of the mean (SEM) and the smallest worthwhile change (SWC) were included to demonstrate changes in the error, and allow for the sensitivity of metrics to reveal whether differing results were a consequence of error or behavioural variation (Hopkins, et al., 2009). Specifically, the SEM and SWC were calculated according to equation 11 and SWC = 0.2*metric SD for each group (Atkinson &Nevill, 1998). Subsequently, if SEM ≤ SWC the resulting observation was most likely due to behavioural variation between participants, if SEM = SWC the result observed may equally be a result of variation in behaviour or error association with the measurement, but if SEM ≥ SWC the result observed was possibly a consequence of error associated with the measurement (Hopkins, et al., 2009).

Equation 10.

$$Coefficient\ of\ variation\ (CV) = (\frac{\log_{10} group\ \sigma}{\log_{10} group\ \overline{x}})\ \times 100$$

$$where\ \sigma = Standard\ deviation\ and\ \overline{x} = mean$$

Equation 11.

$$Standard\ error\ of\ measurement\ (SEM) = \sigma\ of\ each\ metric\ repetition\ \times (1 - metric\ ICC)$$

$$where\ \sigma = Standard\ deviation$$

3.4.3 Compositional Analysis

Compositional analysis of physical activity, sedentary time and sleep data was performed in Chapters 4 and 7, with use of R (http://cran.r-project.org) and the compositions package (Version 1.40-2; Chastin, et al., 2015). Compositional analysis has been postulated to provide greater insight as to the influence of the combined effects of all movement behaviours in a day on health outcomes, with increasing utilisation in physical activity research (Carson, et al., 2016; Chastin, et al., 2015; Stefelová, et al., 2018). Consequently, this technique was included to gain a greater understanding of the influences of physical activity, sedentary time and sleep on cardiovascular health.

Compositional analysis was originally proposed by Aitchison (1982) and is based on the principle that any bounded and finite data can be expressed as ratio parts of a whole, for example movement behaviours (sedentary time, LPA, MVPA, sleep) as parts of a 24-hour day. Compositional data is expressed as log-ratio co-ordinates, thereby transforming it from constrained, bounded data to allow for the application of traditional multivariate statistics (Mateu-Figueras, Pawlowsky-Glahn, & Egozcue, 2011). The most prominent log-ratio transformation approaches to create co-ordinate systems in compositional analysis are: isometric log-ratio (ILR), additive log-ratio (ALR) and centred log-ratio (CLR), each using a different system to transform constrained variables (Dumuid, et al., 2018; Pawlowsky-Glahn, Egozcue, & Tolosana-Delgado, 2015). For physical activity analyses, ILR has been identified as the most appropriate approach, as ALR does not allow for singular movement behaviours to be quantified, and the use of CLR does not support the assumption of independence between individual movement behaviours (Dumuid, et al., 2018). The co-ordinates produced by ILR convert the simplex composition of movement behaviours to the real space, allowing for the creation of an isometric map of the composition in real space (Dumuid, et al., 2018). Subsequently, analysis using a sequential technique was employed, where each component was partitioned from the remaining parts sequentially, using these ILR co-ordinates (Dumuid, et al., 2018; Hron, Filzmoser, & Thompson, 2012).

The first step of compositional analysis in Chapters 4 and 7 was the calculation of the compositional geometric mean, percentage time of the day and the pair-wise log variance for each movement behaviour, with a log contrast determined between the geometric means of the entire sample and each of the health variable subgroups (Chastin, et al., 2015). Specifically, geometric means were achieved with time spent in sedentary time, LPA, MVPA and sleep were summed and transformed to ILR of time equalling one, as shown in Equation 12 (Chastin, et al., 2015). Pair-wise log variance was displayed in a variation matrix to infer co-dependency between behaviours, with log variance closer to zero indicative of a greater co-dependency. Compositional linear regression models of ILR co-ordinates were then produced for each health variable (equation 13), adjusted for age, sex (Chapters 6 and 7) and disease status (Chapter 7), computed using the transformed ratios. The transformed behaviours were entered in a sequential fashion to assess the collective influence on relative

distribution in relation to each health variable (Equations 14). The produced p and r^2 values indicated the significance of any associations between activity intensities and health variables, and how the variance was influenced by the composition. These models also examined the relationship of time in each activity intensity with each health variable compared to the volume of time in other activity intensities. The first p and r^2 values for each of the rotated models indicated the significance and fit of each model.

Predicted change models were produced to examine the effect of displacing time from one intensity to another (Equation 15). This was completed by back transforming ILR intensity co-coordinates to represent real time plotted against percentage change in health variable. A model was produced for each health variable against the individual sample means, displayed as a change matrices for each health variable. Previous studies employing predictive analysis of time substitution from one behaviour to another typically use 10-minute blocks for time reallocation as this was the lowest volume of change recognised to create a beneficial effect for health (Chastin, et al., 2015). However, 20 minutes was employed, in Chapters 4 and 7, as the substitution of this period of time between behaviours would still be meaningful for health, but would also increase time in MVPA to meet or exceed the UK physical activity guidelines for the samples investigated.

Equation 12. (Isometric log ratio (ILR) approach)

$$ilr(x) = \left[\sqrt{\frac{D-1}{D}}In\left(\frac{x_1}{\sqrt[D-1]{\prod_{K=3}^{D} x_k}}\right), \sqrt{\frac{D-2}{D-1}}In\left(\frac{x_2}{\sqrt[D-2]{\prod_{k=3}^{D} x_k}}\right), \sqrt{\frac{D-j}{D-j+1}}In\left(\frac{x_j}{\sqrt[D-j]{\prod_{k=j+1}^{D} x_k}}\right), \frac{1}{\sqrt{2}}In\left(\frac{x_{D-1}}{x_D}\right)\right]$$

Equation 13. (ILR multiple linear regression model for n compositional observations)

$$y_i = \beta_0 + \sum_{j=1}^{D-1} \beta_j z_{ij} + \varepsilon_i$$

$$where\ z_{ij} = \sqrt{\frac{D-j}{D-j+1}}In\left(\frac{x_{ij}}{\sqrt[D-j]{\prod_{k=j+1}^{D} x_{ik}}}\right) for\ j = 1,2,\ldots\ldots, D-1$$

Equations 14. (4 part composition)

$$ilr_1 = \sqrt{\frac{3}{4}} In\left(\frac{x_1}{\sqrt[3]{(x_2 \cdot x_3 \cdot x_4)}} \cdot \frac{1+r}{1-s}\right)$$

$$ilr_2 = \sqrt{\frac{2}{3}} In\left(\frac{x_2}{\sqrt{(x_3 \cdot x_4)}} \cdot \frac{1-s}{1-s}\right)$$

$$ilr_3 = \sqrt{\frac{1}{2}} In\left(\frac{x_3}{x_4} \cdot \frac{1-s}{1-s}\right)$$

Equation 15. (Estimated change)

$$\Delta\hat{y} = \hat{\beta}_1 \cdot \sqrt{\frac{D-1}{D}} \cdot In\left(\frac{1+r}{1-s}\right)$$

$$where\ -1 < r < \tfrac{1-x_1}{x_1}\ and\ s = r \cdot \tfrac{x_1}{1-x_1}$$

Chapter 4

Investigating the influence of sex on the physical activity composition of healthy children and its relationship with arterial stiffness

Chapter 4 (Study 1): Investigating the influence of sex on the physical activity composition of healthy children and its relationship with arterial stiffness

4.1 Introduction

Paediatric health research has largely focused on the effects of physical activity and sedentary time in isolation, often covarying for the remaining behaviours (Carson &Janssen, 2011; Colley, Garriguet, Janssen, & Wong, 2013; Warburton, Nicol, & Bredin, 2006). However, the inherently co-dependent nature of movement behaviours violates the assumptions of independence in most traditional statistical methods (Carson, et al., 2016; Chastin, et al., 2015). However, the use of compositional analysis, which has the ability to account for co-dependency between daily movements, can facilitate a greater understanding by exploring associations relative to the remaining behaviours in a given time period, such as a day (Chastin, et al., 2015). Moreover, compositional analysis can identify potential interventional targets and reveal potentially 'optimal' compositions for health (Chastin, et al., 2015).

The individual effects of physical activity and sedentary time on cardiovascular risk factors are well researched in youth, with suggestions that physical activity and sedentary time act independently and in an opposing manner on cardiovascular health (Froberg &Andersen, 2005; Kohl, 2001; Vasankari, et al., 2017). In particular, arterial stiffness, a pre-clinical risk marker for cardiovascular disease (CVD; Cheung, 2010; Savant, Furth, & Meyers, 2014), is positively influenced by physical activity (Edwards, et al., 2012; Sakuragi, et al., 2009), but negatively by sedentary time (Haapala, et al., 2016; Nettlefold, et al., 2019). Arterial stiffness progresses naturally with age, but prolonged periods of sedentary time has been found to result in a premature progression and subsequent increases in the risk of developing CVD (Cote et al., 2015; Nettlefold, et al., 2019; Veijalainen, et al., 2016). Conversely, a beneficial relationship between physical activity and arterial health is evident, with active children demonstrating less stiffening with age compared to more inactive and sedentary counterparts (Edwards, et al., 2012; Haapala, et al., 2016; Ried-Larsen et al., 2014; Veijalainen, et al., 2016).

Differences in physical activity behaviours between sexes have been observed, resulting in differing compositions of movement behaviours according to sex (Gordon-Larsen, McMurray, & Popkin, 2000; Olds et al., 2009). Specifically, prepubescent girls and boys both engage in similar levels of physical activity but pubertal girls typically demonstrate greater volumes of light physical activity (LPA) and less moderate-to-vigorous physical activity (MVPA) than their male counterparts (Dumith, Gigante, Domingues, & Kohl, 2011). These differences in movement behaviours and the rate of decline in the volume and intensity of physical activity according to sex may subsequently influence arterial stiffening and possibly increase the risk of premature CVD. Indeed, in young children girls have less compliant and stiffer arteries than boys, although this difference may be ameliorated during puberty (Ahimastos, Formosa, Dart, & Kingwell, 2003; Rossi, Francès, Kingwell, & Ahimastos, 2011; Stoner, Faulkner, Westrupp, & Lambrick, 2015).

Whilst the effects of physical activity and sedentary time on markers of arterial health have been explored in isolation, few studies have utilised compositional analysis to investigate the relative influence of movement behaviours within a day. Carson et al. (2016) investigated the effects on cardiometabolic risk factors, reporting an increased MVPA, relative to remaining behaviours, to be associated with a decreased body mass index (BMI) and waist circumference in children. However, equivocal findings have been reported regarding the influence of sedentary time, LPA and sleep on cardiometabolic risk (Stefelová, et al., 2018). These equivocal findings may be related to inter-study differences in the measures of health considered, the study population characteristics and/or to the accelerometer data processing decisions. Further work is therefore warranted to address these equivocal findings.

The primary aim of the present study was therefore to explore the relative effects of daily movement behaviours on markers of arterial stiffness in children and adolescents. Secondary aims were to ascertain whether differences in physical activity composition, according to sex, influenced these arterial markers and the influence of reallocating time between behaviours on health outcomes.

4.2 Methods

In total, 129 children and adolescents (12.4 ± 1.6 years; 56 boys), recruited from schools in South Wales, participated in this cross-sectional study. This study was approved by the institutional research ethics committee, with all procedures completed in accordance with the Declaration of Helsinki. Prior to data collection, written informed consent and assent were obtained from parents/guardians and participants, respectively. Exclusion criteria included any known hypertensive, metabolic or cardiovascular condition that could influence assessment of vascular health.

4.2.1 Anthropometrics

Stature, sitting stature and body mass were measured to the nearest 0.01 m, 0.01 m and 0.1 kg using a portable standing stadiometer (Seca 213, Seca, Chino, CA, USA), sitting stadiometer (Holtain Ltd, Crymych, Pembrokeshire, Wales) and electronic scales (Seca 803, Seca, Chino, CA, USA), respectively. Subsequently, BMI was calculated. Maturity was estimated using sex-specific maturity offset equations to predict time from peak height velocity (PHV; Mirwald, et al., 2002). Participants were classified into three stages of puberty: pre-pubertal if more than one year pre-PHV, pubertal if less than one year pre- or post-PHV, and post-pubertal if more than one year post-PHV (Mirwald, et al., 2002).

4.2.2 Pulse Wave Analysis and Pulse Wave Velocity Procedure

Arterial stiffness was non-invasively assessed using an osillometric device (Vicorder, Skidmore Medical, Bristol, UK) and accompanying blood pressure cuffs (D.E.Hokanson Inc, Bellevue, WA, USA). Measurements were completed with the participant in the supine position with the torso elevated to 30^{o}, in a quiet environment and after a five-minute resting period to ensure stable haemodynamics. Indirect central arterial stiffness was estimated with a cuff placed over the brachial artery on the upper left arm, with blood pressure taken a minimum of two times via an inbuilt automated function. Pulse pressure (PP) and augmentation index (AIx) were derived from the PP waveform recording, with AIx derived as augmented pressure expressed as a percentage of PP (Wilkinson, et al., 2000). Stiffness was assessed with a partial cuff placed over the carotid artery and a brachial cuff over the femoral artery. The sum of the distance between the sternal notch and umbilicus and the umbilicus to the middle

of the femoral cuff was measured, with PWV, in $m \cdot sec^{-1}$, subsequently derived according to the time between carotid and femoral pulse waves. Each assessment was completed a minimum of three times to obtain at least two congruent measures within 5 mmHg, 5% or 0.5 $m \cdot sec^{-1}$ of each other.

4.2.3 Habitual Physical Activity Recording and Analysis

Participants were asked to wear an ActiGraph GT3X accelerometer (ActiGraph, Pensacola, Florida, USA), sampling at 100 Hz on the right hip, for seven-consecutive days. The ActiGraph GT3X has been shown to be valid for the assessment of habitual sedentary time and physical activity in children (Hänggi, et al., 2013). Furthermore, participants were asked to complete wear-time and sleep diaries, to record monitor removal and the duration and quality of sleep. Accelerometry data was extracted using ActiLife v6.13.4 software (ActiGraph, Pensacola, Florida, USA) and processed to 15s epochs. Participants were required to meet a wear-time of ≥ 10 hours on any three days in order to be included in the analyses (Fairclough, et al., 2016). Evenson et al. (2008) physical activity cut-points, identified as the most appropriate cut-points to give a reliable representation of light, moderate and vigorous intensity physical activities were used.

4.2.4 Statistical Analysis

Initial statistical analyses were performed using IBM SPSS software package (IBM SPSS Statistics for Macintosh, Version 22.0, IBM, Portsmouth, UK), with significance set as $p < 0.05$ and all data expressed as mean ± standard deviation (SD), unless stated otherwise. A one-way ANOVA was used to establish any significant differences in arterial stiffness measures or movement behaviours according to sex.

The Compositions package (Version 1.40-2; Chastin, et al., 2015), and its dependencies, in R (http://cran.r-project.org) were used to conduct compositional analysis. For all participants, time in each movement behaviour (i.e. sedentary time, LPA, MVPA and sleep) was normalised as a proportion of the total time in all behaviours, with the geometric means and the variation matrix then calculated for each behaviour and grouping (Chastin, et al., 2015). A log contrast between each movement behaviour, the geometric mean for the whole sample and the mean of each subgroup

was subsequently calculated. Next, the relative distribution of physical activity behaviours and the effects on arterial stiffness measures were examined by transforming to isometric log-ratios (ILR) of time, equalling a total of one, and producing sequential compositional linear regression models for each stiffness measure, covarying for sex and age. The initial coefficient and p-value for each sequential model was taken as the direction of effect and significance of the ILR analysis for each health outcome (Carson, et al., 2016). Predictive change models to examine the effect of displacing time from one behaviour to another (e.g. displacing 20 minutes of sedentary time to MVPA) on arterial stiffness measures were produced based on the initial compositions for sex. Specifically, each predictive model back-transformed the previous ILR behaviour co-ordinates to determine the effect based on the average composition for each grouping and expressed as the percentage change in the outcome parameter, around the group mean (Chastin, et al., 2015). The predicted percentage change in each measure was then compared against the percentage smallest worthwhile change (SWC%) to identify a meaningful and significant change. The SWC% was calculated for the group mean of each arterial measure, to represent the minimally clinically important difference (MCID; Wells et al., 2001b).

4.3 Results

The final sample consisted of 101 participants following the exclusion of 28 participants who failed to meet the wear-time criteria, with no significant differences between those included and excluded. Overall, boys were taller ($F_{(1, 98)} = 3.91$, $p \leq 0.05$), heavier ($F_{(1, 98)} = 5.41$, $p \leq 0.05$), less mature ($F_{(1, 98)} = 8.61$, $p \leq 0.01$), and had a lower AIx ($F_{(1, 98)} = 3.94$, $p \leq 0.05$), than their female counterparts (Table 4.1).

As a whole, participants spent waking hours in predominantly sedentary pursuits, with physical activity only accounting for 17.2% of this time (Table 4.2). Sleep and sedentary time, and sedentary time and LPA, demonstrated the smallest pair-wise log variances, suggesting higher levels of co-dependence. In contrast, MVPA showed the highest log-ratio variance with all other movement behaviours and therefore the least co-dependency (Table 4.3). Moreover, MVPA was found to explain 67% of variance, with LPA accounting for 26% and the remaining 7% explained by sedentary time and sleep (Table 4.3).

Table 4.1. Participant descriptives and arterial stiffness according to sex.

	Girls (n = 45)	Boys (n = 56)
Age (years)	12.1 ± 1.5	12.6 ± 1.7
Maturity offset	-0.30 ± 0.80*	-1.16 ± 1.76
Height (m)	1.52 ± 0.09*	1.58 ± 0.14
Mass (kg)	47.9 ± 11.0*	52.2 ± 6.415.3
BMI ($kg \cdot m^{-2}$)	20.5 ± 3.6	20.6 ± 4.0
PP (mmHg)	60 ± 8	60 ± 10
AIx (%)	11.9 ± 5.2*	10.4 ± 5.5
MAP (mmHg)	78 ± 7	76 ± 7
PWV ($m \cdot sec^{-1}$)	4.92 ± 0.55	4.97 ± 0.60

Data is presented as mean ± SD. Body mass index (BMI), pulse pressure (PP), augmentation index (AIx), mean arterial pressure (MAP), pulse wave velocity (PWV). * Significant differences according to sex.

Table 4.2. Actual mean, geometric mean and percentage of 24-hours for each movement behaviour and sleep for the whole sample.

	SED	LPA	MVPA	SLEEP
Mean ($min \cdot day^{-1}$)	510.9	192.9	30.4	470.9
Geometric Mean ($min \cdot day^{-1}$)	617.8	215.4	31.8	574.1
Percentage of 24 hours (%)	42.9	15.0	2.2	39.9

Sedentary time (SED), light physical activity (LPA), moderate-to-vigorous physical activity (MVPA).

Table 4.3. Pair-wise log-ratio variation matrix for the duration of sedentary time, LPA, MVPA, and sleep in $min \cdot day^{-1}$ for the whole sample.

	SED	LPA	MVPA	SLEEP
ST	-	-0.017	-0.054	0.014
LPA	-0.017	-	-0.122	-0.021
MVPA	-0.054	-0.122	-	-0.037
SLEEP	0.014	-0.021	-0.037	-

Sedentary time (SED), light physical activity (LPA), moderate-to-vigorous intensity physical activity (MVPA).

Comparison of geometric means by sex indicated that girls accrued a similar volume of sedentary time, a greater volume of LPA and less time in MVPA and sleep, relative to boys (Figure 4.1). Moreover, the overall movement behaviour composition for the whole sample, as demonstrated by the model p-value, was not significantly associated with any arterial measure (Table 4.5).

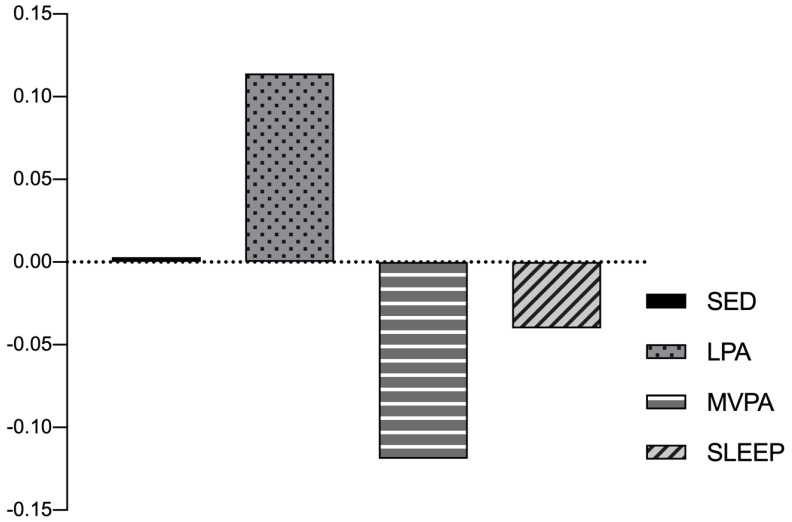


Figure 4.1.. Compositional geometric mean bar plots comparing the compositional means of girls against boys for sedentary time (SED), light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA), and sleep.

Table 4.4. Compositional model of movement behaviours, sedentary time, LPA, MVPA and sleep, for each measure of arterial health in the overall sample, adjusted for age, maturity and sex.

	Model p	Model R^2	Y_{SED}	p	Y_{LPA}	p	Y_{MVPA}	p	Y_{SLEEP}	p
PP	0.27	0.01	-1.52	0.41	1.78	0.12	0.04	0.96	-0.03	0.88
AIx	0.57	-0.01	0.00	0.99	-0.83	0.22	-0.07	0.87	0.90	0.45
PWV	0.31	0.01	-0.08	0.51	0.04	0.60	-0.02	0.76	0.05	0.67
BMI	0.26	0.02	0.83	0.27	-0.36	0.44	-0.06	0.87	-0.42	0.61

Sequential rotated ILR modelling for each arterial health measure, adjusted for age, maturity and sex. Sedentary time (SED), light physical activity (LPA), moderate-to-vigorous physical activity (MVPA), pulse pressure (PP), augmentation index (AIx), mean arterial pressure (MAP), pulse wave velocity (PWV) and body mass index (BMI). Regression coefficients relate to the change in log-ratio for a given behaviour, relative to other behaviours.

According to the ternary heat maps presented in Figure 4.2, the relative influences of MVPA and sedentary time indicate that a high MVPA and low sedentary time result in a more favourable aPWV in girls. In contrast, in boys, the relative influences of movement behaviours on aPWV is less clear but suggests moderate to low sedentary time (Figure 4.3 a, c and d) and moderate to high LPA and MVPA predict a more favourable aPWV.

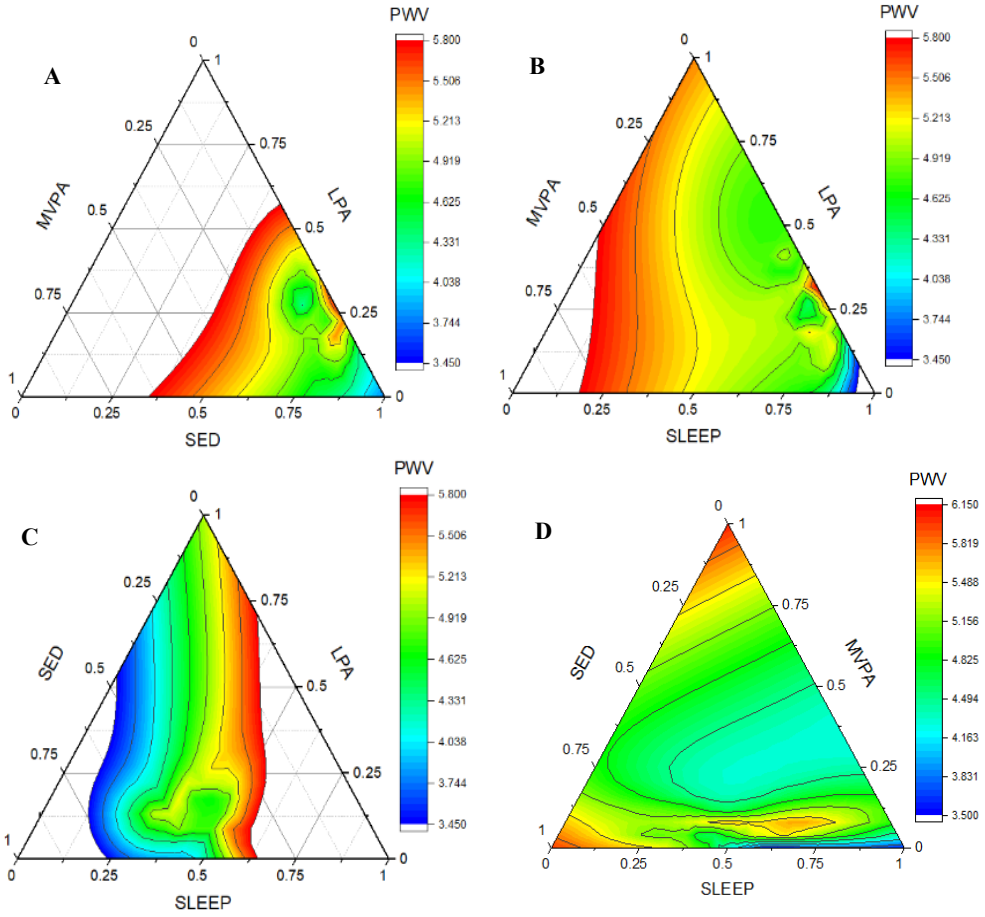


Figure 4.2. Heatmap ternary plots of aortic pulse wave velocity for different combinations of physical activity compositions in girls. Each ternary diagram focuses on one part of the four part composition (sedentary time (SED), light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA), and sleep), relative to the remaining behaviours.

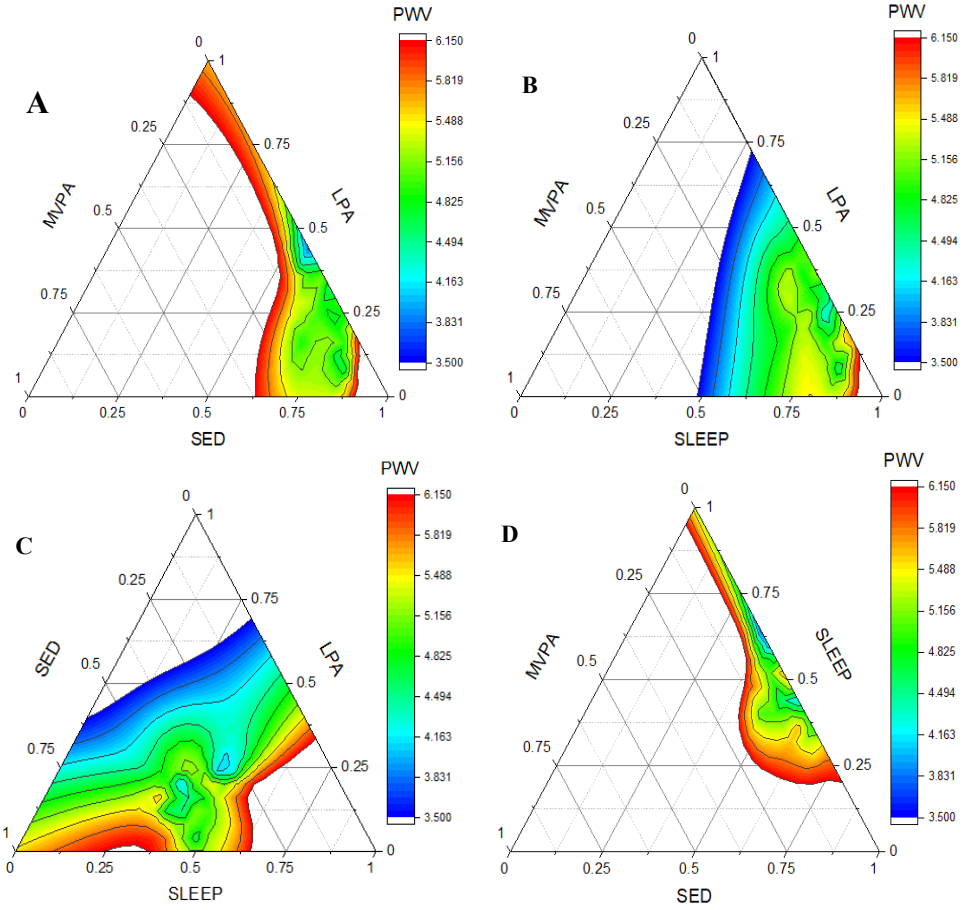


Figure 4.3. Heatmap ternary plots of aortic pulse wave velocity for the different combinations of movement behaviour compositions in boys. Each ternary diagram focuses on one part of the four part composition (sedentary time (SED), light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA), and sleep), relative to the remaining behaviours.

No significant percentage changes were present in any cardiovascular measures or BMI, with the reallocation of 20 minutes from one behaviour to another (Table 4.5). The non-significant predictive changes with reallocation of time were predominantly symmetrical, except for substituting time between sedentary time and MVPA in PP and BMI, irrespective of sex. While non-significant, the greatest increases in AIx and PWV were predicted with the reallocation of time from MVPA to sleep, and in AIx by substituting time in LPA to sleep. However, decreasing time from sleep to LPA resulted in a decreased AIx, irrespective of sex. Moreover, the reallocation of time in

LPA and MVPA to sedentary time resulted in an increased predicted BMI, whereas substituting sedentary time to LPA, resulted in a decreased predicted BMI, for both sexes.

Table 4.5. Effect of reallocating 20 minutes of time from behaviour in columns to behaviours in rows for boys and girls, presented as percentage change**.**

	Girls				Boys			
PP								
	SED	LPA	MVPA	Sleep	SED	LPA	MVPA	Sleep
SED	-	-0.30	0.10	-0.25	-	-0.33	0.05	-0.26
LPA	0.29	-	0.39	0.03	0.32	-	0.36	0.05
MVPA	0.04	-0.27	-	-0.22	0.06	-0.28	-	-0.21
Sleep	0.25	-0.05	0.35	-	0.34	-0.07	0.31	-
AIx								
	SED	LPA	MVPA	Sleep	SED	LPA	MVPA	Sleep
SED	-	0.74	0.91	-0.49	-	0.96	0.86	-0.56
LPA	-0.66	-	0.24	-1.16	-0.85	-	0.00	-1.42
MVPA	-0.37	0.37	-	-0.86	-0.39	0.58	-	-0.95
Sleep	0.48	1.22	1.38	-	0.58	1.51	1.40	-
PWV								
	SED	LPA	MVPA	Sleep	SED	LPA	MVPA	Sleep
SED	-	0.07	0.95	-0.28	-	0.09	0.77	-0.28
LPA	-0.05	-	0.89	-0.34	-0.07	-	0.70	-0.35
MVPA	-0.37	-0.31	-	-0.66	-0.33	-0.25	-	-0.62
Sleep	0.27	0.34	1.22	-	0.32	0.36	1.05	-
BMI								
	SED	LPA	MVPA	Sleep	SED	LPA	MVPA	Sleep
SED	-	1.04	1.21	0.39	-	1.14	1.07	0.40
LPA	-0.98	-	0.23	-0.59	-1.07	-	0.02	-0.66
MVPA	-0.73	0.32	-	-0.34	-0.72	0.44	-	-0.31
Sleep	-0.40	0.66	0.82	-	-0.59	0.75	0.68	-

Predicted effects were based on the mean composition. Sedentary time (SED), light physical activity (LPA), moderate-to-vigorous physical activity (MVPA), pulse pressure (PP), augmentation index (AIx), pulse wave velocity (PWV). * A percentage change greater than the SWC % for each arterial measure.

4.4 Discussion

This is the first study to employ compositional analysis to explore the combined effects of movement behaviours on arterial measures in a paediatric population. Overall, there was no significant effect of the mean physical activity composition on any cardiovascular measure, with the composition found to be similar regardless of sex. Furthermore, predictive analysis found no effect of reallocating 20 minutes of MVPA to either sedentary time, LPA or sleep on central stiffening or BMI, irrespective of sex. Conversely, PWV was predicted to be non-significantly reduced for both groups with the substitution of time from sedentary time, LPA and sleep to MVPA.

Previous studies have employed compositional analysis to explore the relative associations of movement behaviours with cardiometabolic health, in both children (Carson, et al., 2016) and adults (Chastin, et al., 2015), however to our knowledge no study has explored the associations of these measures with arterial stiffening. Carson et al. (2016) reported that the overall movement composition was significantly associated with all cardiometabolic markers, though, when considered in isolation, only BMI was significantly predicted by all behaviours. In contrast, the present study found no significant relationships for the overall composition, or individual effects, of movement behaviours with markers of arterial stiffening and BMI. The lack of significant associations suggests that the movement composition alone does not explain all of the variance in the outcome, with additional confounding factors, in addition to age and sex, affecting arterial stiffening more significantly. For example, cardiorespiratory fitness (CRF) has been shown to have a mediatory effect on the age-related progression of central stiffening (Ogola et al., 2018; Veijalainen, et al., 2016), with lower CRF associated with premature stiffening in children (Sakuragi, et al., 2009) and also suggested to be related to physical activity levels and compositions. Future studies should therefore also explore the influence of CRF in explaining the relationship between physical activity and arterial stiffness.

Compositional research, irrespective of population, indicates that the relative associations of movement behaviours do not necessarily emulate those of individual behaviours in isolation (Carson, et al., 2016; Chastin, et al., 2015). Specifically, negative correlations between sedentary time and cardiometabolic health were

identified in children, relative to remaining behaviours, whereas previous research utilising traditional analyses found sedentary time to have equivocal effects on such markers (Carson, et al., 2016). In the current sample, sedentary time was not associated with AIx, but an increased time in sedentary pursuits was associated with decreases in PP and PWV. Such findings are in contrast to previous research investigating the influence of sedentary time in isolation where greater time sedentary was consistently associated with an elevated arterial stiffening in children and adolescents (Haapala, et al., 2016; Nettlefold, et al., 2019). Whilst sedentary time has been demonstrated to act negatively on arterial health in isolation (Väistö et al., 2019), it could therefore be postulated that inactivity may be a more important target to slow premature increases in CVD risk. Interestingly, higher levels of LPA showed a trend towards a greater decrease in AIx and BMI than MVPA. Conversely, a higher MVPA was non-significantly associated with a decreased PWV, with the opposite found for LPA. These findings are discordant to studies in adolescents (Edwards, et al., 2012), overweight children (Sakuragi, et al., 2009), and children with chronic health conditions (Wadwa, et al., 2010), which found significant negative associations between MVPA and stiffness measures. Moreover, while evidence for the influence of LPA on stiffening is less established than MVPA, preliminary research indicates that greater volumes of LPA in adolescents are associated with a more favourable PWV (Edwards, et al., 2012).

The non-significant effect of MVPA on vascular measures in the present sample may be a consequence of a number of factors, including differences in patterns of accumulation of sedentary time and LPA, and disparities in the spread of data for AIx (2.0 – 27.5 %) and PWV (3.5 – 6.2 $m \cdot sec^{-1}$). Specifically, girls accrued a greater volume of LPA, but less MVPA, with similar volumes of sedentary time and sleep, compared to boys. It could therefore be postulated that girls may interrupt prolonged periods of sedentary time with periods of LPA. Alternatively, such findings could be due to the misclassification of sedentary time and LPA from accelerometer data (Byrom, et al., 2016). Conversely, the observed differences may, at least in part, be due to the differing spread of data between arterial measures, with the SD varying from 11% for PWV, to 44% for AIx in girls. Consequently, the differences in magnitude of the relationship may inappropriately suggest a lesser influence of physical activity on vascular health and adiposity. Indeed, the current findings indicate a minimal effect of

MVPA, discordant with Väistö et al. (2019) who found LPA was more weakly associated with cardiometabolic health than MVPA. Nonetheless, these findings provide further evidence that the intensity of physical activity is important for arterial health in paediatric populations (Germano-Soares et al., 2018).

Although not significant, increased time in sleep, LPA and MVPA were associated with decreases in BMI, with greater sedentary time associated with an increased BMI. These findings are in accord with research investigating the effects of movement behaviours in isolation (Chaput, et al., 2012; Kwon, Janz, Burns, & Levy, 2011; Wijndaele, et al., 2019; Yoong et al., 2016). Moreover, with the exception of LPA, these findings are congruent with previous compositional research in children (Carson, et al., 2016), supporting the need to target both inactivity and sedentary time to promote the maintenance of a healthy weight. The consistent negative reciprocal relationship between sedentary time and BMI provides further evidence of the negative effect of time in sedentary pursuits (Nettlefold, et al., 2019; Wijndaele, et al., 2019). Indeed, these findings suggest that reducing sedentary time may play a pivotal role in maintaining a more favourable weight status and reduced risk of obesity.

Reducing time in MVPA by 20 minutes and thereby increasing ST, LPA or sleep, whilst not significant, consistently predicted negative effects on arterial stiffening and adiposity. These findings may highlight the importance of MVPA for the maintenance of vascular health and a healthy weight, independent of sex. However, it may be pertinent to note that for the same 20-minute reallocation of time from MVPA to any other movement behaviour, the non-significant predicted changes were consistently higher in girls, possibly due to girls accruing less MVPA prior to reallocation. Furthermore, the ternary heat maps (Figure 4.2) suggest higher MVPA is associated with a lower aPWV in girls, potentially suggesting intensity of physical activity may be key to achieve change in arterial health for this population. Conversely, in boys, intensity may be of less importance for arterial health, as demonstrated by the lack of effect of reallocating MVPA to LPA on AIx, as shown in the ternary heat maps (Figure 4.3). This therefore suggests that both LPA and MVPA are important for aPWV in boys. However, as boys accrued a greater volume of MVPA compared to girls this must be interpreted with caution. Nonetheless, these predictive changes support the importance of MVPA in children (Chief Medical Officers, 2019) whilst also indicating

that LPA may have a greater positive effect on arterial health and adiposity than previously perceived (Füzéki, Engeroff, & Banzer, 2017).

The primary strength of this study was the use of a compositional approach to understand the overall influence of movement behaviours on arterial measures. Additionally, the use of SWC as a representation of the MCID, as opposed to the traditional method of 1 SD, provided a more meaningful context to predictive changes in arterial measures (Wells et al., 2001a). However, this study is not without limitations. First, it is important to acknowledge that accelerometers without inclinometers may not fully distinguish between sedentary time and LPA, due to a lack of sensitivity and inability to identify postural changes (Carson, et al., 2016; Howard et al., 2015). Moreover, given that this study only monitored participants for seven consecutive days, with as little as three days included for some participants, some movement behaviours may have been under- or over-estimated, as behavioural variation may not have been accounted for. It is also pertinent to note that a significant difference in maturity was present between girls and boys, therefore, whether observed differences in health outcomes were solely attributable to sex independent of maturity remains to be elucidated and warrants further investigation. Finally, whilst the predictive changes suggest the effects of reallocating 20 minutes of time between behaviours in future interventions, these models are based on the present data, thereby limiting generalisability. Additionally, predictive modelling provides no indication regarding the duration of intervention necessary to elicit such changes, nor the duration over which they should be sustained to impact health.

4.5 Conclusion

In conclusion, MVPA was the most potent stimulus for change in arterial health, however, even with 20-minute reallocation from any other movement (i.e., sleep, sedentary time and LPA) to MVPA no significant predicted changes were evident in either arterial or adiposity. This highlights the high potential dose of MVPA required to improve arterial health in healthy populations. However, of importance, daily movement behaviours cannot predict arterial stiffening nor weight status in isolation, demonstrating the need to adopt a compositional approach in future research. Future research should not only seek to further explore the relationship between movement

compositions and arterial health, but to identify and control for additional mediatory or modulatory factors.

Chapter 5

Association of physical activity metrics with indicators of cardiovascular function and control in children with and without type 1 diabetes

Chapter 5 (Study 2) - Association of physical activity metrics with indicators of cardiovascular function and control in children with and without type 1 diabetes

5.1 Introduction

Type 1 diabetes (T1D), characterised by chronic lifelong insulin deficiency, is estimated to affect 400,000 people in the UK, 7.25% of whom are children (Royal College of Paediatrics and Child Health, 2018). The most prevalent cause of mortality in T1D is cardiovascular disease (CVD), and individuals with T1D have a four-fold higher risk of developing cardiovascular complications relative to their non-diabetic peers (Diabetes UK, 2016). Pre-clinical indications of this increased cardiac risk may be evident as early as two years post-diagnosis, suggesting that those who develop T1D early in life have a significantly increased premature risk of developing CVD, compared with their non-diabetic peers and those with a later onset (Chessa, et al., 2002; Shah, et al., 2015).

The aetiology of the increased CVD risk in those with T1D is suggested, at least in part, to be related to chronic hyperglycaemia and its deleterious effects on the vascular and nervous systems caused by increases in oxidative stress and inflammation (American Diabetes Association, 2010; NICE, 2015). Vascular dysfunction, which is typically characterised by poor vascular elasticity and reactivity (Hadi, Carr, & Al Suwaidi, 2005), is a common complication in T1D (Greenwald, 2007; Laurent, et al., 2006). This reduced arterial compliance also potentially exacerbates the direct role of chronic hyperglycaemia in the autonomic dysfunction often reported in the paediatric diabetic population (M. Jaiswal, et al., 2013; Verrotti, Prezioso, Scattoni, & Chiarelli, 2014). The consequently impaired control of cardiac rhythm and heart rate responsiveness, mediated by the autonomic nervous system and measurable through the indices of heart rate variability (HRV), is associated with an increased risk of short- and long-term complications, and specifically with an elevated risk of CVD (Astrup, et al., 2006; Verrotti, et al., 2014).

Physical activity, along with the application of exogenous insulin and the strict control of diet, is essential for the management of T1D and is associated with a reduced risk

of both acute and long-term complications, and improved quality of life (NICE, 2015). Moreover, research suggests that meeting the UK physical activity recommendations of, on average, 60 minutes of moderate-to-vigorous physical activity (MVPA) per day across the week (Chief Medical Officers, 2019), is strongly correlated with additional health-associated benefits for those with T1D (Beraki, Magnuson, Sarnblad, Aman, & Samuelsson, 2014; Warburton, et al., 2006). In children with T1D, physical activity improves glucose control (Beraki, et al., 2014; Chimen, et al., 2012; Herbst, Bachran, Kapellen, & Holl, 2006), helps prevent insulin resistance (Landt, et al., 1985; Nadeau, et al., 2010; Sell, Eckel, & Dietze-Schroeder, 2006), reduces traditional CVD risk factors (Herbst, Kordonouri, Schwab, Schmidt, & Holl, 2007; Heyman et al., 2007; Sell, et al., 2006), maintains a healthy vascular reactivity (Liese, Ma, Maahs, & Trilk, 2013) and healthy autonomic function (Chen, et al., 2008; Nagai, et al., 2004; Routledge, et al., 2010). However, recent research found that only 39% of children with T1D met the current UK physical activity guidelines (Chief Medical Officers, 2019), with these children engaging in significantly less MVPA than their non-diabetic peers (de Lima, et al., 2017).

While MVPA is associated with important health benefits, longer durations of light-intensity physical activity (LPA) in healthy children have also been associated with multiple benefits (Aggio, Smith, & Hamer, 2015), including a lower stiffness in the small arteries (Haapala, et al., 2016; Stone, et al., 2009). This suggests that all physical activity, irrespective of intensity, can elicit health-associated benefits and highlights the need to consider the whole physical activity profile. However, research has predominantly focused on exploring the health influences of the volume of time spent in different intensities, rather than exploring the overall effect of accumulated physical activity, irrespective of intensity. Furthermore, this focus on the volume of physical activity has been almost exclusively based on various cut-points that were derived from different protocols, segmenting the available data (Fairclough, et al., 2019) and largely precluding inter-study comparisons. In contrast, utilising all available movement data to determine the distribution of physical activity intensity and volume accrued, in the form of the activity profile, enables the identification of those patterns and variances in physical activity that are most strongly associated with health outcomes (Rowlands, et al., 2018). Vitally, such metrics enable inter-study comparisons (Rowlands, et al., 2018) and could thereby facilitate the accumulation of

sufficient evidence to support individually-targeted interventions for reducing long-term health complications. Such approaches would be particularly valuable in a diabetic population, as even relatively small changes can elicit improvements in disease management, cardiovascular health and quality of life (Anderson et al., 2016).

The primary aim of the current study was therefore to determine the influence of T1D on the accumulation of physical activity in diabetic youths and to determine whether it is the volume or the intensity of physical activity, or a combination of these, that has the greater influence on their cardiovascular health.

5.2 Methods

The present cross-sectional study was conducted in paediatric diabetes clinics and schools in South Wales. Following written informed assent and consent from participants and parents/guardians, respectively, measurements and assessments were taken over a two-hour testing period, with physical activity subsequently assessed over seven consecutive days. The study was approved by a National Health Service (NHS) Research Ethics Committee (16/NE/0082 195492) and conducted in accordance with the Declaration of Helsinki.

5.2.1 Participants

29 children with T1D (12.1 ± 2.1 years; 14 girls) and 19 without T1D (11.8 ± 2.2 years; 6 girls) participated in this study. The data included in the present study is a sub-sample of a larger dataset used in Chapter 7. While an a-priori power calculation was not conducted due to the convenience sampling approach utilised in this observational study, *post-hoc* power analysis indicates a power of 0.93. Control participants were recruited opportunistically within the community to ensure they were age- and sex-matched to the participants with diabetes. Potential participants with any known cardiovascular disease, kidney disease, metabolic disease or hypertension were excluded. Diabetes-specific exclusion criteria were: a diabetes duration of less than one year; currently being in poor glycaemic control (HbA1c >75.0 $mmol \cdot mol^{-1}$); or identified by the paediatric diabetes team as otherwise unsuitable for participation in the study.

5.2.2 Anthropometric, Maturity and Metabolic Measures

Standing and sitting stature were measured to the nearest 0.1 cm using a Holtain stadiometer (Holtain, Crymych Dyfed, UK), with body mass measured to the nearest 0.1 kg using electronic scales (Seca 803, Seca, Chino, CA, USA). Body mass index (BMI) and BMI z-score (BMIz) were subsequently calculated. Data on each participant's blood glucose control, lipid profile and HbA1c were obtained from medical records. Maturity was estimated using sex-specific maturity offset equations in order to approximate the time in years pre- or post-peak height velocity (PHV). Maturity status was defined as prepubertal if > 1 year pre-PHV, pubertal if 1 year pre- or post-PHV, and post-pubertal if > 1 year post-PHV (Mirwald, et al., 2002).

5.2.3 Habitual Physical Activity Measurements

Participants wore a GENEActiv triaxial accelerometer (GENEActiv, Activinsights Ltd, Cambridgeshire, UK) sampling at 20 Hz on their right wrist for seven-consecutive days. The GENEActiv has been validated for use in children (Phillips, et al., 2013) and has been shown to be reliable in comparison to other validated accelerometers (Esliger, et al., 2011). During the habitual physical activity assessment period, participants were given diaries to monitor sleep quality and duration, and to record times and reasons for accelerometer removal.

5.2.4 Vascular Assessment

Non-invasive assessment of vascular function was carried out employing a cuff-based osillometric technique (Vicorder, Skidmore Medical, Bristol, UK; D.E.Hokanson Inc, Bellevue, WA, USA), with the participant in the supine position, torso elevated to approximately 30^{o}, in a quiet environment and having rested for five minutes prior to assessment to ensure stable haemodynamics (heart rate and blood pressure). Pulse wave analysis (PWA) was completed with a cuff on the upper left arm, at the brachial artery. A stable blood pressure (BP) was initially obtained to inform the inbuilt automated protocol, then the pulse-pressure waveform was recorded deriving central augmentation pressure and index (AIx) by integral transfer function. Specifically, AIx was calculated as the difference in pressure between peaks one and two on the systolic waveform expressed as a percentage of pulse pressure (Wilkinson, et al., 2000). Aortic stiffness was estimated from the carotid to femoral pulse wave velocity (aPWV),

completed by placing a partial cuff over the carotid pulse and a cuff at the upper thigh, then measuring the distance between the sternal notch and the middle of the femoral cuff. Carotid and femoral waveforms were then recorded, deriving aPWV in $m \cdot sec^{-1}$. Three recordings for each process, PWA and aPWV, were taken to obtain at least two congruent measures within 0.5 $m \cdot sec^{-1}$, 5 mmHg and 5% of each other, respectively.

6.2.5 Assessment of cardiac autonomic function

A short-term ECG recording, from which normal cardiac interval data (RR-intervals) can be derived, was obtained with the use of a 3-lead Reynolds CF Holter monitor (Spacelabs Medical Ltd, Hertford, UK), producing 12-bit resolution ECG data at a sampling frequency of 1,024 Hz. Three electrodes were positioned on the anterior of the torso, at the manubrium of the sternum and the V5 and V5R positions. Accurate placement of each electrode was ensured by visually observing each channel prior to recording. A representative resting measure of autonomic function was obtained by recording for five minutes during paced breathing at six-breaths per minute in the supine position, after a 15 minute rest period.

5.2.6 Heart Rate Variability Data Processing

ECG data from the Reynolds CF Holter recorder were exported and processed using the Reynolds Pathfinder ECG analysis system (Spacelabs Medical Ltd, Hertford, UK). The pathfinder system classified QRS cycles as either normal (resulting from sinus node depolarisations) or aberrant, and normal cardiac (RR) interval data were then extracted using the Reynolds Research Tools software (Spacelabs Medical Ltd, Hertford, UK). The resulting RR data were visually assessed to identify and delete any obvious artefacts (those of non-physiological origin). The processed RR data were then analysed using Kubios HRV V3.0 (Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland) to derive time-domain, frequency-domain and geometric indices of HRV. RR data were detrended using the 'Smoothn priors' option with Lamdba set to 500. Time domain analysis of the RR data yielded RMSSD, the square root of the mean of the sum of the squares of differences between adjacent RR intervals, a measure of the short-term variability of RR intervals in the recording (European Society of cardiology, 1996). Frequency domain indices were spectrally estimated by Welch's method of power spectral density

estimation and autoregressive modelling, then divided into the frequency bands of low and high frequency (LF: 0.04-0.15 Hz; HF: 0.15-0.40 Hz). These indices were then expressed as both absolute power and power normalised to total spectral power (TSP; 0.04-0.40 Hz) as an indication of the distribution of spectral power and the variance of all RR intervals (European Society of cardiology, 1996). The derived geometric HRV index was SD1, indicating short-term variation in RR intervals, determined from the standard deviation of paired consecutive differences on the line of the Poincaré plot (European Society of cardiology, 1996).

5.2.7 Habitual Physical Activity Data and Analysis

Raw accelerometer data were extracted using the GENEActiv PC software v2.2 (Activinsights Ltd, Cambridgeshire, UK). Signal processing was subsequently completed with R software (https://cran.r-project.org) using the GGIR package (https://cran.rproject.org/web/packages/GGIR/vignettes/GGIR.html) to convert the triaxial acceleration values to an omnidirectional acceleration in the form of the signal vector magnitude (SVM). Raw acceleration values were processed by the Euclidian Norm Minus One (ENMO) method (van Hees, Gorzelniak, Dean Leon, et al., 2013), then reduced to 5 second epochs and expressed in milligravity-based acceleration units (mg; Hildebrand, et al., 2017). Minimum wear-time was classified as ≥ 16 hours during waking hours, defined as 0600 to 2300, over three weekdays and one weekend day (Fairclough, et al., 2016). Hildebrand et al. (2014)'s raw acceleration thresholds were utilised to determine the time spent in different intensity domains as < 50 *mg* for sedentary time, 50-99 *mg* for light physical activity (LPA), ≥ 100 *mg* for MVPA (Hildebrand, et al., 2017). Tolerance thresholds for LPA and MVPA bouts were set as ≥ 10 minutes of continuous 5s epochs, where 80% of epochs were ≥ 50 or ≥ 100 *mg*, respectively (Menai et al., 2017). Sleep was classified based on the van Hees et al. (2015) nocturnal sleep algorithm as no arm angle change > 5^{o} for ≥ 5 minutes. Total physical activity was quantified as the average acceleration over a 24-hour period (Fairclough, et al., 2019).

The intensity gradient, a metric of physical activity intensity distribution (Rowlands, et al., 2018), was calculated for each participant. Specifically, the curvilinear relationship between intensity and time spent in in each successive 25 *mg* time bin

between 0 and 4,000 *mg* was transformed to a linear relationship using the natural log of each variable. The R^2 value obtained indicated the goodness of fit of the linear model, whilst the gradient and constant of the linear regression represented the activity distribution. A higher constant and a more negative gradient represent a steeper decline and therefore less time accumulated at mid-to-high intensities. Conversely, a lower constant and a less negative gradient represents a shallower drop and is therefore indicative of more time spread across the intensities (Rowlands, et al., 2018).

5.2.8 Statistical Analysis

The SPSS software package (IBM SPSS Statistics for Macintosh, Version 22.0, Plymouth, UK) was used to perform statistical analyses, with significance set as $p < 0.05$ and all data expressed as mean ± SD. Initially, independent t-tests were completed to determine whether differences were present between included and excluded participants, followed by assessing between-group differences in participant characteristics. Linear mixed models with a random intercept were then conducted to compare differences in physical activity between children with and without T1D according to the intensity gradient, average acceleration, LPA, bouted LPA (LPAb), MVPA or bouted MVPA (MVPAb). Following the use of an initial unadjusted model, further models were adjusted for potential covariates of age, sex, maturation and BMI, then for covariates and the alternative physical activity metrics to test for independence. Pearson's correlations were used to determine the magnitude of associations between intensity gradient, average acceleration, MVPA and MVPAb, and to ascertain whether the intensity gradient showed greater independence of average acceleration than MVPA or MVPAb. Finally, linear mixed models were utilised to explore the associations between volume/intensity of physical activity and measures of cardiovascular function and control. Specifically, following an initial unadjusted model, a fully adjusted model was iteratively conducted for each alternative physical activity metric, followed by a final adjusted model including the alternative activity metric (intensity gradient or average acceleration) to determine their independent association with each measure of cardiovascular function or control.

5.3 Results

Following the exclusion of eight participants (six T1D participants were removed due to failed calibration and failing to meet the wear-time criteria; two controls, due to failing to meet wear-time criteria), the final sample consisted of 40 participants (23 T1D, 17 non-diabetic). There were no significant differences between those included or excluded with regards to age, anthropometric measures or maturity (data not shown). Participant descriptive characteristics and physical activity outcomes are presented in Table 5.1. Participants with T1D were observed to have HbA1c levels greater than the NICE recommended level of 48 mmol·mol^{-1}, above which the risk of developing long-term complications is significantly increased (NICE, 2015).

Table 5.1. Participant characteristics, physical activity and glycaemic control.

	Children with T1D (n = 23)	Non-diabetic children (n = 17)
Age (yrs)	12.1 ± 2.1	11.8 ± 2.2
BMI (kg·m^{-2})	20.7 ± 3.7	19.3 ± 4.1
Maturity offset (yrs)	-1.55 ± 1.65	-1.30 ± 2.04
Sedentary time (mins·day^{-1})	492.0 ± 119.4	527.8 ± 101.3
LPA (mins·day^{-1})	471.0 ± 61.6**	410.9 ± 71.5
LPAb (mins·day^{-1})	166.4 ± 66.0	148.0 ± 63.6
MVPA (mins·day^{-1})	82.9 ± 37.2	114.0 ± 72.1
MVPAb (mins·day^{-1})	4.5 ± 4.7*	12.9 ± 15.3
Average acceleration (mg)	37.2 ± 9.7*	46.2 ± 18.1
Intensity gradient	-2.11 ± 0.18**	-1.90 ± 0.23
Intensity constant	13.02 ± 0.66**	12.36 ± 0.76
Sleep efficiency (%)	82.9 ± 11.0	83.1 ± 11.5
HbA1c (mmol·mol^{-1})	68.24 ± 12.14	-
HbA1c (%)	8.4 ± 1.1	-
Total- C (mmol·l^{-1})	4.22 ± 0.39	-
LDL-c (mmol·l^{-1})	2.30 ± 0.33	-
Disease duration (yrs)	5.0 ± 3.2	-

Values are presented as mean (SD). Body mass index (BMI), sedentary time (ST), light physical activity (LPA), bouted light physical activity (LPAb), moderate-to-vigorous physical activity (MVPA), bouted moderate-to-vigorous physical activity (MVPAb), glycated haemoglobin (HbA1c), total cholesterol (Total-C), low density lipoprotein (LDL-c), * significant difference between groups at $p<0.05$, **significant differences at $p<0.01$

.

Linear mixed model analyses highlighted significant differences in the intensity gradient ($p < 0.01$), average acceleration ($p < 0.05$) and time spent in LPA ($p < 0.05$) for diabetic and non-diabetic children, when accounting for age, sex, maturity status and BMI (Table 5.2). There were no significant differences in MVPA ($p > 0.05$), MVPAb ($p = 0.058$, 1-ß = 0.74), bouted LPA or sedentary time ($p > 0.05$) between the two groups. Amongst the boys, those without diabetes showed the highest average acceleration and highest intensity gradient but the lowest LPA; amongst the girls, those with diabetes demonstrated the lowest LPA, lowest intensity gradient and lowest average acceleration.

Intensity gradient was strongly associated with both MVPA and MVPAb ($r = 0.80$, $p < 0.01$; $r = 0.79$, $p < 0.01$, respectively), but less strongly correlated with sedentary time ($r = -0.36$, $p < 0.05$). Average acceleration was similarly strongly correlated with both intensity gradient and cut-point metrics. Specifically, average acceleration was correlated with the intensity gradient ($r = 0.89$, $p < 0.01$), MVPA ($r = 0.85$, $p < 0.01$) and MVPAb ($r = 0.83$, $p < 0.01$), while only moderately correlated to sedentary time ($r = -0.36$, $p < 0.05$). Intensity gradient and average acceleration showed no significant correlation with LPA or bouted LPA.

Cardiovascular outcomes for both groups are presented in Table 5.3, while the spread of key cardiovascular outcomes are presented in Figure 5.1. Modest negative correlations were observed between PWV and intensity gradient ($r^2 = -0.38$, $p < 0.05$), average acceleration ($r^2 = -0.40$, $p < 0.05$), MVPA ($r^2 = -0.43$, $p < 0.05$) and MVPAb ($r^2 = -0.45$, $p < 0.05$). Average acceleration was also modestly correlated to resting absolute LF ($r^2 = 0.44$, $p < 0.05$) and TSP ($r^2 = 0.43$, $p < 0.05$). Neither intensity gradient nor average acceleration were significantly correlated to AIx or any of the HRV indices measured under conditions of stress ($p > 0.05$). Furthermore, across the HRV measures the present sample resulted in a relatively poor statistical power, ranging from 0.4 for LF (ms^2) to 0.7 for TSP.

The association between physical activity metrics and measures of cardiovascular function are presented in Table 5.4. Both intensity gradient and average acceleration were significant predictors of PWV, RMSSD, LF, total spectral power and SD1 when unadjusted, but not when adjusted for covariates.

Table 5.2. Linear mixed model of between-group differences in activity metrics according to disease status.

	Model 1		Model 2		Model 3		
	β	95% CI	β	95% CI	β	95% CI	Independent (model 3)
Intensity gradient	-0.22**	-0.35, -0.08	-0.19**	-0.33, -0.05	-0.13*	-0.25, -0.02	Y
Intensity constant	0.66**	0.19, 1.13	0.60*	0.10, 1.11	0.45	-0.01, 0.91	X
Average acceleration (mg)	-9.58*	-19.07, -0.10	-4.67	-11.84, 2.49	2.08	-3.77, 7.94	X
Sedentary time (mins·day^{-1})	-35.8	-111.1, 39.5	-36.4	-110.8, 38.0	-63.2	-141.7, 15.3	Y
LPA (mins·day^{-1})	60.1**	15.1, 105.1	63.5**	8.5, 108.4	74.7**	26.3, 123.1	Y
LPAb (mins·day^{-1})	18.5	-25.5, 62.4	10.4	-33.1, 54.0	19.9	-27.2, 67.0	Y
MVPA (mins·day^{-1})	-31.2	-69.4, 7.1	-12.6	-44.3, 19.1	0.6	-32.3, 33.6	X
MVPAb (mins·day^{-1})	-8.3*	-15.8, -0.8	-6.3	13.3, 0.7	-0.9	-7.0, 5.3	Y

Model 1 unadjusted model grouped with disease status, model 2 adjusted for potential covariates: age, sex, maturity status, BMIz, model 3 adjusted for covariates and alternative physical activity metric to determine if independent (average acceleration for intensity gradient, intensity gradient for all other metrics), with an independent and non-independent relationships denoted by Y and X, respectively.

Light physical activity (LPA), bouted light physical activity (LPAb), moderate to vigorous physical activity (MVPA), bouted moderate to vigorous physical activity (MVPAb). * Significant difference between groups at $p < 0.05$, with ** significant difference at $p < 0.01$

Table 5.3. Measures of cardiovascular function for diabetic and non-diabetic participants.

	Children with T1D (n=29)	Non-diabetic children (n=19)
Resting BP (mmHg)	114/60	116/62
MAP (mmHg)	83.3 ± 6.6	84.9 ± 5.4
AIx (%)	13.52 ± 6.47	15.25 ± 7.02
aPWV ($m \cdot sec^{-1}$)	5.04 ± 0.66**	4.58 ± 0.70
TSP (ms^2)	3,291 ± 3,982	5,060 ± 7,308
LF (ms^2)	1,309 ± 1,217	2,204 ± 2,720
HF (ms^2)	1,917 ± 2,806	2,715 ± 5,283
LF (n.u)	50.9 ± 16.9	53.1 ± 14.0
HF (n.u)	49.0 ± 16.9	46.7 ± 14.0
RMSSD (ms)	53.5 ± 32.1	65.2. ± 52.3
SD1 (ms)	37.9 ± 22.7	46.1 ± 37.1

Values are presented as mean ± SD. Mean arterial pressure (MAP), augmentation index (AIx), aortic pulse wave velocity (aPWV), total spectral power (TSP), Low frequency (LF), High frequency (HF), Root mean square of the successive differences of RR (RMSSD), standard deviations of successive differences on the line of Poincare plot (SD1).**significant difference between groups at $p < 0.01$

Figure 5.1. – Individual variation in pulse wave velocity (PWV), root mean square of successive differences (RMSSD), and normalised low and high frequency data in those with and without diabetes.

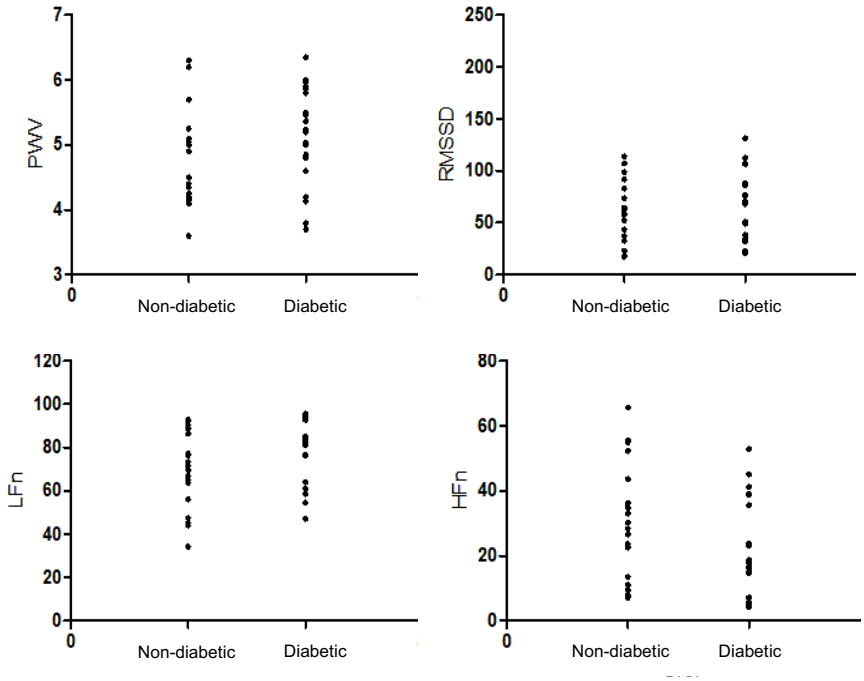


Table 5.4. Associations between physical activity metrics and measures of cardiovascular function and control for the overall study population, accounting for age, sex, maturity and disease status.

	Model 1		Model 2		Model 3		Independent
	β	95% CI	β	95% CI	β	95% CI	(model 3)
aPWV							
Intensity gradient	-1.62**	-2.82, -0.42	-1.27	-2.77, 0.23	-1.27	-3.56, 1.02	Y
Average acceleration	-0.02*	-0.04, -0.004	-0.01	-0.03, 0.01	-0.00	-0.03, 0.03	X
AIx							
Intensity gradient	-1.26	-13.30, 10.78	8.14	-8.09, 24.37	-5.79	-29.55, 17.97	X
Average acceleration	0.03	-0.13, 0.19	0.18	-0.02, 0.37	0.23	-0.07, 0.53	Y
MAP							
Intensity gradient	10.53	-0.45, 21.51	5.96	-8.14, 20.05	11.31	-10.05 ,32.66	Y
Average acceleration	0.10	-0.04, 0.25	0.02	-0.16, 0.20	-0.10	-0.36, 0.18	X
RMSSD							
Intensity gradient	78.0*	1.8, 154.3	44.4	-74.6, 163.3	16.1	-148.3, 180.4	Y
Average acceleration	1.1*	0.1, 2.2	0.7	-0.9, 2.3	0.6	-1.7, 2.8	Y
LF							
Intensity gradient	4,403*	759, 8,046	1,822	-3,777, 7421	-1,634	-9,171, 5,903	X
Average acceleration	73**	25, 120	53	-22, 127	68	-35, 172	Y
HF							
Intensity gradient	6,333	-1,245, 13,910	3,776	-8,127, 15,680	2,681	-13,713, 19,075	Y
Average acceleration	82	-22, 186	43	-119, 205	20	-204, 245	Y
TSP							
Intensity gradient	11,025*	742, 21,309	5,440	-10,550, 21,448	978	-21,091, 23,047	Y
Average acceleration	158*	19, 298	98	-120, 316	88	-214, 391	Y
SD1							
Intensity gradient	55.3*	1.3, 109.3	31.5	-52.7, 115.7	11.4	-105.0, 127.8	X
Average acceleration	0.8*	0.055, 1.5	0.5	-0.6, 1.7	0.4	-1.2, 2.0	Y

Model 1 unadjusted model; model 2 adjusted for potential covariates: age, sex, maturity and disease status; model 3 adjusted for covariates and alternative physical activity metric to determine if independent.

95% confidence interval (CI), aortic pulse wave velocity (aPWV), augmentation index (AIx), mean arterial pressure (MAP), root mean square of successive differences of RR (RMSSD), low frequency (LF), high frequency (HF), total spectral power (TSP), standard deviation of successive differences on the line of the Poincare (SD1). Significant prediction between independent and dependent variable denoted by * $p < 0.05$, ** $p < 0.01$.

5.4 Discussion

This is the first study to explore physical activity in children with T1D using more novel, intensity-based, rather than conventional volume-based, measures to consider how physical activity is accumulated. Moreover, this study sought to investigate whether these metrics differ according to disease status and health outcomes. The key findings from the study were that children with T1D engaged in significantly less higher intensity physical activity and had a poorer (higher) aPWV than their non-diabetic peers. Finally, intensity of physical activity was most strongly associated with a lower aPWV and higher HRV indices, as demonstrated by the intensity gradient, though the intensity gradient was not independent of average acceleration or MVPA.

Physical activity is known to be associated with numerous short- and long-term health benefits in children (Janssen & Leblanc, 2010), as well as in the management of T1D (Chimen, et al., 2012). In accordance with previous research (Nguyen et al., 2015; Tully, Aronow, Mackey, & Streisand, 2016), the current study found that children with T1D typically undertake less MVPA than their non-diabetic peers. Indeed, previous research has postulated that those with T1D might engage in a lower volume of MVPA because of a lack of understanding about how to compensate for different types and intensities of exercise, and due to a fear of subsequent hypoglycaemia (Pivovarov, Taplin, & Riddell, 2015). However, whilst conventional, volume-based measures of physical activity have been extensively researched in the paediatric diabetic population, little is known regarding the physical activity profile as a whole. The current study therefore extends these earlier studies, demonstrating that diabetic children have a steeper, less favourable, intensity profile and lower average acceleration than their non-diabetic peers. These findings indicate that diabetic participants engaged in significantly more LPA than MVPA and moved less at higher intensities compared to their non-diabetic peers. Whilst these findings highlight LPA as a potential target for interventions, with suggestions that targeting LPA may represent a more feasible and sustainable target than MVPA for those with low physical activity levels at baseline (Keadle, et al., 2017; Matthews et al., 2016), it is worth noting that the greatest health benefits are elicited through MVPA, with significantly longer periods of LPA required to obtain similar benefits (Carson, et al., 2016). Therefore, future studies in children with chronic diseases should utilise the

activity profile to gain a greater insight into the accumulation of physical activity, to facilitate an accurate comparison of physical activity patterns between populations, and to identify key targets for intervention.

Previous studies in healthy children found that the intensity gradient was associated with conventional volume-based metrics, independent of average acceleration (Fairclough, et al., 2019; Rowlands, et al., 2018). The strongest association in these studies was demonstrated between the intensity gradient and MVPA, suggesting that the intensity gradient best represents more vigorous intensity physical activity (Fairclough, et al., 2019; Rowlands, et al., 2018). In contrast, time spent in MVPA in the current sample was similarly correlated with both the intensity gradient and average acceleration ($r^2 = 0.80$ and 0.85 respectively, both $p<0.01$). Consequently, the intensity gradient was not independently associated with conventional cut-points, a finding in contrast with previous literature. This lack of independence from MVPA might therefore limit the ability to explore the relative importance of physical activity volume and intensity in cardiovascular health (Buchan, et al., 2019). Such discrepancies might be partially due to the high volume of physical activity in which both populations engaged, which could mask the importance of intensity. Alternatively, accelerometer wear-location is thought to influence the magnitude of average acceleration, possibly resulting in increased variance in intensity gradient (Rowlands, et al., 2018).

Research has suggested that physical activity slows the progression of premature arterial stiffening in children with T1D, thereby reducing the risk of long-term complications later in life (Haapala, et al., 2016; Sakuragi, et al., 2009). Congruent with previous research (Terlemez et al., 2016), significant differences were observed in aPWV, with diabetic children presenting a 10% higher aPWV than their non-diabetic peers. This difference may indicate premature central stiffening, a likely indicator of increased long-term CVD risk. Furthermore, negative associations were observed, irrespective of disease status, between aPWV and intensity gradient, average acceleration, MVPA and bouted MVPA, but not LPA. Thus, a more positive or shallow gradient, indicative of engagement in more vigorous intensities, and a higher average acceleration, suggesting higher volumes of physical activity were associated with a lower aPWV. Such findings suggest that higher volumes and a greater

engagement in more vigorous intensities of physical activity positively influenced central stiffness. Additionally, the steeper gradient, lower average acceleration and the lower volume of MVPA, observed in this diabetic sample, suggests that the volume and intensity undertaken might not be sufficient to ameliorate the negative changes in central stiffening. Therefore, these findings further support a need to encourage and aid children with T1D to engage in more vigorous intensity physical activity, in order to slow the progression of disease-related central arterial stiffening.

Previous research has demonstrated that children with T1D who participate in lower volumes of physical activity have significantly lower HRV at rest, than more physically active participants with and without diabetes (Chen, et al., 2008). The clinical sample in the current study participated in significantly lower volumes of physical activity and showed non-significant, but characteristically lower values for absolute HF, total power, RMSSD and SD1, in comparison to their healthy controls. Lower magnitudes of total power, RMSSD, HF and SD1 in the short-term can indicate reduced overall cardiac autonomic activity, particularly of the parasympathetic (vagally-mediated) neural control of heart rate (European Society of cardiology, 1996). This suggests a possible shift towards systemic autonomic dysfunction that may increase the risk of developing autonomic neuropathy, a common complication in T1D (Vinik, et al., 2003). However, a positive association between physical activity intensity/volume and cardiac autonomic function, across both populations in this study, suggests that both intensity and volume could positively influence age- and disease-related decline in autonomic function (Herzig et al., 2017; Nagai, et al., 2004). Specifically, attaining a greater volume of physical activity, represented by a greater average acceleration, and accruing more vigorous intensities of physical activity were both associated with greater overall autonomic activity and vagal tone, therefore suggesting a potentially reduced risk of developing autonomic neuropathy. Furthermore, increased autonomic activity and vagal tone has been found to be a predictor of central arterial stiffness, a pre-clinical indicator of CVD in T1D (Liatis, et al., 2011), as observed in the current study. Thus, taken together, physical activity of sufficient volume and intensity may ameliorate age- and disease-related declines in autonomic function and central arterial stiffening in children with T1D.

There are numerous strengths associated with the current research, not least the use of recently devised physical activity metrics to explore how disease status influences physical activity accumulation. Nonetheless, this study is not without limitations, such as the sample size and sex distribution within the samples, which could limit the generalisability of the results. However, the metrics utilised facilitate inter-study comparisons, potentially enabling the use of this data in larger cohort analyses. Finally, the present study did not control for general lifestyle factors, such as diet, nor disease duration or HbA1c for those with T1D.

5.5 Conclusion

In conclusion, this study demonstrated that the accumulated daily volume of vigorous intensity physical activity has the greatest influence on arterial stiffening and cardiac autonomic function, both of which are indicators of CVD risk for children with T1D. Therefore, future physical activity interventions should focus on increasing the intensity of physical activity undertaken by this population. Children with T1D demonstrated significantly increased in central arterial stiffness and impaired cardiac autonomic function, compared to those without diabetes. Finally, quantifying intensity gradient and average acceleration enabled the identification of overall physical activity accumulation, which is important in preventing long-term risk of CVD in this population.

Chapter 6

Investigating the influence of measurement duration on physical activity metrics and their relationship with cardiovascular measures in healthy youth and adults

Chapter 6 (Study 3): Investigating the influence of measurement duration on physical activity metrics and their relationship with cardiovascular measures in healthy youth and adults

6.1 Introduction

Irrespective of age, physical activity is associated with numerous physiological and psychosocial benefits (Warburton, et al., 2006), including a reduced risk of chronic health conditions, such as type 2 diabetes and cardiovascular disease (CVD). While conditions such as CVD typically present clinically in adulthood, the pathophysiology is often instigated during childhood, with adverse changes in early risk indicators, such as arterial stiffening and autonomic function (Núñez et al., 2010). However, physical activity is suggested to ameliorate, or at least slow, the progression of such premature changes in risk factors in both children (Ekelund, et al., 2019; Haapala, et al., 2016) and adults (Benatti &Ried-Larsen, 2015; Chomistek et al., 2013). Despite the importance of physical activity, only approximately 47% of children and 67% of adults (National Health Service Digital, 2020) are suggested to meet the current physical activity guidelines (Chief Medical Officers, 2019).

Conventionally, device-based physical activity assessments are conducted over seven consecutive days, with a minimum required wear-time of at least eight hours on any three days (Herrmann, et al., 2013, 2014; Vanhelst et al., 2019). Such criteria have been recommended to provide a valid and reliable indication of habitual physical activity levels (Herrmann, et al., 2013). Whilst more stringent wear-time criteria within the seven day timeframe are often used and are widely recommended (Herrmann, et al., 2013, 2014), even an entire seven-day monitoring period represents only 2% of the year, raising questions as to its representativeness. Indeed, physical activity levels are influenced by numerous factors, including, but not limited to, the type of day (Kristensen, et al., 2008; Matthews, et al., 2002), season (Atkin, et al., 2016; O'Connell, et al., 2014) and vacations (Atkin, et al., 2016). Therefore, reliance on a single seven-day period, or subsample thereof, is likely to be insufficient to account for behavioural differences, both within and between populations (Shephard, 2017).

Accelerometers have rapidly evolved over recent decades, progressing from uniaxial devices limited to poor sampling rates and count-based data over relatively short time periods, to tri-axial devices capable of measuring at high sampling frequencies for prolonged periods of time (Arvidsson, Fridolfsson, & Börjesson, 2019). For example, the wrist-worn GENEActiv can measure at 20 Hz for over 28 consecutive days (Pavey, Gomersall, Clark, & Brown, 2016). These longer measurement durations have the potential to provide important insights into the natural fluctuation of physical activity over time (Rowlands, et al., 2015). Indeed, understanding the degree and pattern of such fluctuations has been suggested to be vital for the design of successful physical activity interventions (Rowlands, et al., 2015), and may help elucidate whether an ActivityStat, which serves to maintain relatively constant physical activity levels over time, is present. However, few studies have utilised monitoring periods longer than seven days, with those implementing 28 consecutive day measurement periods not considering week-to-week variability (Castonguay &Miquelon, 2018; Matthews, et al., 2002; Menai, et al., 2017; Pereira et al., 2015).

Monitoring habitual physical activity over a longer duration may increase the reliability and accuracy of the measure, and, in turn, provide a greater insight into the dose-response relationship of physical activity with various health markers. A substantial volume of research has explored the relationship between physical activity and health markers, particularly risk factors of CVD (Froberg &Andersen, 2005; Kohl, 2001; Maddison et al., 2016). However, our understanding of the relationship between physical activity behaviours and CVD is predominantly based on epidemiological studies (Wannamethee &Shaper, 2001), which typically utilised subjective measures and almost exclusively concentrate on the total volume of physical activity rather than the manner in which it is accrued. Recent research has highlighted that it is not only the quantity but also the intensity and the pattern of accumulation of physical activity that are important in determining the relationship with health (Jefferis et al., 2019; Poitras et al., 2016). Subsequently, little is known regarding the pattern of physical activity accumulation over long (i.e., more than seven days) time frames. However, recent the development of more data-driven metrics, intensity gradient and average acceleration, can aid in providing a more in-depth and consistent depiction of the full physical activity profile, independent of cut-point associated bias (Rowlands, et al.,

2018). Furthermore, these metrics may support the exploration of the independent effects of intensity and volume (Rowlands, et al., 2018).

Therefore, the primary aim of this study was to determine the influence of measurement duration on conventional and data driven physical activity metrics, and subsequently their relationship with cardiovascular measures, in both children and adults. Moreover, the study sought to provide recommendations for optimal recording durations for both children and adults.

6.2 Methods

In total, 61 participants, 19 children (11.6 ± 2.0 years; 7 girls) and 42 adults (44.1 ± 13.0 years; 16 female) were recruited from local schools, a university in South Wales, and the wider community via poster and email advertisements. Written informed consent was obtained from adult participants and parents/guardians of participants under 16 years, with children also providing written informed assent. Exclusion criteria for involvement in the study were any known cardiovascular, kidney or metabolic disease, hypertension or anyone deemed unsuitable to take part in the maximal exercise test according to the American College of Sports Medicine pre-exercise screening guidelines (Riebe et al., 2015). The study was approved by the institutional research ethics committee and conducted in accordance with the Declaration of Helsinki.

6.2.1 Anthropometrics

Stature and body mass were measured to the nearest 0.1 cm and 0.1 kg using a Holtain stadiometer (Holtain, Crymych Dyfed, UK) and electronic scales (Seca 803, Seca, Chino, CA, USA), respectively. Body mass index (BMI) was subsequently calculated for each population. Sitting stature was also obtained to the nearest 0.1 cm for children and adolescents (participants < 16 years) utilising a sitting height stadiometer (Harpenden Sitting Height Table model 607VR, Holtain Ltd, Crymych, Pembrokeshire, Wales). For children and adolescents, maturity was estimated using sex-specific maturity offset equations to estimate the time from peak height velocity (PHV). Maturity status was defined as pre-pubertal if the participant was more than

one year pre-PHV, pubertal if within one year pre- or post-PHV, and post-pubertal if greater than one year post-PHV (Mirwald, et al., 2002).

6.2.2 Pulse Wave Analysis and Pulse Wave Velocity Procedure

An oscillometric device (Vicorder, SMT Medical GmBH & CO, Wuerzburg, Germany) combined with specialised blood pressure cuffs (D.E.Hokanson Inc, Bellevue, WA, USA) were used to non-invasively assess arterial stiffness. Central stiffness was assessed at the brachial artery deriving augmentation index (AIx) and augmentation pressure, while central aortic stiffness was assessed between the carotid and femoral arteries deriving aortic pulse wave velocity (aPWV). Carotid-femoral distance was measured from the sternal notch to the femoral cuff, via the navel (Van Bortel et al., 2018). The assessment was completed after a five-minute rest period in a quiet environment and with the participant in the supine position to ensure stable waveforms were obtained. A minimum of three waveform recordings per assessment were captured over a 5- to 10-minute period for central stiffness, with the average of each measure taken for further analysis (Wilkinson, et al., 2000).

6.2.3 Assessment of HRV

A short-term electrocardiogram (ECG) was recorded at a frequency of 1,024 Hz, with the use of a 12-bit, three-lead ECG recorder (Reynold CF Holter monitor, Spacelabs Medical Ltd, Hertford, UK). Electrodes were placed in three positions on the front of the torso, specifically, at the manubrium and on the left- and right-hand side of the 5th rib, with placements tested by checking channels prior to recording. An indication of autonomic function was obtained, with the participant in the supine position, as a five-minute recording using ventilatory control at six inhalation-expiration cycles per minute (Williams &Lopes, 2002). The raw ECG data was initially processed utilising the Reynolds Research Tool (Spacelabs Medical Ltd UK) to obtain RR intervals, then analysed using Kubios HRV V3.0 processing software (Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland). Time and frequency domain measures were obtained from the processed data, with short-term variability represented by the root mean square of successive RR differences (RMSSD), overall RR interval variance represented by total spectral power (TSP; 0.04-0.40), and sympathetic and parasympathetic activation indicated by absolute and

normalised powers of low and high frequencies, respectively (LF; 0.04-0.15 Hz, HF; 0.15-0.40 Hz; Kromenacker, Sanova, Marcus, Allen, & Lane, 2018; Tarvainen, et al., 2014).

6.2.4 Cardiorespiratory Fitness

Participants were asked to complete an incremental ramp exercise test to volitional exhaustion on a cycle ergometer (Lode Excalibur Sport, Groningen, Netherlands). Throughout the ramp test, breath-by-breath gas exchange was measured (Carefusion Jaeger Vyntus CPX, Carefusion-Jaeger, Höchberg, Germany) in order to determine peak aerobic capacity ($\dot{V}O_{2peak}$) and the gas exchange threshold (GET). The protocol consisted of a three-minute warm-up at 10 W after which the work rate was increased by 30 $W \cdot min^{-1}$ for adults and children > 13 years, or 15 $W \cdot min^{-1}$ for children < 13 years (Boone &Bourgois, 2012; Ten Harkel, Takken, Van Osch-Gevers, & Helbing, 2011), until volitional exhaustion, identified as a failure to maintain > 50 revolutions per minute despite strong verbal encouragement. The test was immediately followed by a five-minute cool-down of unloaded cycling. $\dot{V}O_{2peak}$ ($l \cdot min^{-1}$) was identified as the highest 15s rolling average during the test. The GET was determined via the V-slope method (Beaver, et al., 1986), with $\dot{V}O_2$ plotted against expired CO_2 ($\dot{V}CO_2$) and the point of intersection taken as the GET. $\dot{V}O_{2peak}$ was presented in absolute units ($l \cdot min^{-1}$) and allometrically scaled for body mass ($ml \cdot kg^{-b} min^{-1}$). Allometric scaling of $\dot{V}O_{2peak}$ was calculated according to $\dot{V}O_{2peak}$ divided by body mass, to the power of the allometrically derived beta coefficient of body mass (McNarry, et al., 2014). Allometric scaling was employed to account for differences in body mass and enable the comparison between children, adolescents and adults, as traditional ratio scaling has been found to penalise heavier, more mature children and does not facilitate such a comparison (Chamari, et al., 2005; Welsman &Armstrong, 2019).

6.2.5 Habitual Physical Activity Measurement

Physical activity was recorded using a triaxial GENEActiv accelerometer (Activinsights Ltd, Cambridgeshire, UK), sampling at 20 Hz on the non-dominant wrist for 28-consecutive days. The GENEActiv accelerometer has been validated in both children (Phillips, et al., 2013) and adults (Pavey, et al., 2016; Powell, et al., 2017). Participants were asked to complete a wear-time and sleep diary, which

provided a record of when, and why, the monitor was taken off, and the duration and quality of sleep.

6.2.6 Processing of Habitual Physical Activity Data and Analysis

Accelerometry data extraction and processing were completed utilising the GENEActiv PC software v2.2 (Activinsights Ltd, Cambridgeshire, UK) and the GGIR package (https://cran.rproject.org/web/packages/GGIR/vignettes/GGIR.html), respectively. Raw accelerometry data was converted to omnidirectional signal vector magnitude (SVM), further processed to Euclidian Norm Minus One (ENMO) and presented in milligravity acceleration units (*mg*; van Hees, Gorzelniak, Dean Leon, et al., 2013). Minimum wear-time was applied as ≥ 16 hours during waking hours, defined as 0600 to 2300, on three weekdays and one weekend day per week of recording (Fairclough, et al., 2016). Raw acceleration thresholds for moderate-to-vigorous physical activity (MVPA) were set as ≥ 191.6 *mg* and ≥ 93.2 *mg* for children and adults, respectively (Hildebrand, et al., 2017). Bout tolerance was set as ≥ 10 minutes of continuous 5s epochs, where 80% of epochs were greater than the MVPA threshold (Menai, et al., 2017). Average acceleration was obtained to represent total physical activity over a 24-hour period (Fairclough, et al., 2019). The intensity gradient was calculated to indicate distribution of physical activity over a 24-hour period, by obtaining the gradient, constant and r^2 value from the curvilinear relationship between intensity and time spent in successive 25 *mg* bins between 0 – 4,000 *mg* (Rowlands, et al., 2018). Specifically, the intensity gradient was employed to give an indication of the movement intensities attained for a given duration, with a more negative gradient indicative of accruing lower intensities while a less negative gradient indicates the accrual of low through to higher intensities. All physical activity metrics were averaged for the full 28-day period, then for each of the individual four weeks, to enable the exploration of variation. The key outcome variables were MVPA, bouted MVPA (MVPAb), intensity gradient and average acceleration.

6.2.7 Statistical Analysis

The SPSS software package (IBM SPSS Statistics for Macintosh, Version 22.0, IBM, Portsmouth, UK) was used to perform statistical analyses, with significance set as $p < 0.05$ and all data expressed as mean ± standard deviation (SD). Age groups were

defined as children (≤ 18 yrs) and adults (≥ 18 yrs). A MANOVA was used to compare participant characteristics, $\dot{V}O_{2peak}$ and cardiovascular measures according to age group and sex. Subsequently, a repeated measures ANOVA was conducted to compare the daily average physical activity each week according to age group and sex. Linear mixed models with a random intercept were conducted to explore the association of health and cardiovascular outcomes with physical activity metrics from increasing measurement duration, adjusted for age and sex. Finally, Pearson's correlations were conducted to establish the magnitude of association between cardiovascular measures and physical activity metrics across the four weeks.

Coefficient of variation (CV), intraclass correlation coefficient (ICC), standard error of the mean (SEM) and the smallest worthwhile change (SWC) analyses were used to determine week-to-week consistency in movement behaviours over increasing measurement periods, analysed separately for children and adults. Specifically, the average data for the first seven days were compared to increasing durations (7, 14 and 21 days) of physical activity not including these first 7 days. The CV analysis was conducted to assess absolute reliability of physical activity metrics across a 28 consecutive-day monitoring period, with a repeated measures ICC analysis used to assess relative reliability (Eliasziw, et al., 1994). The CV was derived from the mean of the SD of the log10 for each metric, whilst ICCs were obtained from the mean squared values, back transformed log data and 95% confidence intervals (Eliasziw, et al., 1994). The consistency thresholds for two repeated measures were employed as consensus for the thresholds of greater than three measures is lacking (Runacres, et al., 2019). Subsequently, physical activity metrics were deemed highly consistent when ICC ≥ 0.75 and CV ≤ 10%, moderately when ICC > 0.75 and CV > 10% or ICC < 0.75 and CV < 10%, and unacceptable when ICC < 0.75 and CV > 10% (Eliasziw, et al., 1994). . The SEM was calculated to show any change in error associated with each metric by measurement duration and was calculated as the SD of each weekly metric*(1-metric ICC), while the SWC was calculated as 0.2*overall metric SD (Atkinson &Nevill, 1998). The sensitivity of each metric was tested to determine whether observations were due to behavioural variation or error associated with measurement. Therefore, SEM ≤ SWC, SEM = SWC and SEM ≥ SWC meant that the result was either likely due to behaviour, could be equally a result of behaviour or

error, or was likely due to the error associated with measurement, respectively (Hopkins, et al., 2009).

6.3 Results

Following the exclusion of four participants (one adult for monitor failure and three (one child and two adults) for failing to meet the wear-time criteria for each week of recording), the final sample consisted of 57 participants (18 children, 39 adults; Table 1). No significant differences in age, anthropometric measures, or maturity were evident between the participants included or excluded ($p < 0.05$).

In the children, girls were significantly more mature but had a lower $\dot{V}O_{2peak}$, irrespective of the method of expression, than boys ($p < 0.05$); there were no other anthropometric or cardiovascular sex differences. In the adults, men were significantly taller, heavier and had a higher absolute and relative $\dot{V}O_{2peak}$ ($p < 0.05$) but a significantly lower augmentation pressure (-5.31 mmHg, $p < 0.05$) and AIx (-6.5%, $p < 0.05$) than females. However, the sex differences in augmentation pressure and AIx were ameliorated when allometrically scaled $\dot{V}O_{2peak}$ was accounted for ($p > 0.05$). Although absolute $\dot{V}O_{2peak}$ was higher in adults, there was no significant difference between children and adults when $\dot{V}O_{2peak}$ was allometrically scaled ($p > 0.05$; Table 6.1). Finally, all vascular measures were higher in adults ($p < 0.05$), irrespective of sex, with the greatest difference between children and adults evident in aPWV (2.39 $m \cdot s^{-1}$, $p < 0.01$; Table 6.2 and displayed in Figure 6.1). No significant differences according to sex or age group were observed in indices of HRV ($p > 0.05$; Table 6.2).

Adults engaged in significantly more MVPA ($p < 0.01$) and MVPAb ($p < 0.05$) across all weeks compared to children (Table 6.3). In adults, average acceleration was dependent on week, with the average acceleration higher in weeks one and two than weeks three and four, but all other physical activity metrics were comparable between weeks. In contrast, in children, MVPAb increased across the weeks, with a significant difference between weeks one and four ($p < 0.05$) but, as in adults, the other physical activity metrics were similar between weeks.

Table 6.1. Participant characteristics and aerobic capacity.

	Children (n = 18)		Adults (n = 39)	
	Boys (n = 12)	Girls (n = 6)	Male (n = 26)	Female (n = 13)
Age (yrs)	11.7 ± 2.2	11.7 ± 2.1	41.9 ± 12.7	43.9 ± 15.1
Height (cm)	150.7 ± 8.5	149.4 ± 11.7	175.8 ± 7.4	162.6 ± 4.3**
Body mass (kg)	45.0 ± 14.6	43.7 ± 15.1	77.9 ± 10.7	65.0 ± 9.0**
Maturity offset (yrs)	-1.76 ± 1.99	-0.30 ± 1.75*	-	-
$\dot{V}O_{2peak}$ ($l \cdot min^{-1}$)	1.95 ± 0.37[a]	1.57 ± 0.65[a]	3.37 ± 0.77	2.02 ± 0.37**
$\dot{V}O_{2peak}$ ($ml \cdot kg^{-1} \cdot min^{-1}$)	49.6 ± 10.9[a]	38.5 ± 16.5[a]	43.5 ± 8.9	31.6 ± 8.0**
Scaled $\dot{V}O_{2peak}$ ($ml \cdot kg^{-b} \cdot min^{-1}$)	167.4 ± 29.7	139.6 ± 59.0	198.6 ± 41.6	133.9 ± 29.4**

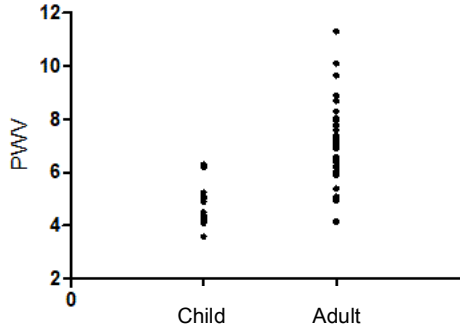
Values are presented as mean ± SD, peak aerobic capacity (VO_{2peak}), * Significant difference between sex within age groups at $p < 0.05$, with **denoting significance at $p < 0.01$, [a] Significant difference between age groups ($p < 0.05$)

Table 6.2. Cardiovascular function and control measures.

	Children		Adults	
	Boys	Girls	Males	Females
MAP (mmHg)	87 ± 4[a]	81 ± 5[a]	94 ± 8	95 ± 9
Augmentation (mmHg)	7.6 ± 3.8[a]	8.4 ± 4.6[a]	10.4 ± 4.7	15.8 ± 5.8*
AIx (%)	14.6 ± 7.3[a]	16.3 ± 6.5[a]	18.1 ± 7.8	24.7 ± 8.9*
aPWV ($msec^{-1}$)	4.56 ± 0.42[a]	4.60 ± 0.98[a]	7.19 ± 1.44	6.82 ± 1.27
TSP (ms^2)	5,489 ± 8,467	4,204 ± 3,967	2,046 ± 1,161	3,022 ± 1,832
LF (ms^2)	2,146 ± 2,725	2,320 ± 2,707	2,282 ± 2,017	2,842 ± 1,605
HF (ms^2)	3,190 ± 6,345	1,767 ± 1,362	1,166 ± 2,007	1,266 ± 1,794
LF (n.u)	66.0 ± 17.7	75.1 ± 15.3	77.5 ± 13.0	88.2 ± 9.0
HF (n.u)	34.0 ± 17.7	24.9 ± 15.3	22.4 ± 13.0	11.8 ± 9.0
RMSSD (ms)	63.0 ± 59.2	69.4 ± 34.4	28.4 ± 8.3	35.1 ± 10.7

Values are presented as mean ± SD, augmentation index (AIx), mean arterial pressure (MAP), aortic pulse wave velocity (aPWV), total spectral power (TSP), low frequency (LF), high frequency (HF), root mean square of the successive differences (RMSSD), *Significant difference between gender within age groups, [a] Significant differences between age groups.

Figure 6.1. Individual variation in pulse wave velocity (PWV) children and adults.



The results of the reliability analysis are presented in Tables 6.4 and 6.5 for children and adults, respectively. The CV, SEM and ICC revealed that, as the measurement duration increased, adult MVPA, MVPAb and the average acceleration remained relatively constant and became more consistent, whereas the intensity gradient fluctuated, irrespective of duration. In children, the CV and ICCs showed that the average acceleration and intensity gradient fluctuated the least and became more consistent with increasing length of the monitoring period, while MVPA, and in particular MVPAb, showed less consistency in comparison. Additionally, according to sensitivity thresholds for detecting behavioural variation or error, the average acceleration, intensity gradient and MVPA were deemed similarly sensitive to detect within participant behavioural change across all durations, irrespective of group (SEM ≤ SWC). For the initial seven-day duration in adults, MVPAb was also deemed sensitive to variations, however for all other monitoring durations, and indeed all monitoring durations in children, MVPAb was identified as inappropriate to detect such variation due to error associated with the measurement (SEM ≥ SWC).

The association between physical activity metrics according to measurement duration and cardiovascular measures derived from mixed model analysis, adjusted for age and sex, are presented in Table 6.6. For seven day measurements, an increased MVPA, MVPAb and average acceleration were all associated with a decreased augmentation, AIx and RMSSD, with an increased intensity gradient correlated with a decreased augmentation and AIx ($p \leq 0.05$). However, no significant associations were found between either volume or intensity metrics and aPWV, LF and HF ($p \geq 0.05$) when using a seven-day measurement period. Conversely, using a 28 day measurement period resulted in MVPAb being significantly associated with an increased augmentation, AIx, RMSSD and HF, but a decreased aPWV and LF ($p \leq 0.05$).

Additionally, a 28-day measurement duration resulted in a significant association between MVPA and RMSSD, LF and HF, while an increased average acceleration was correlated with a greater AIx and RMSSD ($p \leq 0.05$). Finally, for a 28-day measurement duration, a more negative intensity gradient was significantly associated with an increased augmentation ($p \leq 0.05$).

Table 6.3. Daily average of physical activity metrics per week with increasing measurement duration for children and adults.

	Children					Adults				
	Overall	Week 1	Week 2	Week 3	Week 4	Overall	Week 1	Week 2	Week 3	Week 4
MVPA (mins·day^{-1})	78.3 ± 37.3#	73.4 ± 41.3#	67.7 ± 18.1#	83.0 ± 43.5#	90.5 ± 52.1#	119.8 ± 40.7	126.2 ± 43.8	124.3 ± 41.8	118.6 ± 34.0	117.6 ± 42.3
MVPAb (mins·day^{-1})	25.1 ± 22.7#	16.8 ± 16.7#	18.6 ± 18.1#	24.9 ± 19.2#	72.7* ± 52.7#	35.6 ± 26.2	35.7 ± 31.1	34.7 ± 30.5	33.0 ± 19.9	31.6 ± 27.8
Average acceleration (*mg*)	47.7 ± 19.0	45.5 ± 18.1	46.5 ± 19.1	53.4 ± 20.1	56.3 ± 22.7	38.1 ± 11.3	37.8 ± 11.4	37.1 ± 12.0[a]	35.0 ± 8.2[a]	35.1 ± 11.0*
Intensity gradient	-1.76 ± 0.23	-1.78 ± 0.23	-1.80 ± 0.26	-1.70 ± 0.22	-1.67 ± 0.23	-1.86 ± 0.22	-1.86 ± 0.23	-1.88 ± 0.24	-1.90 ± 0.21	-1.95 ± 0.27
Intensity gradient intercept	11.48 ± 0.87	11.60 ± 0.90	11.62 ± 0.97	11.29 ± 0.84	11.18 ± 0.86	11.77 ± 0.94	11.79 ± 0.97	11.86 ± 1.04	11.90 ± 0.96	12.13 ± 1.15

Values are presented as mean ± SD, moderate-to-vigorous physical activity (MVPA), bouted moderate-to-vigorous physical activity (MVPAb), * Significant difference between time-points within groups at $p \leq 0.05$. # Significant difference between all weeks according to group [a] Significant difference between weeks 2 and 3 in adults.

Table 6.4. Variability and sensitivity analysis of children's physical activity metrics with increasing measurement duration.

	Overall Mean	95% Confidence Interval		SEM (%)	SWC	ICC	CV (%)
		Lower Bound	Upper Bound				
Week 1 v Week 2							
Average acceleration (*mg*)	46.0	37.3	54.7	4.4 (9.6)	9.2	0.95	4.50 ± 3.62
Intensity gradient	-1.79	-1.90	-1.67	0.05 (2.75)	0.36	0.96	3.59 ± 7.27
Intensity gradient intercept	11.61	11.17	12.05	0.18 (1.55)	2.32	0.97	0.73 ± 0.64
MVPA (mins)	70.5	51.6	89.5	13.5 (19.1)	14.1	0.89	10.95 ± 12.36
MVPAb (mins)	17.7	9.5	25.9	5.6 (31.7)	3.5	0.90	14.57 ± 9.91
Week 1 v Weeks 2+3							
Average acceleration (*mg*)	46.4	37.5	55.2	3.67 (7.91)	9.27	0.96	3.84 ± 3.12
Intensity gradient	-1.79	-1.90	-1.67	0.04 (2.19)	0.36	0.98	2.38 ± 7.42
Intensity gradient intercept	11.60	11.17	12.03	0.14 (1.19)	2.32	0.98	0.50 ± 0.57
MVPA (mins)	71.6	52.4	90.9	12.6 (17.6)	14.3	0.91	8.67 ± 9.92
MVPAb (mins)	17.9	9.7	26.0	5.1 (28.2)	3.6	0.92	14.55 ± 11.90
Week 1 v Weeks 2-4							
Average acceleration (*mg*)	46.8	37.9	55.7	4.09 (8.74)	9.36	0.96	4.66 ± 3.09
Intensity gradient	-1.78	-1.90	-1.67	0.04 (2.30)	0.36	0.97	2.48 ± 7.43
Intensity gradient intercept	11.60	11.16	12.03	0.14 (1.20)	2.32	0.98	0.49 ± 0.58
MVPA (mins)	72.8	53.4	92.2	14.0 (19.3)	14.6	0.89	10.36 ± 9.40
MVPAb (mins)	21.5	11.0	32.0	9.7 (45.3)	4.3	0.80	21.45 ± 18.11

Moderate-to-vigorous physical activity (MVPA), bouted moderate to vigorous physical activity (MVPAb), average acceleration (AA), intensity gradient (IG), standard error of the measurement (SEM), smallest worthwhile mean (SWC), intraclass correlation coefficient (ICC), coefficient of variation (CV; presented as mean ± SD)

Table 6.5. Variability and sensitivity analysis for adults physical activity metrics with increasing measurement durations.

		95% Confidence Interval					
	Overall Mean	Lower Bound	Upper Bound	SEM (%)	SWC	ICC	CV (%)
Week 1 v Week 2							
Average acceleration (mg)	38.4	34.5	42.3	3.65 (9.50)	7.68	0.92	3.83 ± 3.79
Intensity gradient	-1.85	-1.93	-1.77	0.10 (5.67)	0.37	0.84	7.32 ± 8.85
Intensity gradient intercept	11.73	11.38	12.07	0.43 (3.66)	2.35	0.85	1.47 ± 1.17
MVPA (mins)	127.6	113.3	141.8	13.9 (10.9)	25.5	0.91	5.00 ± 5.16
MVPAb (mins)	39.4	28.3	50.5	7.4 (18.8)	7.9	0.96	10.86 ± 15.21
Week 1 v Weeks 2 & 3							
Average acceleration (mg)	37.7	34.3	41.2	3.12 (8.28)	7.54	0.92	3.85 ± 3.08
Intensity gradient	-1.85	-1.92	-1.78	0.09 (5.00)	0.37	0.85	4.79 ± 5.54
Intensity gradient intercept	11.74	11.42	12.06	0.38 (3.25)	2.35	0.86	1.24 ± 1.15
MVPA (mins)	125.5	112.5	138.6	11.6 (9.2)	25.1	0.92	4.54 ± 3.68
MVPAb (mins)	38.3	28.5	48.1	8.0 (21.0)	7.7	0.94	11.30 ± 13.98
Week 1 v weeks 2, 3 & 4							
Average acceleration (mg)	37.6	34.2	41.1	3.02 (8.03)	7.53	0.93	3.84 ± 2.89
Intensity gradient	-1.86	-1.93	-1.78	0.08 (4.38)	0.37	0.89	5.09 ± 6.73
Intensity gradient intercept	11.76	11.44	12.09	0.34 (2.92)	2.35	0.89	1.13 ± 1.03
MVPA (mins)	125.3	112.2	138.4	10.9 (8.7)	25.1	0.93	4.51 ± 3.14
MVPAb (mins)	28.2	28.2	48.1	8.0 (20.9)	7.6	0.94	12.04 ± 13.76

Moderate to vigorous physical activity (MVPA), Bouted moderate to vigorous physical activity (MVPAb), Average acceleration (AA), Intensity gradient (IG), Standard error of the measurement (SEM), Smallest worthwhile mean (SWC), Intraclass correlation coefficient (ICC), Coefficient of variation (CV; presented as mean ± SD)

Table 6.6. Associations of physical activity derived from 7- and 28-days with cardiovascular measures, adjusted for age and sex.

	7-Days			28-Days		
	β	p	95% CI	β	p	95% CI
Aug						
MVPA	-0.07*	0.027	-0.14, 0.01	0.06	0.090	-0.01, 0.13
MVPAb	-0.12**	0.006	-0.21, -0.04	0.11*	0.032	0.01, 0.21
Intensity gradient	-15.12*	0.012	-26.92, -3.31	12.04*	0.052	-0.10, 24.18
Average acceleration	-0.23*	0.047	-0.46, -0.00	0.22	0.063	-0.01, 0.46
AIx						
MVPA	-0.12*	0.023	-0.22, -0.02	0.10	0.074	-0.01, 0.22
MVPAb	-0.24**	0.001	-0.38, -0.10	0.21*	0.007	0.06, 0.37
Intensity gradient	-20.92*	0.034	-40.21, -1.63	19.19	0.058	-0.68, 39.05
Average acceleration	-0.46*	0.014	-0.83, -0.09	0.46*	0.018	0.08, 0.83
aPWV						
MVPA	0.01	0.143	-0.00, 0.03	-0.01	0.137	-0.03, 0.00
MVPAb	0.02	0.060	-0.00, 0.05	-0.03*	0.042	-0.05, -0.00
Intensity gradient	-1.20	0.443	-4.26, 1.86	-0.17	0.915	-3.33, 2.98
Average acceleration	0.01	0.778	-0.05, 0.07	-0.02	0.579	-0.08, 0.04
RMSSD						
MVPA	-1.05*	0.035	-2.02, -0.07	0.99*	0.034	0.08, 1.90
MVPAb	-2.25**	0.002	-3.67, -0.83	2.31**	0.001	1.00, 3.62
Intensity gradient	2.58	0.985	-261.71, 266.87	63.50	0.624	-190.72, 317.72
Average acceleration	-3.60*	0.039	-7.02, -0.19	3.83*	0.026	0.45, 7.21
LF(nu)						
MVPA	0.32	0.075	-0.32, 0.68	-0.02*	0.037	-0.69, 0.02
MVPAb	0.38	0.188	-0.18, 0.94	-0.57*	0.030	-1.09, -0.05
Intensity gradient	-15.74	0.749	-112.29, 80.81	-9.27	0.845	-102.14, 83.60
Average acceleration	0.31	0.640	-0.99, 1.60	-0.60	0.359	-1.88, 0.68
HF(nu)						
MVPA	-0.32	0.074	-0.68, 0.03	0.36*	0.036	0.02, 0.69
MVPAb	-0.38	0.187	-0.94, 0.18	0.57*	0.030	0.06, 1.09
Intensity gradient	15.72	0.749	-80.65, 112.08	9.24	0.845	-83.45, 101.93
Average acceleration	-0.30	0.639	-1.60, 0.98	0.60	0.359	-0.68, 1.88

Adjusted model grouped for adults and children, adjusted for age and sex, with β coefficient depicting direction and magnitude of association, corresponding p value and the 95% confidence interval (CI). Augmentation pressure (Aug), augmentation index (AIx), aortic pulse wave velocity (aPWV), moderate-to-vigorous physical activity (MVPA), outed moderate-to-vigorous physical activity (MVPAb), total spectral power (TSP), low frequency (LF), high frequency (HF), root mean square of the successive differences (RMSSD). * Significant association between physical activity and cardiovascular measure at $p < 0.05$, ** Significant association at $p < 0.01$.

6.4 Discussion

This study explored how physical activity metrics reflecting volume and intensity varied across a single 28 consecutive day monitoring period, compared to seven consecutive days, in a sample of active children and adults with the aim of providing recommendations for future studies regarding the optimal measurement duration. Average acceleration and intensity gradient fluctuated the least across the measurement duration in children, with both metrics deemed sensitive to detect behavioural variation in children. In adults, MVPA, MVPAb and average acceleration were similarly suggested to fluctuate minimally. Both physical activity volume and intensity metrics using a 28-day measuring duration were more strongly and meaningfully associated with central stiffening and measures of sympathetic and parasympathetic activation, in comparison to a seven-day measurement duration.

Adults and children showed opposing decreasing and increasing trends in physical activity behaviours across the four weeks of monitoring, suggesting that a single seven days of monitoring, irrespective of population, may not provide an accurate indication of habitual physical activity behaviours. While these trends could be attributed to factors such as the Hawthorne effect (Wickström &Bendix, 2000), there are numerous contextual factors, such as occupation (Vandelanotte et al., 2015), routines, injuries/illness (Dishman, Sallis, & Orenstein, 1985) and seasonality (Atkin, et al., 2016; O'Connell, et al., 2014), which were not considered but highlights the need to consider these factors in future. Nonetheless, these findings suggest physical activity should be measured over multiple weeks, to not only account for the influence of key contextual factors, but to gain a better understanding of the natural and habitual fluctuations (Rowlands, et al., 2015), important given the significance of understanding physical activity for health (WHO, 2010b).

There was minimal fluctuation in the intensity gradient and average acceleration across 28 days for children in the present study. This, therefore, suggests that the intensities and total volume of movement accrued across the four-week period were relatively consistent. The limited fluctuation could be due to the use of acceleration data-driven metrics, which are less susceptible to variation than conventional MVPA and MVPAb metrics (Rowlands, et al., 2018). Indeed, MVPA and MVPAb were more variable

across the four-week monitoring duration. However, despite being more variable, these metrics were still deemed highly reproducible, with higher ICC values than previously reported for a single seven days (Barreira, et al., 2015; Trost, et al., 2000). Furthermore, the variation observed in MVPA was identified as likely behavioural variation, however, in contrast, the variation shown in MVPAb is likely to be more indicative of error associated with the measurement. These findings with regard to MVPAb may be due to 10-minute bouts being unable to reliably classify the sporadic nature of children's movement behaviours (Rowlands &Eston, 2007). Taken together, the current findings support the notion of children's behaviour being based on routines (Rowlands &Eston, 2007). Moreover, this limited fluctuation at a week-to-week level could be indicative of the presence of an ActivityStat, as behaviour may have fluctuated day-to-day within the week but compensation around a mean resulted in minimal weekly variation (Gomersall, Rowlands, English, Maher, & Olds, 2012).

Interestingly, physical activity metrics, and indeed their variation, differed according to age. Specifically, adults accrued consistent volumes of physical activity with low between and within person variation across the four weeks. Such findings are discordant with previous research, which suggest that adult's habitual behaviours may be less consistent than children's (Loyen et al., 2016), who's habitual behaviours are based on routines likely associated with school and family life (Brazendale et al., 2017; Pouliou et al., 2015). In contrast, recreational and occupational physical activity (Nooijen, et al., 2018; Vandelanotte, et al., 2015) and environmental factors (Dollman, 2018) in adults may engender greater inter- and intra-personal variation. The greater consistency in terms of volume of movement found in this sample of adults may also be attributable to them being highly active and thus potentially involved in regular, structured physical activity. Interestingly, the intensity gradient in the present adults was less consistent compared to the volume-based metrics. This may suggest that the time period over which an ActivityStat occurs could differ between volume and intensity (Gomersall, Rowlands, English, Maher, & Olds, 2013a). Specifically, volume may fluctuate daily and therefore remains constant at a weekly level, whereas intensity could fluctuate week-to-week but more research is needed to confirm these postulations. Consequently, these findings, independent of group, highlight the need to consider longer periods of data collection to facilitate the analysis of overall patterns of accumulation over time using novel analyses techniques, such as time series

analysis. Such analyses could provide greater insights regarding the natural variation that occurs within a day, week or month, thereby improving our understanding of how movement behaviours influence health outcomes, subsequently informing key interventional targets.

The differences in arterial measures between children and adults were anticipated due to normal age-related arterial stiffening (Cecelja &Chowienczyk, 2012). However, the central stiffening values for both populations were lower in comparison to age- and sex-specific reference values for aPWV (Reference Values for Arterial Stiffness Collaboration, 2010; Reusz, et al., 2010). Furthermore, a more favourable stiffening was associated with a higher relative $\dot{V}O_{2peak}$ and higher volume of physical activity, supporting the beneficial influence of high physical activity levels and CRF (Gomez-Marcos et al., 2014; Jakovljevic, 2018; Veijalainen, et al., 2016). A higher AIx and aPWV in girls compared to boys who were, on average less mature, is congruent with research which found the progression in arterial stiffening to occur to a greater extent during and after adolescence (Cheung, 2010). Moreover, given that indirect central stiffening is known to progress to a greater extent up to 50 years of age in healthy females compared to males, it is unsurprising that the present study found that males had a lower AIx (Ogola, et al., 2018). However, these sex-related differences in aPWV in adults were unexpectedly independent of physical activity but not $\dot{V}O_{2peak}$, indicating that the sex differences in CRF even after body size was accounted for may be more important than physical activity levels for stiffening. These findings highlight the need to promote CRF during aging in order to potentially slow age-related stiffening (Ogola, et al., 2018).

The lack of significant differences between children and adults for all measures of HRV was unanticipated, as the age-related decline in vagal tone between childhood and mid-adulthood typically results in the promotion of sympathetic dominance (De Meersman &Stein, 2007; Ingall, et al., 1990). The relatively high level of parasympathetic activation in the adults of the present study compared to the children may indicate a protective effect of high physical activity levels and a relatively high $\dot{V}O_{2peak}$, compared to age and sex norms in this population (Armstrong, Williams, Balding, Gentle, & Kirby, 1991; Kaminsky, Arena, & Myers, 2015). Further research

is warranted which seeks to distinguish the independent effects of age, sex, physical activity and CRF on arterial and autonomic health.

Physical activity metrics calculated from a 28-day measurement period were more strongly associated with aPWV and HRV indices, possibly indicating that a longer measurement duration may have captured habitual behavioural variations that are potentially meaningful for health not revealed by seven days. Conversely, physical activity metrics from a seven-day measurement were more strongly associated with augmentation pressure and AIx. Possible reasoning for the differing associations of physical activity metrics with arterial stiffening measures could be the properties quantified and influences on measurement. In particular, height can influence measures of indirect arterial augmentation as it assesses the return of pulse waves and can thus be biased towards shorter individuals (Lemogoum et al., 2004). Conversely, aPWV accounts for height with a measurement of the distance between the points at which it is assessed (Wilkinson, et al., 2019). Subsequently, augmentation pressure and AIx have been found to be more sensitive indicators of stiffening during childhood and young adulthood, while aPWV is indicated to be more sensitive and reliable in adults (McEniery et al., 2005). Therefore, the combination of adults and children, and the subsequent differences between movement behaviour and stiffening indices, may have masked the associations of metrics derived from the 28 day duration. Consequently, if an assessment of parasympathetic activation or central stiffening is the primary health outcome, a longer measurement duration than seven days is required to account for fluctuations in movement to advance our understanding of dose-response relationships. However, future research in clinical populations, which could be postulated to be more variable in their physical activity levels, and fewer active individuals is warranted.

While this study provides novel information regarding the variation of physical activity over different monitoring periods, it is important to acknowledge the limitations. First, this study analysed the overall physical activity volume from the daily average for each week of recording, and therefore does not consider how physical activity is accumulated within and between each day. Future studies should therefore seek to investigate intra-day variations in the accumulation of physical activity to ascertain whether, and if so how, compensation occurs. Moreover, given the seasonal

variation observed between repeated monitoring periods over a year (Atkin, et al., 2016; O'Connell, et al., 2014), it is noteworthy that an isolated monitoring period, albeit over 28 days, may not fully account for such variation. Thus, not taking seasonality into account could potentially incorrectly estimate an individual's habitual movement behaviours, and mask associations between these behaviours and health. Whilst the present study provided key details regarding the effect of increasing measurement duration on MVPA, MVPAb, intensity gradient and average acceleration, future studies should seek to ascertain these effects across the full range of movement behaviours. Finally, although the participants were randomly sampled this sample were active across the monitoring duration therefore would likely have a different attitude to physical activity, potentially limiting the generalisability of the results. Nonetheless, it is pertinent to note that the use of a 24-hour wrist-worn monitoring protocol, as opposed to just waking hours, is a key strength (Rosenberger, Buman, Haskell, McConnell, & Carstensen, 2016) which resulted in a high mean wear compliance.

6.5 Conclusion

In conclusion, a 28 day measurement duration revealed that intensity, but not volume, of physical activity fluctuated in adults, while children's physical activity behaviour remained relatively consistent. Additionally, volume and intensity metrics obtained over 28 days were more relevant and strongly associated with key cardiovascular measures than equivalent seven day metrics, thus longer measurement durations could be key to facilitating a greater understanding of dose-response relationships with health outcomes. Finally, future research investigating day-to-day fluctuation in movement behaviours, in addition to exploring the associations with other health parameters, and in different populations, is warranted.

Chapter 7

Using compositional analysis to explore the relationship between physical activity and cardiovascular health in children and adolescents with and without type 1 diabetes

Chapter 7 (Study 4): Using compositional analysis to explore the relationship between physical activity and cardiovascular health in children and adolescents with and without type 1 diabetes

7.1 Introduction

Physical activity research has predominantly explored the effect of isolated physical activity behaviours on health in various populations and for various health outcomes, particularly cardiovascular health (Leclair, De Kerdanet, Riddell, & Heyman, 2013; Warburton, et al., 2006). Specifically, moderate-to-vigorous physical activity (MVPA), one of the most consistently explored movement behaviours, is well established to have a positive effect on cardiovascular health in both healthy (Froberg &Andersen, 2005; Kohl, 2001; Vasankari, et al., 2017) and clinical populations (Chimen, et al., 2012; Riddell et al., 2017), whilst prolonged periods spent in sedentary pursuits exert a negative influence, independent of physical activity (Hamer, et al., 2017; Nettlefold, et al., 2019). However, the reliance of the majority of these studies on a single movement behaviour, which in the case of MVPA is likely to account for less than 4% of the day (Chastin, et al., 2015), is not only unlikely to provide a representative insight into habitual physical activity behaviours, and indeed their relationship with health, but also fails to consider the inherent co-dependencies between behaviours (Carson, et al., 2016; Chastin, et al., 2015).

Research on the inter-relationship between movement behaviours and their impact on health is becoming increasingly prevalent (Carson, et al., 2016; Chastin, et al., 2015; Stefelová, et al., 2018). Indeed, studies have utilised compositional analysis to explore the combined and relative effects of sedentary time, physical activities and sleep on various cardiometabolic health indicators (Carson, et al., 2016; Chastin, et al., 2015). Compositional analysis utilises log-ratio transformational techniques to account for the finite and bounded nature of movement behaviours within a day (Mateu-Figueras, et al., 2011), and more appropriately explores the relative associations with health outcomes. Specifically, Chastin et al. (2015) demonstrated the interaction and inherent collinearity between these movement behaviours, highlighting the need to move away from traditional statistical methods which cannot account for such dependence

(Chastin, et al., 2015). A linear regression model is often used to investigate associations between physical activity behaviours or sedentary time with health, covarying for other pertinent behaviours or factors (Pearson, 1896). However, regression models assume independence between variables, therefore, the high dependency and collinearity between movement behaviours could result in untrustworthy or spurious results (Pearson, 1896). Conversely, the use of compositional data analysis can reveal valuable insights to the relative associations between movement behaviours and health (Chastin, et al., 2015; Stefelová, et al., 2018).

Compositional analysis could facilitate a greater understanding of the effect of physical activity in clinical conditions, where behaviours, such as MVPA, are identified as a crucial factor in disease management (Riddell, et al., 2017). One such condition is type 1 diabetes (T1D), a chronic condition characterised by the lack of endogenous insulin production, often resulting in glycaemic extremes, and most often diagnosed during childhood (American Diabetes Association, 2010). Physical activity is one of the three key components of disease management, alongside exogenous insulin application and diet, required to maintain blood glucose levels and reduce the risk of developing complications (Riddell, et al., 2017). The most prevalent long-term complication for adults with T1D is cardiovascular disease (CVD; de-Ferranti, et al., 2014). While CVD most often results in mortality during adulthood, the disease process is often instigated during childhood (Perchard &Amin, 2015; Snell-Bergeon &Nadeau, 2012). Specifically, for children with T1D, chronic hyperglycaemia engenders a two-fold increase in the risk of developing CVD as a complication later in life (Perchard &Amin, 2015; Snell-Bergeon &Nadeau, 2012). Pre-clinical markers for this increased risk, including premature increases in arterial stiffening and declines in cardiac autonomic function, can be demonstrated from as early as two years post diagnosis in children (M. Jaiswal, et al., 2013; Urbina, et al., 2019; Vinik, Erbas, & Casellini, 2013).

A greater volume of MVPA is reported to be individually associated with a more favourable central stiffening and cardiac autonomic activity in those with T1D (Chen, et al., 2008; Edwards, et al., 2012), with suggestions that MVPA could potentially ameliorate the increased CVD risk. However, children with T1D have been

consistently found to accrue less MVPA than their non-diabetic peers, with many studies finding that this population do not meet the recommended 60 minutes of MVPA per day deemed necessary to achieve these risk-reducing benefits (Chief Medical Officers, 2019; Czenczek-Lewandowska, Leszczak, Baran, et al., 2019; Tully, et al., 2016). However, of interest, children with T1D demonstrate significantly greater volumes of light intensity physical activity (LPA) than non-diabetic peers, potentially as compensation for lower MVPA (Czenczek-Lewandowska, Leszczak, Baran, et al., 2019). Indeed, whilst research in healthy children have found LPA to beneficially act on arterial stiffening and autonomic function, this has been to a lesser extent than MVPA (Nettlefold, et al., 2019; Veijalainen, et al., 2019), indicating significantly greater volumes of LPA may be necessary to achieve the same health-associated benefits as 60 minutes of MVPA.

The increasing trend for prolonged periods of sedentary time in all child and adolescent populations has been associated with greater insulin resistance and less favourable lipid profiles (Carson, et al., 2016; Sardinha, et al., 2008; Saunders, et al., 2014), both of which have detrimental effects on glycaemic control and CVD risk for children with T1D (Snell-Bergeon &Nadeau, 2012). Given that behaviours are known to track from childhood to adolescence, and beyond, the increasing sedentary time in children is especially concerning, potentially further exacerbating the risks of premature, and possibly preventable, deleterious changes in cardiovascular health (Farooq et al., 2018). Consequently, a much greater understanding of the effects of all movement behaviours in T1D is crucial to identify important targets for intervention, to provide recommendations for clinical teams and, ultimately, to reduce the risk of both short- and long-term complications.

Whilst compositional analysis is highly valuable to provide insight regarding the combined and relative effects of all daily movement behaviours, considering these behaviours as the overall daily average across a monitoring period may mask important variations. Specifically, variation in individual movement behaviours has been observed by accelerometer-based monitoring according to season (Atkin, et al., 2016), type of day (Kristensen, et al., 2008; Pereira, et al., 2015), between weeks (Aadland et al., 2017) and due to influences including holidays and school (Kristensen, et al., 2008). However, hypotheses such as the ActivityStat postulate that while there

are fluctuations in movement behaviour volumes and patterns, these fluctuations occur around a central mean (Gomersall, et al., 2013b; Wilkin, et al., 2006). As of yet, no study has explored whether the movement behaviour complex is influenced by these variations or fluctuations. However, as postulated by the ActivityStat, an increase in one behaviour must occur concomitantly with a decrease in another in order to remain within the finite 24 hours. Subsequently, the compositional nature of movement behaviours and the ActivityStat may be interlinked.

Therefore, the primary aim of this study was to utilise compositional analyses to explore the associations of daily movement behaviours with markers of cardiovascular health in children with T1D and non-diabetic peers. A secondary aim was to use predictive modelling to investigate how reallocating time from one behaviour to another influenced key cardiovascular measures for children with and without T1D. Finally, the study sought to determine whether the daily average of movement behaviours fluctuated across a four-week monitoring period.

7.2 Methods

In total, 48 children and adolescents (11.9 ± 2.1 years; 29 with T1D; 20 girls) were included in the present study from paediatric diabetes clinics and local schools in South Wales, with all procedures conducted within local outpatient clinics or the research laboratories at Swansea University. A sub-sample of this data was also used in Chapter 5. Written informed consent and assent were obtained from parents/guardians and participants, respectively, with all assessments and measurements, other than physical activity, collected over a two-hour period. Physical activity was then monitored over seven consecutive days. Ethics approval was obtained from the Tyne and Wear South National Health Service Research Ethics Committee (16/NE/0082 195492), with all procedures conducted in accordance with the Declaration of Helsinki. General exclusion criteria were any cardiovascular conditions, kidney or metabolic disease, or hypertension, with diabetes-specific criteria including a diabetes duration of less than one year or those identified by the respective diabetes team as unsuitable for participation due to complications or currently being in poor glycaemic control as indicated by glycated haemoglobin (HbA1c >75.0 $mmol \cdot mol^{-1}$/ 9%). Blood glucose

control, according to HbA1c was obtained from the latest reading present in medical records.

7.2.1 Anthropometrics

Height, sitting height and body mass were measured to the nearest 0.1 cm, 0.1 cm and 0.1 kg, with the use of a calibrated stadiometer (Holtain, Crymych Dyfed, UK), a sitting height stadiometer (Harpenden Sitting Height Table model 607VR, Holtain Ltd, Crymych, Pembrokeshire, UK), and electronic scales (Seca 803, Seca, Chino, CA, USA), respectively. Body mass index (BMI) was subsequently derived. An estimation of maturity was calculated using sex-specific, maturity offset equations as the approximate time in years from the greatest rate of increase in height during puberty, or peak height velocity (PHV; Mirwald, et al., 2002).

7.2.2 Arterial stiffness

A non-invasive assessment of arterial stiffness was conducted with all participants using an osillometric device (Vicorder, Skidmore Medical, Bristol, UK) and accompanying blood pressure (BP) cuffs (D.E.Hokanson Inc, Bellevue, WA, USA). The assessment was conducted after a five-minute resting period in a quiet environment, to ensure a stable HR and BP, with the participant in the supine position. Pulse wave analysis (PWA) was conducted with a BP cuff over the brachial artery on the upper left arm. Initially, a stable BP was acquired to inform the inbuilt automated function. Subsequently, pulse pressure (PP) was derived with a transfer function employed to derive augmentation pressure (AP) and augmentation index (AIx), as an estimation of central stiffening. The AP was derived from the systolic waveform as the pressure difference between peaks one and two, while AIx was calculated as AP as a percentage of pulse pressure (Wilkinson, et al., 2000). Aortic pulse wave velocity (aPWV) was assessed with a partial and brachial cuff placed over the carotid and femoral arteries, respectively. The distance between the sternal notch and the centre of the femoral cuff, via the umbilicus, was measured. The time taken for a pulse wave to travel between the two cuffs was recorded according to the carotid and femoral waveforms, giving PWV in $m \cdot s^{-1}$. Both processes were repeated a minimum of three times, or until at least two measures within 5 mmHg, 5% or 0.5 $m \cdot s^{-1}$ were obtained.

7.2.3 Cardiac Autonomic Activity

A three-lead Reynolds CF Holter monitor (Spacelabs Medical Ltd, Hertford, UK), sampling at 1,024 Hz, was used to obtain a short-term, 12-bit electrocardiogram (ECG) recording from which RR intervals were obtained. Electrodes were positioned at three points - the manubrium and the V5 and V5R positions on the anterior of the torso, with placement verified by visually checking each of the three channels prior to recording. A 15-minute rest period in a supine position was followed by a five-minute recording of paced breathing at a rate of six breaths per minute. The ECG recording was processed to identify QRS cycles resulting from sinus node depolarisation, disregarding abnormal cycles, with the normal cardiac (RR) intervals extracted using the Reynolds Pathfinder ECG analysis system (Spacelabs Medical Ltd, Hertford, UK). The extracted RR intervals were then visually inspected to identify and remove any artefacts before being analysed using Kubios-HRV V3.0 (Biomedical Signal Analysis Group, Department of Applied Physics, University of Kuopio, Finland) to derive heart rate variability (HRV) indices in the time and frequency domains. Specifically, the root mean square of successive differences (RMSSD), and low frequency (LF) and high frequency (HF), both absolute and normalised, were obtained to give an estimation of sympathetic and parasympathetic activation, respectively, at rest (European Society of cardiology, 1996).

7.2.4 Habitual physical activity

Participants were asked to wear a triaxial accelerometer sampling at 20 Hz (GENEActiv, Activinsights Ltd, Cambridgeshire, UK) on their right wrist for 28-consecutive days, 24 hours a day. The GENEActiv has been validated and reported to provide reliable representations of physical activity behaviours in children (Esliger, et al., 2011; Phillips, et al., 2013). Accelerometer data was downloaded from each device utilising the GENEActiv PC software v2.2 (Activinsights Ltd, Cambridgeshire, UK), with the GGIR package (https://cran.rproject.org/web/packages/GGIR/vignettes/GGIR.html), built in R (https://cran.r-project.org), employed for signal processing to convert triaxial data to omnidirectional acceleration. This omnidirectional data was then processed using the Euclidian Norm Minus One (ENMO; Van Hees, Gorzelniak, Dean León, et al., 2013), reduced to 5s epochs and converted to milligravity-based acceleration (Hildebrand, et

al., 2017). Wear-time criteria was applied to the processed data with ≥ 16 hours per day over three week days and one weekend day required for inclusion in further analysis (Fairclough, et al., 2016). Raw acceleration thresholds, derived according to the Hildebrand et al. (Hildebrand, et al., 2014) predictive equations, were applied to classify sedentary time (≤ 23.5 *mg*), LPA (> 23.5-191.6 *mg*) and MVPA (≥ 191.6 *mg*). Sleep was determined according to the Van Hees et al. (van Hees, et al., 2015) sleep algorithm as no arm angle change of > 5^{o} for ≥ five minutes.

7.2.5 Data analysis

Compositional analyses were conducted by normalising the time in each behaviour as a proportion of total time in the overall composition, giving the geometric mean for each behaviour and grouping. The geometric mean of each behaviour was then used to produce a variation matrix based on pairwise log contrasts for the total sample. Sequential isometric log ratios (ILRs), equal to one, were produced from the composition of movement behaviours as compositional linear regression models for each cardiovascular measure, covarying for age, sex, maturity and disease status. The p-value for each set of models was obtained as the significance of the model, with the initial coefficient and p-value for each movement behaviour in sequential models taken as an indication of the effect and significance on the outcome measure. Predictive change models, conducted by back-transforming co-ordinates from pervious ILRs for each behaviour, were then employed to explore the influence of reallocating 20 minutes from one behaviour to another on cardiovascular measures, based on the geometric composition for each group (Chastin, et al., 2015).

Twenty minutes, as opposed to the 10 minutes used in previous studies (Carson, et al., 2016; Chastin, et al., 2015) was chosen to explore the impact of meeting physical activity guidelines for children with T1D, as substituting 20 minutes to MVPA would increase time in this behaviour to the recommended 60 minutes per day. Predictive changes were expressed as percentage change for each cardiovascular measure, based on the group mean, then compared to the SWC% to identify a meaningful and significant difference.

7.2.6 Statistical analysis

Statistical analyses were performed in IBM SPSS Version 22.0 (IBM SPSS Statistics for Macintosh, IBM, Portsmouth, UK) or the compositions package (Version 1.40-2; Chastin, et al., 2015), and its dependencies, in R (http://cran.r-project.org). Significance was set as $p \leq 0.05$, with all data expressed as mean ± SD, unless stated otherwise. The minimum clinically important difference (MCID) was identified as more representative of a significant change in cardiovascular measures than the typically employed 1 SD (Wells, et al., 2001b). Therefore, the MCID for cardiovascular measures was represented by the smallest worthwhile change (SWC) and the percentage SWC (SWC%), calculated according to mean of cardiovascular outcomes for each group (Wells, et al., 2001b). Potential differences in all measures, according to disease status and sex, were explored with the use of a multivariate ANOVA with Bonferroni corrections. The movement composition for both groups was derived for each separate week and for increasing measurement durations (14, 21 and 28 days), with a repeated measures ANOVA with Bonferroni correction subsequently used to explore whether the compositions varied with increasing measurement duration.

7.3 Results

The final sample consisted of 37 participants (20 T1D; 16 girls), following the exclusion of 11 participants (6 T1D and 5 control) for monitor failure or failure to meet the weekly wear-time criteria. No significant differences were found between those included and excluded regarding age, anthropometrics, maturity or physical activity ($p > 0.05$). Participant anthropometrics and metabolic measures are presented in Table 7.1, with cardiovascular outcomes presented in Table 7.2. Regardless of disease status, girls were more mature than boys (1.32 yrs, $F_{1,33}=6.39$, $p < 0.05$), but engaged in significantly less MVPA (-27.6 min·day^{-1}, $F_{1,33}=4.66$, $p < 0.05$; Figure 7.1). Additionally, healthy participants, irrespective of sex, accrued significantly more MVPA compared to T1D peers (26.4 min·day^{-1}, $F_{1,33}=4.26$, $p < 0.05$; Figure 7.2). The HbA1c level for all participants with T1D was above the National Institute for Health and Care Excellence (NICE) recommended levels of 48 mmol·mol^{-1} (NICE, 2015).

Table 7.1. Participant anthropometric characteristics and glycaemic control, according to disease status and sex.

	T1D (n = 20)		Healthy (n = 17)	
	Girls (n = 10)	Boys (n = 10)	Girls (n = 6)	Boys (n = 11)
Age (yrs)	12.1 ± 1.1	11.7 ± 2.0	11.8 ± 2.3	11.4 ± 2.0
BMI ($kg \cdot m^{-2}$)	21.8 ± 4.3	19.8 ± 3.8	19.0 ± 4.7	19.2 ± 4.2
Maturity offset (yrs)	-1.46 ± 0.78*	-1.76 ± 1.69	-0.30 ±1.92*	-2.19 ± 1.75
HbA1c ($mmol \cdot mol^{-1}$)	76.3 ± 13.6	65.4 ± 11.9	-	-
HbA1c (%)	9.1 ± 1.3	8.1 ± 1.1	-	-
Total- C ($mmol \cdot l^{-1}$)	4.3 ± 0.4	4.1 ± 0.3	-	-
LDL-c ($mmol \cdot l^{-1}$)	2.5 ± 0.3	2.2 ± 0.3	-	-
Disease duration (yrs)	4.7 ± 3.5	5.4 ± 3.2	-	-

Data is presented as mean ±SD. Body mass index (BMI), glycated haemoglobin (HbA1c), total cholesterol (total-c), total cholesterol (Total-c), low density lipoprotein (LDL-c). * A significant difference between sexes within a disease group.

Table 7.2. Arterial and autonomic outcomes, according to disease status and sex.

	T1D		Healthy	
	Girls	Boys	Girls	Boys
PP	55 ± 11	59 ± 10	56 ± 16	58 ± 9
AIx	15.1 ± 5.8	12.1 ± 7.1	17.3 ± 6.3	13.3 ± 5.9
MAP	84.3 ± 7.8	80.3 ± 5.2	84.1 ± 6.5	86.1 ± 4.7
PWV	5.24 ± 0.58	4.96 ± 0.66	4.66 ± 0.90	4.74 ± 0.66
RMSSD	53.5 ± 26.9	75.69 ± 37.46	76.6 ± 34.7	66.8 ± 53.6
LF	6,519 ± 6,882	5,367 ± 2,976	4,860 ± 4,285	5,632 ± 8,503
HF	1,349 ± 1545	3,468 ± 4050	1,430 ± 1279	2,577 ± 3,699
LF nu	79.2 ± 16.5	69.1 ± 24.9	75.1 ± 16.8	66.2 ± 19.4
HF nu	20.7 ± 16.4	30.8 ± 24.9	24.9 ± 16.7	33.8 ± 19.3

Data is presented as mean ±SD. Pulse pressure (PP), augmentation index (AIx), mean arterial pressure (MAP), pulse wave velocity (PWV), root mean square of successive standard deviations of NN intervals (RMSSD), low frequency (LF), high frequency (HF).

No significant differences were found between the daily average composition of movement behaviours for each week, across the monitoring period ($p > 0.05$). Therefore, subsequent analyses were completed using the daily average across all four weeks for all available physical activity data for each participant.

In the full sample, participants spent the majority of waking hours being sedentary or in LPA, with MVPA accounting for less than 4% of waking time and sleep accounting for the greatest percentage of the 24-hour period (Table 7.3). According to the variation matrix (Table 7.4), LPA and sleep had the greatest co-dependence, followed by LPA with sedentary time and sedentary time with sleep, while MVPA showed the least co-dependence with all other behaviours. Additionally, MVPA was found to account for 85% of variance in an average 24 hours, despite only consisting of 3.5% of the day.

Table 7.3. Actual mean, geometric mean and percentage of 24-hours for each movement behaviour and sleep for the whole sample.

	SED	LPA	MVPA	SLEEP
Mean (min·day^{-1})	435.3	467.2	61.8	475.1
Geometric Mean (min·day^{-1})	436.0	472.8	50.2	481.0
Percentage of 24 hours (%)	30.3	32.8	3.5	33.4

Sedentary time (ST), light physical activity (LPA), moderate-to-vigorous physical activity (MVPA).

Table 7.4. Pair-wise log-ratio variation matrix for sedentary time, LPA, MVPA, and sleep for the whole sample.

	SED	LPA	MVPA	SLEEP
SED	-	0.021	-0.188	0.039
LPA	0.021	-	-0.067	0.006
MVPA	-0.188	-0.067	-	-0.103
SLEEP	0.039	0.006	-0.103	-

Sedentary time (SED), light physical activity (LPA), moderate-to-vigorous physical activity (MVPA).

Comparison between group geometric means indicated that boys engaged in similar volumes of sedentary time and sleep, but significantly more MVPA, relative to girls, regardless of disease status (Figure 7.1). Participants with T1D accrued significantly less time in MVPA and slept marginally less but engaged in significantly more LPA when compared to non-diabetic peers (Figure 7.2).

The average composition of movement behaviours for the whole sample, accounting for sex, age and disease status, was a significant determinant of PP and PWV, as demonstrated by the model p-value (Table 7.5). Additionally, sleep and sedentary time were negatively associated with PP and RMSSD ($p \leq 0.05$), respectively.

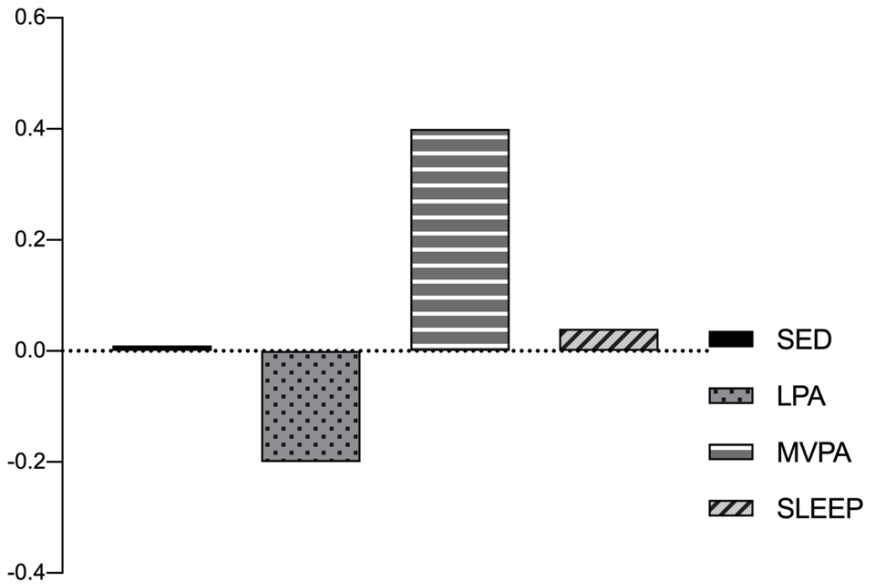


Figure 7.1. Compositional geometric mean bar plots comparing the compositional mean of boys relative to girls, regardless of disease status, for sedentary time (SED), light physical activity (LPA), moderate-to-vigorous physical activity (MVPA), and sleep.

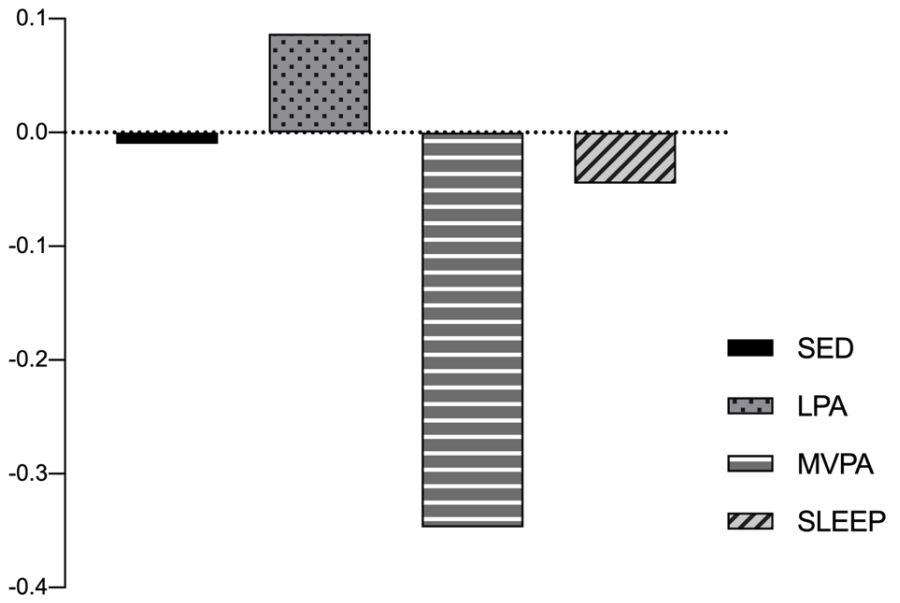


Figure 7.2. Compositional geometric mean bar plots comparing the compositional mean of type 1 diabetes participants compared to healthy children, regardless of sex, for sedentary time (SED), light physical activity (LPA), moderate-to-vigorous physical activity, and sleep.

The ternary heat maps presented in Figure 7.3 indicate that for children with T1D group those with a higher MVPA (Figure 7.3 a, b and c) but also a high sedentary time (Figure 7.3 a, c and d) were most likely to have a more favourable aPWV. In contrast, the non-diabetic sample showed less clear influences of movement behaviours for aPWV but indicated that a moderately high MVPA (Figure 7.4 a, b and d) and a high LPA (Figure 7.4 a, b and c) resulted in a lower aPWV, while those with a high sedentary time had a higher aPWV. Heat mapping for RMSSD in the diabetic sample (Figure 7.5) indicated that those with a high LPA (Figure 7.5 a, b and c) and moderately high MVPA (Figure 7.5 a, b and d) had a higher RMSSD. Conversely, in the non-diabetic sample LPA (Figure 7.6 a, b and c) and MVPA (Figure 6 a, b and d) positively influenced RMSSD, more so than sleep and sedentary time.

The greatest percentage changes, deemed significant according to specific SWC%, were observed with the substitution of 20 minutes from MVPA to the remaining behaviours, which was associated with an increased PP, PWV, and LF, and decreased HF in children with T1D. Increases in PWV were also found with the reallocation of 20 minutes of MVPA to LPA or sleep and in LF with MVPA to sleep, for healthy peers (Table 7.6).

Table 7.5. Compositional model of movement and sleep behaviours for each measure of arterial health in the overall sample, adjusted for age, sex, maturity and disease status.

	Model p	Y_{SED}	p	Y_{LPA}	p	Y_{MVPA}	p	Y_{SLEEP}	p
PP	0.06	3.31	0.32	6.87	0.11	-3.31	0.09	-6.87*	0.05
AIx	0.52	-0.74	0.74	1.74	0.54	1.08	0.40	-2.08	0.36
MAP	0.28	-1.97	0.35	-2.25	0.41	1.29	0.29	2.94	0.18
PWV	0.06	-0.19	0.34	0.14	0.56	-0.14	0.27	0.17	0.44
RMSSD	0.30	-28.94*	0.05	18.13	0.31	-3.06	0.70	13.87	0.35
LF	0.17	-2.25	0.73	-8.09	0.34	-1.76	0.64	12.10	0.09
HF	0.17	2.24	0.73	8.05	0.34	1.75	0.64	-12.04	0.09

Sequential rotated ILR modelling for each arterial health measure, adjusted for age, sex, maturation and disease status. Sedentary time (SED), light intensity physical activity (LPA), moderate-to-vigorous physical activity (MVPA), pulse pressure (PP), augmentation index (AIx), mean arterial pressure (MAP), pulse wave velocity (PWV), root mean square of successive standard deviations of NN intervals (RMSSD), low frequency (LF), high frequency (HF). Regression coefficients relate to the change in log-ratio for a given behaviour, relative to other behaviours. * A Significant association between movement behaviour and cardiovascular measure.

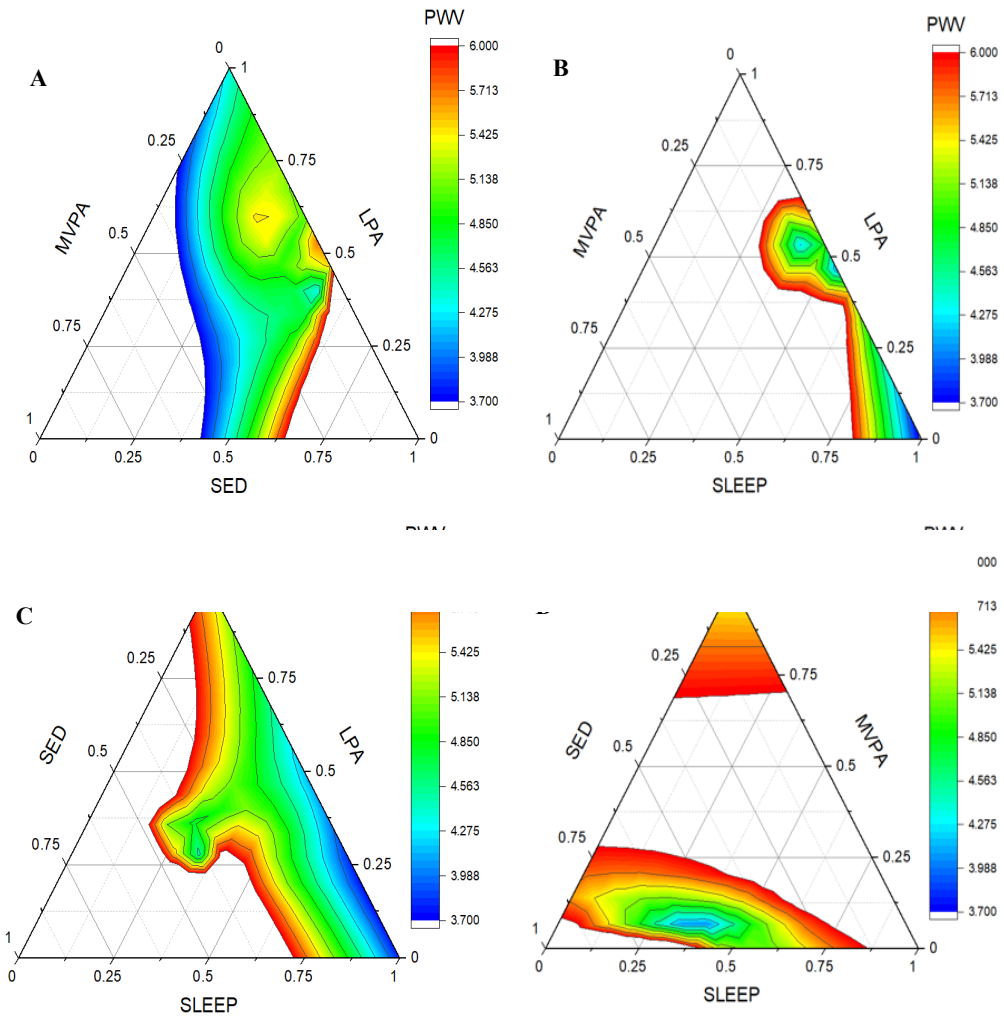


Figure 7.3. Ternary heat plots of aortic pulse wave velocity with different movement compositions in children with type 1 diabetes. Each ternary diagram focuses on one part of the four part composition (sedentary time (SED), light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA), and sleep), relative to the remaining behaviours.

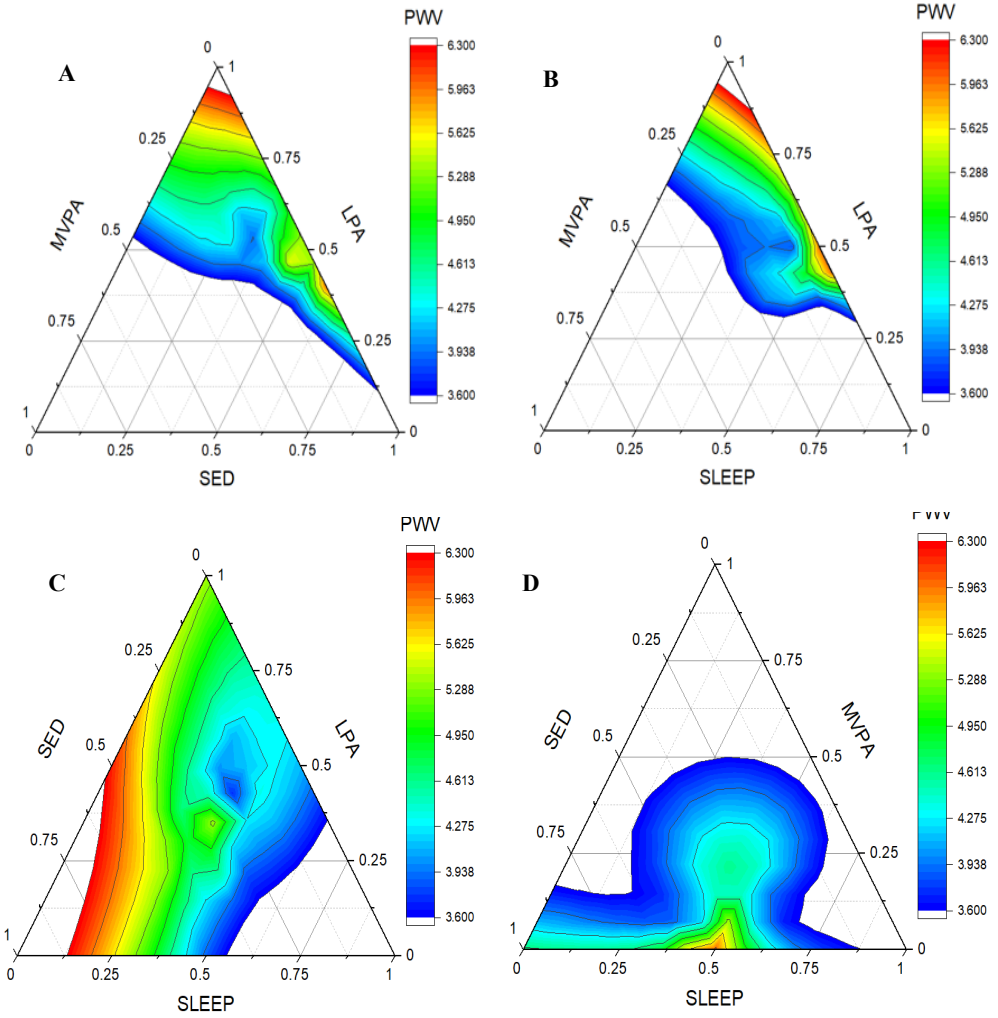


Figure 7.4. Ternary heat plots of aortic pulse wave velocity with different movement compositions in non-diabetic children. Each ternary diagram focuses on one part of the four part composition (sedentary time (SED), light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA), and sleep), relative to the remaining behaviours.

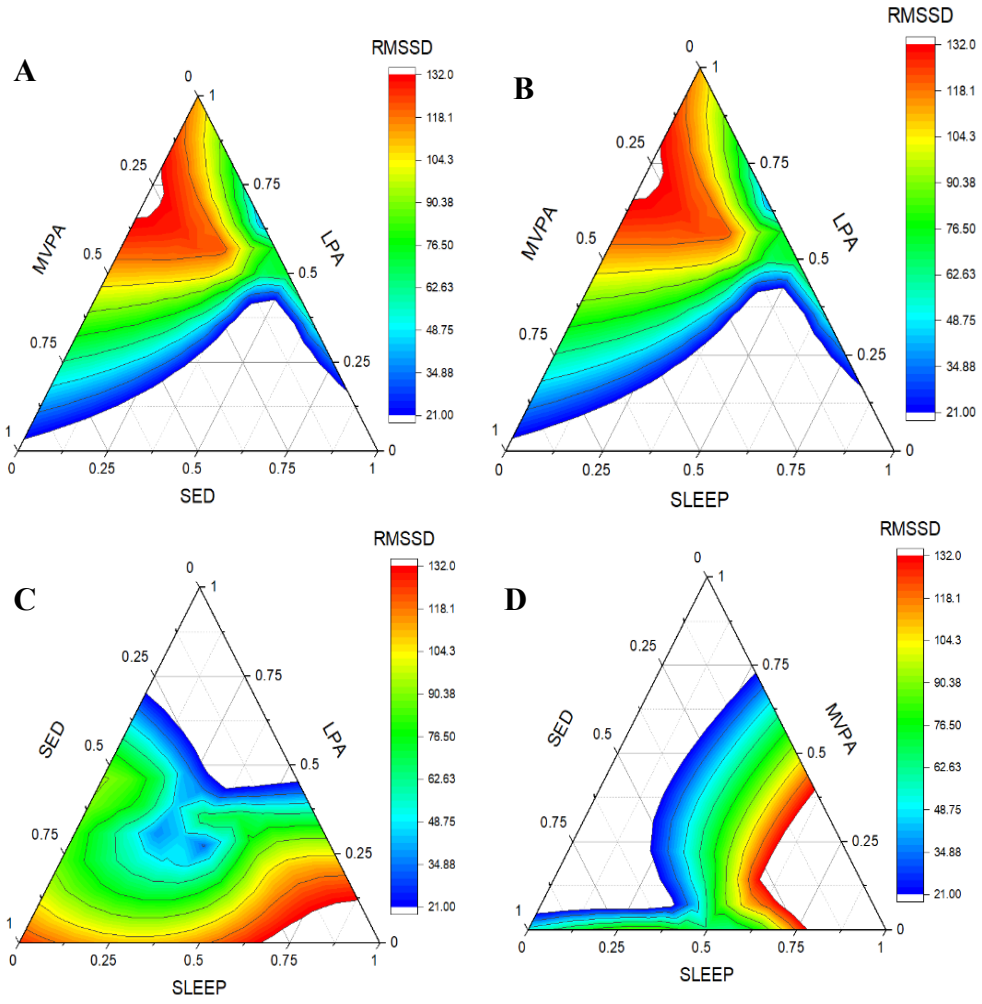


Figure 7.5. Ternary heat plots of root mean squared of successive differences (RMSSD) with different movement compositions in children with type 1 diabetes. Each ternary diagram focuses on one part of the four part composition (sedentary time (SED), light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA), and sleep), relative to the remaining behaviours.

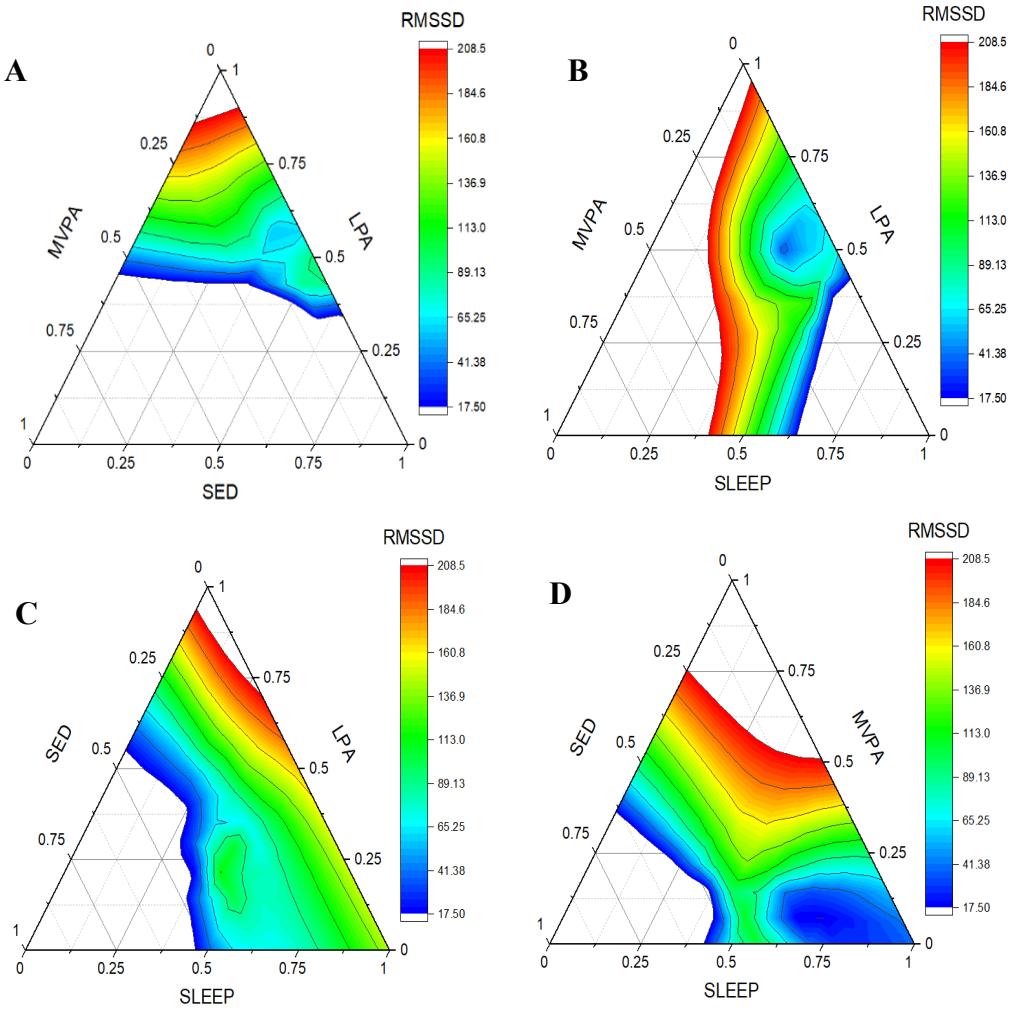


Figure 7.6. Ternary heat plots of root mean squared of successive differences (RMSSD) with different movement compositions in non-diabetic children. Each ternary diagram focuses on one part of the four part composition (sedentary time (SED), light physical activity (LPA) and moderate-to-vigorous physical activity (MVPA), and sleep), relative to the remaining behaviours.

Table 7.6. Effect of reallocating 20 minutes of time from the behaviour in columns to behaviours in rows for T1D and healthy participants, presented as percentage change.

	T1D				Control			
PP								
	SED	LPA	MVPA	Sleep	SED	LPA	MVPA	Sleep
SED	-	0.24	4.72*	1.67	-	0.19	2.95	1.66
LPA	-0.30	-	4.46*	1.41	-0.25	-	2.73	1.44
MVPA	-3.35	-3.08	-	-1.64	-2.48	-2.25	-	-0.78
Sleep	-1.67	-1.40	3.09	-	-1.66	-1.43	1.32	-
AIx								
SED	-	-2.58	2.22	0.86	-	-2.57	0.90	0.76
LPA	2.53	-	4.72	3.36	2.51	-	3.39	3.24
MVPA	-1.22	-3.83	-	-0.39	-0.56	-3.16	-	0.18
Sleep	-0.78	-3.38	1.42	-	-0.69	-3.28	0.19	-
PWV								
SED	-	-0.40	4.58*	-0.51	-	-0.46	2.68	-0.55
LPA	0.40	-	4.97*	-0.12	0.46	-	3.13*	-0.10
MVPA	-2.89*	-3.29*	-	-3.40*	-2.01	-2.48	-	-2.57
Sleep	0.50	0.10	5.07*	-	0.55	0.07	3.21*	-
RMSSD								
SED	-	-5.54	-6.27	-5.73	-	-5.11	-4.66	-5.10
LPA	5.65	-	-0.80	-0.26	5.21	-	0.38	-0.06
MVPA	5.60	-0.12	-	-0.31	4.55	-0.72	-	-0.71
Sleep	5.83	0.11	-0.62	-	5.20	-0.08	0.37	-
LF								
SED	-	-0.06	6.38*	-1.76	-	-0.03	3.68	-1.92
LPA	0.10	-	6.46*	-1.68	0.07	-	3.73	-1.87
MVPA	-3.95	-4.04	-	-5.73*	-2.71	-2.76	-	-4.65
Sleep	1.72	1.64	8.08*	-	1.88	1.83	5.54*	-
HF								
SED	-	0.19	-18.19*	4.99	-	0.08	-7.32	3.80
LPA	-0.29	-	-18.42*	4.76	-0.16	-	-7.43	3.69
MVPA	11.27	11.52	-	16.32*	5.38	5.50	-	9.23
Sleep	-4.89	-4.64	-23.02*	-	-3.73	-3.61	-11.01	-

Predicted effects were based on the mean composition. Adjusted for age, sex and maturation. Sedentary time (SED), light intensity physical activity (LPA), moderate-to-vigorous physical activity (MVPA), pulse pressure (PP), augmentation index (AIx), pulse wave velocity (PWV). * A percentage change greater than the SWC % for each arterial measure.

7.4 Discussion

The current study is the first to utilise compositional analysis to investigate the combined and individual effect of movement behaviours, relative to one another, on cardiovascular health for children with and without T1D. Overall, arterial stiffness markers were most influenced by the overall average movement composition, while autonomic function was most influenced by sedentary time and sleep, relative to all other behaviours. Reallocation of time from MVPA to any other behaviour was predicted to negatively affect all cardiovascular measures, independent of disease status, while allocating time to MVPA was consistently predicted to improve all outcome measures. Additionally, the same intensity of physical activity may be more potent for cardiovascular health in T1D children, compared to non-diabetic peers.

An aim of the present study was to explore how the composition of habitual movement behaviours changed over a month, and to subsequently explore how the postulated fluctuations affected arterial and autonomic health. However, no significant differences in composition were evident between weeks for any habitual behaviour, irrespective of sex or disease status. This lack of significant variation over time may support the ActivityStat hypothesis, which postulates that physical activity behaviours fluctuate around a mean, with extremes above or below this mean followed by reciprocal changes to maintain an overall balance (Gomersall, et al., 2013b). Conversely, studies have refuted the possible presence of an ActivityStat, with Dale et al. (2000) and Saunders et al. (2014) finding no compensatory increase in physical activity in children when school-based activities were restricted and sitting time increased. One potential reason for the equivocal findings regarding a compensatory effect in children may be the different time frames over which fluctuation and cycles of movement behaviours occur, both between and within individuals (Telford, et al., 2013). However, little research has sought to identify a typical time frame for such fluctuations in children and adolescents, likely due to accelerometer monitoring only relatively recently providing high-resolution acceleration data for durations longer than seven days (Arvidsson, et al., 2019). Future research is therefore warranted to investigate the possible fluctuations and repetitive cycles in behavioural patterns and how these influence key health outcomes.

Research in children with T1D and the general paediatric population has found that, individually, MVPA and LPA may slow the rate of premature stiffening and decline in the ANS function, likely due to the anti-inflammatory effects of physical activity and/or to the stabilisation of glycaemic extremes (Chen, et al., 2008; Trigona et al., 2010). Conversely, prolonged periods of sedentary time have been shown to increase insulin resistance and to be associated with a deleterious lipid profile (Sardinha, et al., 2008; Saunders, et al., 2014). However, compositional analyses indicates that when these behaviours are considered as a proportional whole, they do not necessarily replicate the influences observed on health outcomes when considered in isolation (Carson, et al., 2016; Chastin, et al., 2015). Specifically, the present study found that the average behaviour composition was significantly associated with indicators of arterial stiffening but not HRV indices, highlighting that neither age, sex, disease status or movement behaviours fully explain the variances in autonomic function. Given the potent effect of cardiorespiratory fitness on ANS function (Gutin, et al., 2005; Veijalainen, et al., 2019), future studies should consider its mediatory role in the relationship between movement and sleep behaviours and autonomic health.

An increased sedentary time, relative to other behaviours, was associated with lower central stiffening, although it had a significant deleterious effect on parasympathetic activity. Surprisingly, sedentary time was associated with a decreased central stiffening, which is discordant with previous research assessing the individual effects of sedentary time in children, which were unequivocally negative (Nettlefold, et al., 2019; Saunders, et al., 2014; Veijalainen, et al., 2019). However, our findings are congruent with Carson et al. (2016) who found sedentary time had a limited influence on cardiometabolic markers, including blood pressure and lipid profile. Discordant with previous research (Chimen, et al., 2012; Cuenca-García, Jago, Shield, & Burren, 2012), LPA was associated with an increased central stiffening. Indeed, previous research has shown that LPA in children with T1D is beneficial for health, potentially reducing insulin resistance (Chimen, et al., 2012; Cuenca-García, et al., 2012). In the current study, time in MVPA, but not LPA, showed more favourable trends for PP and aortic stiffness, which is in accord with previous research in people with T1D and indicates that intensity of physical activity may be key to preventing premature arterial stiffening (Trigona, et al., 2010). Indeed, in T1D, MVPA is hypothesised to improve insulin sensitivity which is particularly important for adolescents as puberty is

associated with an increase in insulin resistance, thereby increasing risk of glycaemic extremes and, in turn, stiffening and autonomic decline (Chen, et al., 2008; Chimen, et al., 2012; Leclair, et al., 2013). Taken together, these findings highlight the importance of exploring each behaviour as part of the daily movement continuum to identify important associations between daily behaviours and key health outcomes. Overall, this approach can aid future intervention development seeking to reduce disease burden and risk of future complications.

The greatest predicted change was found when reallocating time to and from MVPA for all cardiovascular measures, with the most significant predicted changes observed in those with T1D. The significant change in cardiovascular measures with changes in MVPA is in line with previous research which found that less time in MVPA was associated with less favourable central stiffening and autonomic function in children with (Nettlefold, et al., 2019; Oliveira, Barker, Wilkinson, et al., 2017; Veijalainen, et al., 2019) and without T1D (Chen, et al., 2008; Trigona, et al., 2010). Improvements in cardiovascular measures with increases in MVPA, at the expense of other behaviours, further reinforces the importance of this behaviour for the management of T1D, especially as physical activity levels typically decline with age (Farooq, et al., 2018), and are lower in T1D than their non-diabetic peers, irrespective of age (Valerio, et al., 2007). This therefore highlights the importance of meeting the recommended 60 minutes of MVPA per day (Chief Medical Officers, 2019), especially for children with T1D.

Discordant with Farabi et al. (2016) and Monzon et al. (2019), who found that deprived sleep was associated with poor glucose control and an increased risk of cardiovascular complications, the present study found that reallocating time in sleep to other behaviours was predicted to improve central stiffening and vagal tone. Specifically, the present findings indicate that reallocating 20 minutes of sleep to MVPA may significantly improve central stiffening and parasympathetic activity for children with T1D, thereby suggesting MVPA may be of equal, if not greater, importance than sleep. In addition, it is pertinent to note that the smaller changes from the reallocation of 20 minutes to and from LPA indicates that more than 20 minutes is likely necessary to elicit significant changes in cardiovascular health. Indeed, previous research in healthy children demonstrates that LPA can positively effect cardiometabolic and arterial

health (Haapala, et al., 2016; Poitras, et al., 2016; Stone, et al., 2009), and has been suggested to be an alternative target to MVPA (Poitras, et al., 2016). However, while LPA can positively influence health for children with T1D, the relative time that needs to be displaced is considerably larger than MVPA, and would most likely necessitate a reduction in sedentary time, given the importance of sleep and MVPA in this population. Furthermore, the difference in findings between LPA and MVPA further emphasise that the intensity, and not total volume, of physical activity may be key to preventing premature increases in arterial stiffening and decline in autonomic function in T1D.

A major strength of the present study was the use of compositional analyses to explore how all daily movement behaviours influence cardiovascular health in a paediatric clinical population, rather than exploring these behaviours in isolation. Additionally, the use of predictive modelling regarding the possible effect of reallocating time from one behaviour to another was a key novelty in those with T1D and could inform targets for future interventions in similar populations. Furthermore, the inclusion of 28 days of habitual movement behaviours allowed us to account for potential behavioural variations and more reliably explore the relationship between PA and health. However, this study is not without limitations. Specifically, compositional analyses models may be susceptible to outliers, therefore the relatively small sample size included may limit generalisability, with outliers more likely to influence model outcomes. It is also pertinent to note that the analysis was limited to the whole sample, as opposed to each individual group for disease status and sex. Furthermore, significant differences were evident in the maturity status of the participants, with healthy girls deemed pubertal, while all other remaining participants were pre-pubertal. This was statistically accounted for in the present study but future studies should consider the influence of maturity independently. Finally, while the predictive models provide valuable insight as to predictive change, they do not indicate whether the changes would be acute or chronic, nor how long the change in behaviour needs to be implemented in order for these changes to occur.

7.5 Conclusion

In conclusion, intensity, not just the overall volume, of physical activity is a key factor in reducing risk of premature negative changes in arterial health for children, with and without T1D. Secondly, reducing sedentary time may be key to minimising premature decline in autonomic control, thereby slowing progression of neuropathy for children with T1D. Moreover, increasing time in MVPA, by substituting 20 minutes from any other behaviour, has the potential to slow progression of autonomic decline and central arterial stiffening in children with T1D.

Chapter 8

Synthesis

Chapter 8: Synthesis

The importance of physical activity and sedentary time for cardiovascular health is well recognised, but their fluctuations and the relative importance of the volume and intensity of each component is less well understood. Consequently, the aim of this thesis was to explore the intra and inter-person fluctuations in physical activity and sedentary time to further elucidate the dose-response relationship with cardiovascular health in type 1 diabetes (T1D) and otherwise healthy populations. The current chapter will synthesise the present research, considering the findings of each study relative to the remaining studies, and discuss their strengths, weaknesses and implications as a whole.

8.1 General discussion

8.1.1 Cardiovascular Health and Movement Behaviour in Type 1 Diabetes

The children with T1D in Chapters 5, and 7 demonstrated an increased risk of cardiovascular disease (CVD), as indicated by a higher central stiffening (aortic pulse wave velocity (aPWV)), and decreased parasympathetic activity compared to their non-diabetic peers and to age-specific reference values (Thurn, et al., 2019). Aortic PWV is an independent prognostic indicator for CVD (Ben-Shlomo et al., 2014), with declines in autonomic function indicative of a progression towards diabetic autonomic neuropathy (DAN), a common long-term complication in this population (Vinik, et al., 2003). Progression of these CVD risk factors is proposed to be a consequence of persistent hyperglycaemia, as evidenced by an elevated glycated haemoglobin (HbA1c; American Diabetes Association, 2010; NICE, 2015). The poor glycaemic control evident in the current T1D participants, all of whom were above the recommended levels for HbA1c (NICE, 2015), is in accord with this contention.

The differences observed in cardiovascular measures between those with T1D and their non-diabetic peers may be attributable to differences in the participant's physical activity levels (Chapters 5 and 7) and composition of physical activity (Chapter 7). Indeed, T1D is typically associated with lower moderate-to-vigorous physical activity (MVPA; de Lima, et al., 2017) and prolonged periods of sedentary time (Czenczek-Lewandowska, Leszczak, Weres, et al., 2019), with inactivity (Riddell, et al., 2017) and long periods spent sedentary (Li et al., 2015a) well-established to be associated

with less favourable glycaemic control and deleterious effects on cardiovascular health (Valerio, et al., 2007). However, contrary to these earlier studies, those with T1D (Chapters 6 and 7) did not spend more time sedentary although they did accrue the majority of their physical activity at a lower intensity compared to their non-diabetic counterparts. Specifically, those with T1D demonstrated significantly greater volumes of light physical activity (LPA) and less MVPA in comparison to peers, independent of sex and maturation (Chapter 7). Accumulation of movement at a lower intensity according to disease status was further supported by a significantly more negative intensity gradient and lower average acceleration (Chapter 5) with no significant differences present for sedentary time or sleep (Chapter 7). These findings may therefore be indicative that LPA is less beneficial for health, in accord with the findings of Carson et al. (2019), suggesting that in order for beneficial health effects to be manifest, considerably more time must be spent in LPA. Given the time-poor nature of modern society, these findings therefore question the hypothesis that LPA may represent a more appropriate and feasible target through which to improve public health (Füzéki, et al., 2017; Salmon, 2010). However, it is pertinent to note that the majority of conclusions drawn in the literature, and those in Chapters 4 and 5, are based on up to seven days of physical activity. Given the findings in Chapter 6, this short time-frame may fail to accurately reflect important behavioural variation over time. Indeed, cardiovascular health markers reflect long-term processes and therefore their relatively weak association with an arbitrary seven-day period of physical activity should perhaps be anticipated; given the stronger association between markers of cardiovascular health and physical activity metrics when a 28-day measurement period was used (Chapter 6), future research should consider using longer measurement periods.

Sex has been reported to be a key determinant of disease progression in those with T1D, with females characterised by a less favourable HbA1c, irrespective of age and maturation (Samuelsson et al., 2016). The sex-related differences in blood glucose control have been previously postulated to be attributed, at least in part, to less stringent disease management or avoidance of intensive management with insulin for fear of weight gain (Polonsky et al., 1994). Such sex differences in disease experience may also be exacerbated by the concomitant differences in physical activity and sedentary time typically observed between sexes, with girls with T1D reported to

accrue less physical activity compared to boys . Specifically, the current thesis found LPA and MVPA to differ according to sex (Chapter 7), with girls found to accrue less MVPA but more LPA than boys. These sex-related differences are similar to those typically observed in otherwise healthy children (Farooq, et al., 2018), as well as those found in Chapters 4 and 7. However, an important mediator and/or moderator of these sex differences is maturation, with a decline in MVPA and a concomitant increase in sedentary time known to occur with progression of adolescence (Farooq, et al., 2018).

Whilst the influence of maturation in T1D is well-established (Chowdhury, 2015), few studies have sought to account for the influence of maturation in the relationship of physical activity and cardiovascular measures. Nonetheless, the decline in glycaemic control often observed in T1D pubertal and post-pubertal adolescents has been attributed to the reduced volume and intensity of physical activity typical of adolescents (Chimen, et al., 2012; Kennedy et al., 2013). Consequently, the decline in glycaemic control and increase in blood glucose variability is associated with an increased risk of premature changes in autonomic (Jaiswal et al., 2018) and vascular health (Obermannova, et al., 2017), and subsequently risk of CVD. Taken together, girls with T1D are not only at risk of being less active than their male peers, but are subjected to the negative associations of extremes in glycaemic control and increases in adiposity on vascular (Pandit, Khadilkar, Chiplonkar, Khadilkar, & Kinare, 2014) and autonomic health (Gutin, et al., 2005). These associations may highlight, and possibly explain, why women, irrespective of age, with T1D are at a significantly increased risk of CVD in comparison to men (Soedamah-Muthu et al., 2006). Therefore, targeting inactivity and intensity of movement for children and adolescent with T1D in a preventative manner, particularly for girls, should be a key area of focus for future research.

8.1.2 Measurement Duration and Data-Driven Metrics

Seven-day measurement periods are widely adopted in order to obtain a valid and reliable insight to children and adult's habitual physical activity levels and patterns of accrual (Barreira, et al., 2015; Cain, et al., 2013; Matthews, et al., 2012; Sasaki, et al., 2018; Trost, et al., 2000). However, it has recently been questioned as to whether seven days is sufficient to appropriately reflect potentially meaningful fluctuations in

habitual physical activity. Indeed, routines, type of day (Atkin, et al., 2016; O'Connell, et al., 2014) and the natural variations in physical activity behaviour (Shang, et al., 2018) are well known to influence physical activity levels but the degree of week-to-week fluctuation within an individual remains largely unknown. Such fluctuations in stimuli to physiological systems may have important implications for long-term health.

According to the findings of Chapter 7, daily movement compositions demonstrate little fluctuation across 28-days in children with or without T1D. Similar findings were reported in Chapter 6 when novel metrics of physical activity were considered. This lack of variation may, therefore, be indicative of an ActivityStat which serves to maintain a relatively constant mean level of physical activity, with deviations from the set-point subsequently compensated for (Gomersall, et al., 2013b). Importantly, the presence of an ActivityStat may lead to erroneous conclusions regarding the validity and reliability of a seven-day monitoring period with additional insight able to be elucidated using longer measurement durations. This contention is supported by the findings in Chapter 6, which revealed that, despite the minimal variations, physical activity levels derived from 28 days were more strongly associated with health than those obtained from seven days.

In addition to accelerometer measurement durations, this thesis highlights the importance of moving towards data-driven physical activity metrics, which are based on all available movement data, to improve understanding of how intensity and volume of movement can influence arterial stiffening and autonomic function. Specifically, Chapters 5 and 6 demonstrated that the use of the intensity gradient revealed that intensity, not just overall volume, of movement was key to prevent declines in arterial and autonomic health. Importantly, these findings suggest that the volume of movement is important for health, but possibly to a lesser extent than intensity, which is congruent with previous research which found that MVPA was more potent than LPA for the promotion of vascular (Laursen, et al., 2015) and autonomic health (Chen, et al., 2008). This difference could be attributed to MVPA accounting for less than 4% of a 24-hour day, in comparison to LPA which accounts for a substantially larger proportion, thus larger volumes of LPA are needed to confer similar health benefits. Moreover, the use of the intensity gradient in Chapter 6 revealed possibly meaningful

behavioural variations not identified by volume metrics when applied to a longer monitoring duration. Therefore, it appears that data-driven metrics better describe and quantify total movement and its intensity, facilitating a greater understanding of habitual behaviours which is key to understanding their influence on health. Indeed, utilising such metrics, which do not use thresholds nor data segmenting techniques, as devised by Rowlands et al. (Rowlands, et al., 2018), creates more ecologically valid and easily comparable data. Subsequently, these properties aid inter-study comparability and thus enable the aggregation of numerous studies, thereby addressing issues associated with small sample sizes which hinder the identification of influential dose-response relationships (Rowlands, et al., 2018).

8.2 Strengths and Weaknesses

A significant strength of the present thesis was the inclusion of two sub-clinical indicators of cardiovascular health to give an estimation of CVD risk (Reference Values for Arterial Stiffness Collaboration, 2010; Reusz, et al., 2010). Employing markers such as arterial stiffening and autonomic control alongside conventional cardiometabolic risk indicators may provide greater insight as to the structural and function changes in cardiovascular health (London &Cohn, 2002; Mäki-Petäjä, et al., 2016; Thayer &Lane, 2007). Indeed, arterial stiffness is an independent, pre-clinical prognostic marker for risk of developing atherosclerosis, hypertension and, ultimately, CVD (London &Cohn, 2002), providing an understanding of possible structural and compliance changes in the vasculature prior to the onset of significant increases in BP (Cecelja &Chowienczyk, 2012). In addition to arterial stiffness, measures of cardiac autonomic control are of prognostic value in the prediction of the development of hypertension, neuropathy, CVD and mortality (Palatini &Julius, 2009; Thayer &Lane, 2007). Therefore, by combining arterial stiffness (Chapter 4) and autonomic control (Chapters 5, 6 and 7), in addition to BMI as a marker of adiposity, a holistic assessment of current cardiovascular health was obtained (Juonala, et al., 2011; Mäki-Petäjä, et al., 2016).

Despite numerous strengths regarding the measures of cardiovascular health, and the manner in which they were assessed in this thesis, it is important to acknowledge certain limitations. Specifically, while aPWV is a gold standard assessment of central

stiffening (Laurent, et al., 2006), the oscillometric method by which this was obtained may be less sensitive than ultrasound, transducers or MRI derived measures (Parikh, et al., 2016; Savant, et al., 2014). Furthermore, oscillometric measures are highly influenced by even subtle movements, including talking or swallowing (Van Bortel, et al., 2012). Therefore, assessing aPWV in this manner is prone to error, although this was minimised by a consistent operator procedure (Thurn, et al., 2019; Wilkinson, et al., 2019). It is also pertinent to note the use of short-term ECG recordings during a limited range of controlled manoeuvres to derive indices of heart rate variability may present limitations. Specifically, whilst short-term measures have previously been validated (European Society of cardiology, 1996), they do not provide an insight as to the HR response and variability during free-living conditions (Gaskill, et al., 2001; Williams &Lopes, 2002). Therefore, to improve generalisability, future studies should seek to obtain concomitant ECG and habitual physical activity measures to further elucidate the dose-response relationship between these parameters. Additionally, while the validity of BMI has been questioned due to its inability to distinguish fat-free mass and the possible penalisation of heavier, more mature participants, this measure was considered an adequate indicator of adiposity due to its ease of measurement and its wide-spread use, thereby facilitating inter-study comparisons (Nuttall, 2015). Future research could, however, endeavour to obtain fat-free mass using dual x-ray absorptiometry or using skin-fold thickness (Rodríguez et al., 2005; Slaughter et al., 1988). Additionally, in order to provide a greater understanding of metabolic health and control, future research should include quantification of inflammatory markers (Willerson &Ridker, 2004) and blood lipids for all populations (Arsenault, et al., 2011).

Another major strength of Chapters 5, 6 and 7 was the use of the raw acceleration data to derive movement behaviours. The use of raw tri-axial acceleration data to produce omni-direction gravitational equivalents (*mg*) overcomes specific compression methods used by different brands of accelerometers (de Almeida-Mendes, et al., 2018), such as the ActiGraph and ActivPal. Subsequently, the use of raw acceleration data supports inter-study and inter-accelerometer comparability, as well as enabling the quantification of the intensity of movement from population specific acceleration thresholds (Rowlands, 2018). Indeed, raw acceleration thresholds can be calculated for each population according to resting metabolic rate (RMR), thereby further

facilitating inter-study comparisons (Migueles, et al., 2019). However, a limitation associated with the current thesis was the use of acceleration thresholds calculated using an average RMR for children and adults (Chapters 5, 6 and 7), which may have caused some misclassification of physical activity intensities (Byrne, et al., 2005; Mendes Mde, et al., 2018). Specifically, RMR can vary significantly between individuals, thus future research should aim to use individualised thresholds calculated according to participant-specific RMR (Byrne, et al., 2005).

A limitation to the synthesis and interpretation of the present studies is that two types of accelerometer were utilised; a hip-worn ActiGraph GT3X (Chapter 4) and a wrist-worn GENEActiv (Chapters 5, 6 and 7). Consequently, the use of different monitors and wear-locations could have hindered inter-study comparisons due to the differences in movement obtained between wear-locations (Fairclough, et al., 2016; Rosenberger, et al., 2016). Specifically, studies have explored the comparability of movement outputs between hip- and wrist-worn accelerometers, finding hip-worn monitors to be associated with poorer compliance (Fairclough, et al., 2016; McLellan, et al., 2018; Scott, et al., 2017) and an underestimation of upper body movement (Fairclough, et al., 2016; McLellan, et al., 2018). In contrast, wrist-worn accelerometers have been demonstrated to under-estimate lower body movements due to a lack of arm movement in certain activities such as cycling (Lynch, et al., 2019). Therefore, comparisons of physical activities between studies are made with caution. In accord with previous findings, the hip-worn protocol adopted in Chapter 4 was associated with relatively poor compliance, thereby further limiting potential conclusions and generalisability.

The lack of age- and sex-matched controls in Chapters 5 and 7 is a major limitation of the present thesis, with the influence of disease status on age-related changes having to be interpreted with caution. Furthermore, HbA1c was included in Chapters 5 and 7 to provide an indication of blood glucose control for children with T1D but not the control population, precluding the exploration of the relative influence on cardiovascular outcomes. Additionally, the HbA1c utilised was obtained from most recent clinic testing, subsequently, this may have under- or over-estimated actual blood glucose regulation at the time of the physical activity assessment. Furthermore, the only measure of glycaemic control obtained was HbA1c, which can only provide an indication of mean control over the previous six weeks, thereby failing to account for

extremes during this period (Heinemann &Freckmann, 2015). Consequently, physiologically meaningful extremes may have occurred but may not have significantly influenced this measure. Therefore, inferences as to the effect of glycaemic variability on cardiovascular health in the present populations (Chapters 5 and 7) remains speculative. Consequently, future research should aim to include a more sensitive measure of glycaemic control to understand the influence of extremes on these measures, in addition to how movement behaviours and variation influences such control.

Finally, the generalisability of thesis findings may have been limited by the relatively small sample sizes in Chapters 5, 6 and 7. Indeed, it should be acknowledged that the adults included in Chapter 6 were more active than previously reported in the general population (National Health Service Digital, 2020), with some attaining the recommended weekly volume of physical activity each day (Chief Medical Officers, 2019). Additionally, this sample demonstrated a higher $\dot{V}O_{2peak}$ than expected for age and sex norms. These factors may therefore have altered the observed relationship between physical activity and cardiovascular health (Armstrong, et al., 1991; Kaminsky, et al., 2015). Consequently, the conclusions drawn from this sample are more applicable to active populations. Thus, future research should seek to explore the associations of movement behaviours with cardiovascular health in samples including a range of physical activity levels, to enhance generalisability.

8.3 Future Research Directions

The present thesis has highlighted a number of areas that warrant further investigation to better understand the nuanced relationship between physical activity, sedentary time and cardiovascular health and the influence of disease status, age, sex and maturation on these relationships.

8.8.1 Importance of Targeting Inactivity in Type 1 Diabetes

Adolescent girls with T1D are highlighted in Chapters 5 and 7 as a key target population for future interventions as they demonstrated the greatest risk of CVD when compared to the non-diabetic paediatric populations (Chapters 4, 5, 6 and 7). This is in accord with Soedamah-Muthu et al. (2006), which reported that adolescent and adult

females with T1D are at a significantly increased risk of CVD in comparison to their male counterparts. This increased risk is proposed to be a result of the loss of the cardioprotective effect found in the general female population (Soedamah-Muthu, et al., 2006), although the mechanisms for this loss are poorly understood as the increased risk does not appear to be explained by conventional cardiovascular risk factors (Colhoun, Rubens, Underwood, & Fuller, 2000; Colhoun, et al., 2001). It has therefore been suggested that it may be related to less stringent condition management in females (Larkin et al., 2010; Schofield, et al., 2019), potentially due to fears of weight gain with intensive insulin management (Polonsky, et al., 1994). However, it is also proposed that this may reflect a greater tendency to be physically inactive in females (Silva et al., 2019), compounded by an increased risk of adiposity due to earlier declines in RMR (Poehlman et al., 1993). The potential role of inactivity may be supported by concurrent declines in activity and increases in CVD risk, with adolescence associated with a greater decline in MVPA in girls relative to boys (Farooq, et al., 2018; Telford, Telford, Olive, Cochrane, & Davey, 2016). The findings of this thesis corroborate these suggestions, with girls with T1D, who were predominantly pubertal, found to accrue a lower volume of movement and at lower intensities compared to their non-diabetic and male counterparts (Chapters 5 and 7). Therefore, further work is urgently required that identifies appropriate interventions to promote physical activity and decrease sedentary time in the female T1D population. In order to develop palatable, effective and, importantly, sustainable interventions, it is vital that a co-design strategy is utilised which employs a user-centred approach to elucidate the key population's specific barriers, facilitators and preferences.

Children diagnosed with T1D are known to have a honeymoon period of residual beta cell production of endogenous insulin (Abdul-Rasoul, Habib, & Al-Khouly, 2006), in addition to a temporary 'remission' period of beta cell recovery often occurring with the commencement of exogenous insulin (Fonolleda, Murillo, Vázquez, Bel, & Vives-Pi, 2017). This honeymoon period is associated with better glucose control and a decreased need for exogenous insulin as a result of the prolonged endogenous insulin production, proposed to act more efficiently on glycaemic control (Abdul-Rasoul, et al., 2006). Techniques such as intensive glycaemic control and pharmacological intervention are employed to maintain this honeymoon period as long as possible, not least to decrease disease burden (Abdul-Rasoul, et al., 2006). In adults, MVPA, and

specifically its anti-inflammatory characteristics, are proposed to reduce the autoimmune destruction of beta cells and significantly extend the honeymoon period (Chetan et al., 2019). In newly diagnosed, late-onset individuals, an intervention aiming to increase MVPA for one year found improvements in insulin sensitivity and glycaemic control, with a lower requirement for insulin and reduced disease burden reported. However, the mechanism underpinning these beneficial changes was unclear due to limited evidence of changes to beta cell production of c-peptide (Lascar, et al., 2013; Narendran et al., 2017). Nonetheless, these previous interventions highlight the importance of physical activity. Indeed, whilst differences are present in the pathophysiology of child and late-onset T1D, with child-onset being linked to an increased rate of beta cell decline (Casu et al., 2020), there is a need to understand the influences of physical activity on this paediatric honeymoon period. Specifically, future research should explore the possibility of targeting inactivity during this short period to prolong the benefits, with the aim of reducing the risk of long-term complications (Abdul-Rasoul, et al., 2006), especially given that the long-term effects of many of the current pharmacological treatments remain to be elucidated (Dahl-Jørgensen, Larsen, & Hanssen, 2005).

8.3.2 Quantification of Movement Behaviours

Whilst limited variation was observed between the four weeks monitored in Chapters 6 and 7, the lack of variation was proposed to be an indication of an intra- and inter-day compensatory effect. However, there remains little experimental evidence to support, or refute, the presence of an ActivityStat (Gomersall, et al., 2013b), with the majority of conclusions to date reliant on cross-sectional studies, and therefore correlations that do not allow conclusions to be drawn regarding cause and effect (Gomersall, et al., 2013b). Therefore, future work is warranted that explicitly seeks to manipulate both the volume and intensity of physical activity, as well as the timings of these manipulations, to determine the validity of the ActivityStat hypothesis. This work is highly important as the presence of an ActivityStat has significant implications for the design and implementation of successful physical activity interventions (Ridgers, et al., 2014).

Future research should also focus on the pattern of daily fluctuations in movement behaviours, applying sophisticated analyses techniques, such as time series analysis, which is often used in forecasting and economics (Jebb &Tay, 2016). Specifically, exploring possible trends and cycles on a day-to-day basis could allow for the identification of clinically meaningful variations, and provide more conclusive evidence regarding the potential compensation of movement behaviours. In addition, the reasons for compensatory behaviours should be further explored to enhance our understanding of why these effects and fluctuations occur, and potentially why some individuals compensate for movement while others do not. In order to address these questions, large population level data sets are needed, such as those continuously collected by commercially available activity tracking devices (i.e. Garmin, Fitbit or Apple; Sanders et al., 2018).

8.3.3 Glycaemic Variation and Movement Behaviours

The limited understanding of glycaemic variation in this thesis (Chapters 5 and 7) highlights a need to improve our knowledge of how this control and movement behaviours interact to identify targets to reduce the risk of CVD. Increases in the use of continuous glucose monitoring (CGM) in T1D (Danne et al., 2017), in particular interstitial fluid monitoring or flash monitoring, represents an exciting opportunity for researchers to understand the influences of physical activity on glycaemic variation and identify targets to improve disease burden for this population (Massa et al., 2018). Indeed, flash monitoring is becoming more wide-spread, with large proportions of the paediatric T1D population in the UK now benefiting from these devices to monitor their glycaemic control (Ferguson et al., 2020). Monitoring of this kind provides an in-depth understanding of variations in glycaemic control compared to more blunt measures such as HbA1c (Evans, 2016). Whilst HbA1c can give a good indication of mean glycaemic control over the previous six weeks, this measure does not provide specific detail of glucose fluctuation and can be influenced by extremes in blood glucose, resulting in possible misrepresentation of good control (Heinemann &Freckmann, 2015). However, more real-time monitoring can overcome these issues and can be combined with specific information regarding movement behaviours to gain an understanding of how such variations create acute changes in blood glucose. Such concomitant measures would enable subtle variations in behaviours according to

sex and maturation and their different influences on glycaemic variation to be explored. Pivotal to advancing our understanding of these nuanced behaviours and their relationships with health is the utilisation of more appropriate and sensitive analysis techniques, such as compositional analysis and predictive modelling.

8.4 Conclusions

In conclusion, this thesis investigated the influence of physical activity and sedentary time on markers of cardiovascular disease risk, with the application of emerging methodologies and metrics. The intensity of physical activity was identified as being more influential than volume, irrespective of disease status. Specifically, this thesis found that MVPA was a more potent stimulus for cardiovascular health than the remaining movement behaviours. Furthermore, physical activity metrics derived from 28 days of accelerometer data were more strongly associated with vascular health, despite minimal fluctuations in behaviour. Therefore, in order to improve our understanding of the dose-response between physical activity and health, future research should consider using accelerometry measurement periods longer than seven days. Finally, targeting inactivity, lower intensities of movement and sedentary time for those with T1D may be key for reducing the risk of CVD in this population. In particular, future research should seek to specifically target adolescent girls with T1D to mitigate the greater risk of CVD as adults.

Chapter 9

References

Chapter 9: References

AADLAND, E, ANDERSEN, LB, SKREDE, T, EKELUND, U, ANDERSSEN, SA, & RESALAND, GK. (2017). Reproducibility of objectively measured physical activity and sedentary time over two seasons in children; comparing a day-by-day and a week-by-week approach. *PLoS One, 12*(12), p e0189304. doi: 10.1371/journal.pone.0189304.

ABDUL-RASOUL, M, HABIB, H, & AL-KHOULY, M. (2006). 'The honeymoon phase' in children with type 1 diabetes mellitus: Frequency, duration, and influential factors. *Pediatr Diabetes, 7*(2)doi: 10.1111/j.1399-543X.2006.00155.x.

ABHISHEKH, H, NISARGA, P, KISAN, R, MEGHANA, A, CHANDRAN, S, TRICHUR RAJU, N, et al. (2013). Influence of age and gender on autonomic regulation of heart. *J Clin Monit Comput, 27*(3)doi: 10.1007/s10877-012-9424-3.

ACHARYA, R, JOSEPH, P, KANNATHAL, N, LIM, C, & SURI, J. (2006). Heart rate variability: A review. *Med Biol Eng Comput, 44*(12), pp. 1031-1051. doi: 10.1007/s11517-006-0119-0.

ADJI, A, O'ROURKE, M, & NAMASIVAYAM, M. (2011). Arterial stiffness, its assessment, prognostic value, and implications for treatment. *Am J Hypertens, 24*(1)doi: 10.1038/ajh.2010.192.

AGGIO, D, SMITH, L, & HAMER, H. (2015). Effects of reallocating time in different activity intensities on health and fitness: A cross sectional study. [OriginalPaper]. *Int J Behav Nutr Phy, 12*(1), pp. 1-7. doi: doi:10.1186/s12966-015-0249-6.

AHIMASTOS, A, FORMOSA, M, DART, A, & KINGWELL, B. (2003). Gender differences in large artery stiffness pre- and post puberty. *J Clin Endocrinol Metab, 88*(11)doi: 10.1210/jc.2003-030722.

AHMADI-ABHARI, S, SABIA, S, SHIPLEY, M, KIVIMÄKI, M, SINGH-MANOUX, A, TABAK, A, et al. (2017). Physical activity, sedentary behavior, and long-term changes in aortic stiffness: The whitehall ii study. [research-article]. *J Am Heart Assoc, 6*(8)doi: JAH32327.

AITCHISON, J. (1982). The statistical analysis of compositional data. *J R Star Soc B, 44*(2), pp. 139-177.

AL-MALLAH, MH, SAKR, S, & AL-QUNAIBET, A. (2018). Cardiorespiratory fitness and cardiovascular disease prevention: An update. *Curr Atheroscler Rep, 20*(1), p 1. doi: 10.1007/s11883-018-0711-4.

ALTENBURG, T, DE-NIET, M, VERLOIGNE, M, DE BOURDEAUDHUIJ, I, ANDROUTSOS, O, MANIOS, Y, et al. (2015). Occurrence and duration of various operational definitions of sedentary bouts and cross-sectional associations with cardiometabolic health indicators: The energy-project. *Prev Med, 71*doi: 10.1016/j.ypmed.2014.12.015.

ALVES, AJ, VIANA, JL, CAVALCANTE, SL, OLIVEIRA, NL, DUARTE, JA, MOTA, J, et al. (2016). Physical activity in primary and secondary prevention of cardiovascular disease: Overview updated. *World J Cardiol, 8*(10), pp. 575-583. doi: 10.4330/wjc.v8.i10.575.

AMAN, J, SKINNER, TC, DE BEAUFORT, CE, SWIFT, PG, AANSTOOT, HJ, & CAMERON, F. (2009). 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. *Pediatr Diabetes, 10*(4), pp. 234-239. doi: 10.1111/j.1399-5448.2008.00495.x.

AMERICAN DIABETES ASSOCIATION. (2010). Diagnosis and classification of diabetes mellitus. *Diabetes Care, 33*(Suppl 1), pp. S62-69. doi: 10.2337/dc10-S062.

AMERICAN THORACIC SOCIETY. (2003). Ats/accp statement on cardiopulmonary exercise testing. *Am J Respir Crit Care Med, 167*(2), pp. 211-277. doi: 10.1164/rccm.167.2.211.

ANANEY, O, MCLOUGHLIN, B, LEONARD, A, MAHER, L, GAFFNEY, P, BORAN, G, et al. (2015). Inverse relationship between physical activity, adiposity, and arterial stiffness in healthy middle-aged subjects. [research-article]. *J Phys Activ Health, 12*(12)doi: 10.1123/jpah.2014-0395.

ANDERSEN, LB, HARRO, M, SARDINHA, LB, FROBERG, K, EKELUND, U, BRAGE, S, et al. (2006). Physical activity and clustered cardiovascular risk in children: A cross-sectional study (the european youth heart study). *Lancet, 368*(9532), pp. 299-304. doi: 10.1016/s0140-6736(06)69075-2.

ANDERSON, J, COUPER, J, MPUNDU-KAAMBWA, C, GILES, L, GENT, R, COPPIN, B, et al. (2016). An extra 1,000 steps per day relates to improved cardiovascular health in children with type 1 diabetes. *Diabetes Care, 39*(8), pp. e108-109.

ARMSTONG, N, & MCNARRY, M. (2016). Aerobic fitness and trainability in healthy youth: Gaps in our knowledge. *Pediatr Exerc Sci, 28*(2)doi: 10.1123/pes.2015-0251.

ARMSTRONG, A, WILLIAMS, J, BALDING, J, GENTLE, P, & KIRBY, B. (1991). The peak oxygen uptake of british children with reference to age, sex and sexual maturity. [OriginalPaper]. *Eur J Appl Physiol, 62*(5), pp. 369-375. doi: doi:10.1007/BF00634975.

ARMSTRONG, N, & WELSMAN, J. (2019). Multilevel allometric modelling of maximal stroke volume and peak oxygen uptake in 11-13-year-olds. *Eur J Appl Physiol, 119*(11-12)doi: 10.1007/s00421-019-04241-3.

ARMSTRONG, N, WELSMAN, J, & WINSLEY, R. (1996). Is peak vo2 a maximal index of children's aerobic fitness? *Int J Sports Med, 17*(5)doi: 10.1055/s-2007-972860.

ARSENAULT, BJ, BOEKHOLDT, SM, & KASTELEIN, JJ. (2011). Lipid parameters for measuring risk of cardiovascular disease. *Nat Rev Cardiol, 8*(4), pp. 197-206. doi: 10.1038/nrcardio.2010.223.

ARVIDSSON, D, FRIDOLFSSON, J, & BÖRJESSON, M. (2019). Measurement of physical activity in clinical practice using accelerometers. *J Intern Med, 286*(2)doi: 10.1111/joim.12908.

ASHOR, AW, LARA, J, SIERVO, M, CELIS-MORALES, C, & MATHERS, JC. (2014). Effects of exercise modalities on arterial stiffness and wave reflection: A systematic review and meta-analysis of randomized controlled trials. *PLoS One, 9*(10)doi: 10.1371/journal.pone.0110034.

ÅSTRAND, P. (1952). *Experimental studies of physical working capacity in relation to sex and age*: Munksgaard, E.

ASTRUP, AS, TARNOW, L, ROSSING, P, HANSEN, BV, HILSTED, J, & PARVING, HH. (2006). Cardiac autonomic neuropathy predicts cardiovascular morbidity and mortality in type 1 diabetic patients with diabetic nephropathy. *Diabetes Care, 29*(2), pp. 334-339.

ATKIN, AJ, SHARP, SJ, HARRISON, F, BRAGE, S, & VAN SLUIJS, EM. (2016). Seasonal variation in children's physical activity and sedentary time. *Med Sci Sports Exerc, 48*(3), pp. 449-456. doi: 10.1249/mss.0000000000000786.

ATKINSON, G, & NEVILL, AM. (1998). Statistical methods for assessing measurement error reliability in variables relevant to sports medicine. *Sports Med, 26*(4)doi: 10.2165/00007256-199826040-00002.
BAGGETT, CD, STEVENS, J, CATELLIER, DJ, EVENSON, KR, MCMURRAY, RG, HE, K, et al. (2010). Compensation or displacement of physical activity in middle school girls: The trial of activity for adolescent girls. *Int J Obes (Lond), 34*(7), pp. 1193-1199. doi: 10.1038/ijo.2010.31.
BAILEY, B, CHARMAN, S, PLOETZ, T, SAVORY, L, & KERR, C. (2016). Associations between prolonged sedentary time and breaks in sedentary time with cardiometabolic risk in 10–14-year-old children: The happy study. [research-article]. *J Sport Sci, 35*(22), pp. 2164-2171. doi: 10.1080/02640414.2016.1260150.
BANKENAHALLY, R, & KROVVIDI, H. (2019). Autonomic nervous system: Anatomy, physiology, and relevance in anaesthesia and critical care medicine. *BJA Education, 16*(11), pp. 381-387. doi: 10.1093/bjaed/mkw011.
BANKENAHALLY, R, ST6 ANAESTHESIA, RHH, Dudley, UK, KROVVIDI, H, & CONSULTANT NEUROANAESTHETIST, QEH, Edgbaston, Birmingham B15 2TH, UK. (2019). Autonomic nervous system: Anatomy, physiology, and relevance in anaesthesia and critical care medicine. *BJA Education, 16*(11), pp. 381-387. doi: 10.1093/bjaed/mkw011.
BARKER, A, WILLIAMS, C, JONES, A, & ARMSTRONG, N. (2011). Establishing maximal oxygen uptake in young people during a ramp cycle test to exhaustion. *Br J Sports Med, 45*(6)doi: 10.1136/bjsm.2009.063180.
BARKER, J, SMITH BYRNE, K, DOHERTY, A, FOSTER, C, RAHIMI, K, RAMAKRISHNAN, R, et al. (2019). Physical activity of uk adults with chronic disease: Cross-sectional analysis of accelerometer-measured physical activity in 96 706 uk biobank participants. *Int J Epidemiol, 48*(4)doi: 10.1093/ije/dyy294.
BARREIRA, TV, HAMILTON, MT, CRAFT, LL, GAPSTUR, SM, SIDDIQUE, J, & ZDERIC, TW. (2016). Intra-individual and inter-individual variability in daily sitting time and mvpa. *J Sci Med Sport, 19*(6), pp. 476-481. doi: 10.1016/j.jsams.2015.05.004.
BARREIRA, TV, SCHUNA, JM, TUDOR-LOCKE, C, CHAPUT, JP, CHURCH, TS, FOGELHOLM, M, et al. (2015). Reliability of accelerometer-determined physical activity and sedentary behavior in school-aged children: A 12-country study *Int j obes suppl* (Vol. 5, pp. S29-35).
BEAVER, WL, WASSERMAN, K, & WHIPP, BJ. (1986). A new method for detecting anaerobic threshold by gas exchange. *J Appl Physiol, 60*(6), pp. 2020-2027. doi: 10.1152/jappl.1986.60.6.2020.
BEN-SHLOMO, Y, SPEARS, M, BOUSTRED, C, MAY, M, ANDERSON, SG, BENJAMIN, EJ, et al. (2014). Aortic pulse wave velocity improves cardiovascular event prediction: An individual participant meta-analysis of prospective observational data from 17,635 subjects. *J Am Coll Cardiol, 63*(7), pp. 636-646. doi: 10.1016/j.jacc.2013.09.063.
BENATTI, FB, & RIED-LARSEN, M. (2015). The effects of breaking up prolonged sitting time: A review of experimental studies. *Med Sci Sports Exerc, 47*(10), pp. 2053-2061. doi: 10.1249/mss.0000000000000654.
BERAKI, A, MAGNUSON, A, SARNBLAD, S, AMAN, J, & SAMUELSSON, U. (2014). Increase in physical activity is associated with lower hba1c levels in children and adolescents with type 1 diabetes: Results from a cross-sectional

study based on the swedish pediatric diabetes quality registry (swediabkids). *Diabetes Res Clin Pract, 105*(1), pp. 119-125. doi: 10.1016/j.diabres.2014.01.029.
BERENSON, G. (2002). Childhood risk factors predict adult risk associated with subclinical cardiovascular disease. The bogalusa heart study. *Am J Cardiol, 90*(10C)doi: 10.1016/s0002-9149(02)02953-3.
BERGMAN, P. (2018). The number of repeated observations needed to estimate the habitual physical activity of an individual to a given level of precision. *PLoS One, 13*(2)doi: 10.1371/journal.pone.0192117.
BERNTSON, GG, BIGGER, JT, Jr., ECKBERG, DL, GROSSMAN, P, KAUFMANN, PG, MALIK, M, et al. (1997). Heart rate variability: Origins, methods, and interpretive caveats. *Psychophysiology, 34*(6), pp. 623-648.
BESSON, H, BRAGE, S, JAKES, R, EKELUND, U, & WAREHAM, N. (2010). Estimating physical activity energy expenditure, sedentary time, and physical activity intensity by self-report in adults. *Am J Clin Nutr, 91*(1)doi: 10.3945/ajcn.2009.28432.
BIGGER, J, FLEISS, J, STEINMAN, R, ROLNITZKY, L, KLEIGER, R, & ROTTMAN, J. (1992). Frequency domain measures of heart period variability and mortality after myocardial infarction. *Circulation, 85*(1)doi: 10.1161/01.cir.85.1.164.
BILLMAN, G. (2013). The lf/hf ratio does not accurately measure cardiac sympatho-vagal balance. *Front Physiol, 4*doi: 10.3389/fphys.2013.00026.
BLAIR, S. (2009). Physical inactivity: The biggest public health problem of the 21st century. *Br J Sports Med, 43*(1).
BOEREMA, S, VAN VELSEN, L, VOLLENBROEK, M, & HERMENS, H. (2020). Pattern measures of sedentary behaviour in adults: A literature review. *Digit Health, 6*doi: 10.1177/2055207620905418.
BOONE, J, & BOURGOIS, J. (2012). The oxygen uptake response to incremental ramp exercise: Methodogical and physiological issues. *Sports Med, 42*(6)doi: 10.2165/11599690-000000000-00000.
BORODULIN, K, KARKI, A, LAATIKAINEN, T, PELTONEN, M, & LUOTO, R. (2015). Daily sedentary time and risk of cardiovascular disease: The national finrisk 2002 study. *J Phys Act Health, 12*(7), pp. 904-908. doi: 10.1123/jpah.2013-0364.
BRAGE, S, WEDDERKOPP, N, BO ANDERSEN, L, & FROBERG, K. (2003). Influence of step frequency on movement intensity predictions with the csa accelerometer: A field validation study in children in: Pediatric exercise science volume 15 issue 3 (2003). *Pediatr Exerc Sci, 15*(3), pp. 277-287. doi: 10.1123/pes.15.3.277.
BRAVATA, DM, SMITH-SPANGLER, C, SUNDARAM, V, GIENGER, AL, LIN, N, LEWIS, R, et al. (2007). Using pedometers to increase physical activity and improve health: A systematic review. *Jama, 298*(19), pp. 2296-2304. doi: 10.1001/jama.298.19.2296.
BRAZEAU, AS, RABASA-LHORET, R, STRYCHAR, I, & MIRCESCU, H. (2008). Barriers to physical activity among patients with type 1 diabetes *Diabetes care* (Vol. 31, pp. 2108-2109).
BRAZENDALE, K, BEETS, M, WEAVER, R, PATE, R, TURNER-MCGRIEVY, G, KACZYNSKI, A, et al. (2017). Understanding differences between summer vs. School obesogenic behaviors of children: The structured days hypothesis. *Int J Behav Nutr Phys Act, 14*(1)doi: 10.1186/s12966-017-0555-2.

BRENNAN, M, PALANISWAMI, M, & KAMEN, P. (2002). Poincaré plot interpretation using a physiological model of hrv based on a network of oscillators. *Am J Physiol Heart Circ Physiol, 283*(5)doi: 10.1152/ajpheart.00405.2000.

BRITISH HEART FOUNDATION. (2017). *Physical inactivity report 2017*. https://www.bhf.org.uk/informationsupport/publications/statistics/physical-inactivity-report-2017. 2/7/19.

BROTMAN, DJ, GOLDEN, SH, & WITTSTEIN, IS. (2007). The cardiovascular toll of stress. *Lancet, 370*(9592), pp. 1089-1100. doi: 10.1016/s0140-6736(07)61305-1.

BRUNO, RM, GHIADONI, L, SERAVALLE, G, DELL'ORO, R, TADDEI, S, & GRASSI, G. (2012). Sympathetic regulation of vascular function in health and disease. *Front Physiol, 3*doi: 10.3389/fphys.2012.00284.

BUCHAN, DS, MCLELLAN, G, DONNELLY, S, & ARTHUR, R. (2019). The use of the intensity gradient and average acceleration metrics to explore associations with bmi z-score in children. *J Sports Sci, 37*(23), pp. 2751-2758. doi: 10.1080/02640414.2019.1664536.

BUTLER, G, YAMAMOTO, Y, & HUGHSON, R. (1994). Heart rate variability to monitor autonomic nervous system activity during orthostatic stress. *J Clin Pharmacol, 34*(6), pp. 558-562.

BUTTE, NF, WATSON, KB, RIDLEY, K, ZAKERI, IF, MCMURRAY, RG, PFEIFFER, KA, et al. (2018). A youth compendium of physical activities: Activity codes and metabolic intensities. *Med Sci Sports Exerc, 50*(2), pp. 246-256. doi: 10.1249/mss.0000000000001430.

BYRNE, N, HILLS, A, HUNTER, G, WEINSIER, R, & SCHUTZ, Y. (2005). Metabolic equivalent: One size does not fit all. *J Appl Physiol, 99*(3)doi: 10.1152/japplphysiol.00023.2004.

BYROM, B, STRATTON, G, MC CARTHY, M, & MUEHLHAUSEN, W. (2016). Objective measurement of sedentary behaviour using accelerometers. *Int J Obes (Lond), 40*(11), pp. 1809-1812. doi: 10.1038/ijo.2016.136.

CAIN, KL, SALLIS, JF, CONWAY, TL, DYCK, DV, & CALHOON, L. (2013). Using accelerometers in youth physical activity studies: A review of methods. *J Phys Act Health, 10*(3), pp. 437-450.

CANNING, KL, BROWN, RE, JAMNIK, VK, SALMON, A, ARDERN, CI, & KUK, JL. (2014). Individuals underestimate moderate and vigorous intensity physical activity. *PLoS One, 9*(5)doi: 10.1371/journal.pone.0097927.

CARSON, V, & JANSSEN, I. (2011). Volume, patterns, and types of sedentary behavior and cardio-metabolic health in children and adolescents: A cross-sectional study. [OriginalPaper]. *BMC Public Health, 11*(1), p 274. doi: doi:10.1186/1471-2458-11-274.

CARSON, V, TREMBLAY, MS, CHAPUT, JP, & CHASTIN, SF. (2016). Associations between sleep duration, sedentary time, physical activity, and health indicators among canadian children and youth using compositional analyses. *Appl Physiol Nutr Metab, 41*(6 Suppl 3), pp. S294-302. doi: 10.1139/apnm-2016-0026.

CARSON, V, TREMBLAY, MS, CHAPUT, JP, MCGREGOR, D, & CHASTIN, S. (2019). Compositional analyses of the associations between sedentary time, different intensities of physical activity, and cardiometabolic biomarkers among children and youth from the united states. *PLoS One, 14*(7)doi: 10.1371/journal.pone.0220009.

CARSON, V, WONG, SL, WINKLER, E, HEALY, GN, COLLEY, RC, & TREMBLAY, MS. (2014). Patterns of sedentary time and cardiometabolic risk among canadian adults. *Prev Med, 65*, pp. 23-27. doi: 10.1016/j.ypmed.2014.04.005.

CASPERSEN, CJ, POWELL, KE, & CHRISTENSON, GM. (1985). Physical activity, exercise, and physical fitness: Definitions and distinctions for health-related research. *Public Health Rep, 100*(2), pp. 126-131.

CASTONGUAY, A, & MIQUELON, P. (2018). Motivational profiles, accelerometer-derived physical activity, and acute diabetes-related symptoms in adults with type 2 diabetes. [OriginalPaper]. *BMC Public Health, 18*(1), pp. 1-15. doi: doi:10.1186/s12889-018-5376-y.

CASU, A, KANAPKA, L, FOSTER, N, HIRSCH, I, LAFFEL, L, SHAH, V, et al. (2020). Characteristics of adult- compared to childhood-onset type 1 diabetes. *Diabet Med*doi: 10.1111/dme.14314.

CAVERO-REDONDO, I, PELETEIRO, B, ÁLVAREZ-BUENO, C, RODRIGUEZ-ARTALEJO, F, & MARTÍNEZ-VIZCAÍNO, V. (2017). Glycated haemoglobin a1c as a risk factor of cardiovascular outcomes and all-cause mortality in diabetic and non-diabetic populations: A systematic review and meta-analysis *Bmj open* (Vol. 7).

CAVIEZEL, S, DRATVA, J, SCHNAFFER, E, SCHINDLER, C, ROTHER, T, ROCHAT, T, et al. (2018). Reproducibility of oscillometrically measured arterial stiffness indices: Results of the sapaldia 3 cohort study. *Scan J Clin Lab Invest, 75*(2), pp. 170-176. doi: https://doi.org/10.3109/00365513.2014.993692.

CAYRES, S, VANDERLEI, L, RODRIGUES, A, SILVA, M, CODOGNO, J, BARBOSA, M, et al. (2015). Sports practice is related to parasympathetic activity in adolescents. *Rev Paul Pediatr, 33*(2)doi: 10.1016/j.rpped.2014.09.002.

CECELJA, M, & CHOWIENCZYK, P. (2012). Role of arterial stiffness in cardiovascular disease *Jrsm cardiovasc dis* (Vol. 1).

CHAMARI, K, MOUSSA-CHAMARI, I, BOUSSAIDI, L, HACHANA, Y, KAOUECH, F, & WISLOFF, U. (2005). Appropriate interpretation of aerobic capacity: Allometric scaling in adult and young soccer players. *Br J Sports Med, 39*(2), pp. 97-101. doi: 10.1136/bjsm.2003.010215.

CHAPUT, J, LAMBERT, M, MATHIEU, M, TREMBLAY, M, O' LOUGHLIN, J, & TREMBLAY, A. (2012). Physical activity vs. Sedentary time: Independent associations with adiposity in children. *Pediatr Obes, 7*(3)doi: 10.1111/j.2047-6310.2011.00028.x.

CHASTIN, SF, PALAREA-ALBALADEJO, J, DONTJE, ML, & SKELTON, DA. (2015). 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, 10*(10), p e0139984. doi: 10.1371/journal.pone.0139984.

CHEN, SR, LEE, YJ, CHIU, HW, & JENG, C. (2008). Impact of physical activity on heart rate variability in children with type 1 diabetes. *Childs Nerv Syst, 24*(6), pp. 741-747. doi: 10.1007/s00381-007-0499-y.

CHESSA, M, BUTERA, G, LANZA, GA, BOSSONE, E, DELOGU, A, DE ROSA, G, et al. (2002). Role of heart rate variability in the early diagnosis of diabetic autonomic neuropathy in children. *Herz, 27*(8), pp. 785-790. doi: 10.1007/s00059-002-2340-4.

CHETAN, M, CHARLTON, M, THOMPSON, C, DIAS, R, ANDREWS, R, & NARENDRAN, P. (2019). The type 1 diabetes 'honeymoon' period is five times

longer in men who exercise: A case-control study. *Diabet Med, 36*(1)doi: 10.1111/dme.13802.
CHEUNG, YF. (2010). Arterial stiffness in the young: Assessment, determinants, and implications. *Korean Circ J, 40*(4), pp. 153-162. doi: 10.4070/kcj.2010.40.4.153.
CHIEF MEDICAL OFFICERS. (2019). *Uk chief medical officers' physical activity guidelines - uk-chief-medical-officers-physical-activity-guidelines.Pdf*. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/832868/uk-chief-medical-officers-physical-activity-guidelines.pdf. 15 Nov 2019.
CHIMEN, M, KENNEDY, A, NIRANTHARAKUMAR, K, PANG, TT, ANDREWS, R, & NARENDRAN, P. (2012). What are the health benefits of physical activity in type 1 diabetes mellitus? A literature review. [journal article]. *Diabetologia, 55*(3), pp. 542-551. doi: 10.1007/s00125-011-2403-2.
CHOI, L, LIU, Z, MATTHEWS, C, & BUCHOWSKI, M. (2011). Validation of accelerometer wear and nonwear time classification algorithm. *Med Sci Sports Exerc, 43*(2)doi: 10.1249/MSS.0b013e3181ed61a3.
CHOMISTEK, AK, MANSON, JE, STEFANICK, ML, LU, B, SANDS-LINCOLN, M, GOING, SB, et al. (2013). Relationship of sedentary behavior and physical activity to incident cardiovascular disease: Results from the women's health initiative. *J Am Coll Cardiol, 61*(23), pp. 2346-2354. doi: 10.1016/j.jacc.2013.03.031.
CHOWDHURY, S. (2015). Puberty and type 1 diabetes. *Indian J Endocrinol Metab, 19*(Suppl 1), pp. S51-54. doi: 10.4103/2230-8210.155402.
CHURCH, TS, GILL, TM, NEWMAN, AB, BLAIR, SN, EARNEST, CP, & PAHOR, M. (2008). Maximal fitness testing in sedentary elderly at substantial risk of disability: Life-p study experience. *J Aging Phys Act, 16*(4), pp. 408-415.
COLBERG, S, SIGAL, R, YARDLEY, J, RIDDELL, M, DUNSTAN, D, DEMPSEY, P, et al. (2016). Physical activity/exercise and diabetes: A position statement of the american diabetes association. *Diabetes Care, 39*(11), pp. 2065-2079. doi: 10.2337/dc16-1728.
COLHOUN, H, RUBENS, M, UNDERWOOD, S, & FULLER, J. (2000). The effect of type 1 diabetes mellitus on the gender difference in coronary artery calcification. *J Am Coll Cardiol, 36*(7)doi: 10.1016/s0735-1097(00)00986-4.
COLHOUN, HM, FRANCIS, DP, RUBENS, MB, UNDERWOOD, SR, & FULLER, JH. (2001). The association of heart-rate variability with cardiovascular risk factors and coronary artery calcification: A study in type 1 diabetic patients and the general population. *Diabetes Care, 24*(6), pp. 1108-1114.
COLLEY, R, CONNOR GORBER, S, & TREMBLAY, MS. (2010). Quality control and data reduction procedures for accelerometry-derived measures of physical activity. *Health Rep, 21*(1), pp. 63-69.
COLLEY, R, GARRIGUET, D, JANSSEN, I, & WONG, S. (2013). The association between accelerometer-measured patterns of sedentary time and health risk in children and youth: Results from the canadian health measures ….
COLLEY, RC, GARRIGUET, D, JANSSEN, I, CRAIG, CL, CLARKE, J, & TREMBLAY, MS. (2011). Physical activity of canadian adults: Accelerometer results from the 2007 to 2009 canadian health measures survey. *Health Rep, 22*(1), pp. 7-14.
COLLINS, RT, SOMES, GW, & ALPERT, BS. (2008). Differences in arterial compliance among normotensive adolescent groups: Collins arterial compliance

in adolescents. *Pediatr Cardiol, 29*(5), pp. 929-934. doi: 10.1007/s00246-008-9239-7.
CONGET, I, & GIMÉNEZ, M. (2009). Glucose control and cardiovascular disease: Is it important? No. *Diabetes Care, 32*(Suppl 2), pp. S334-336. doi: 10.2337/dc09-S334.
CONSENSUS COMMITTEE OF HBA1C STANDARDARDISATION. (2007). Consensus statement on the worldwide standardization of the hemoglobin a1c measurement: The american diabetes association, european association for the study of diabetes, international federation of clinical chemistry and laboratory medicine, and the international diabetes federation. *Diabetes Care, 30*(9), pp. 2399-2400. doi: 10.2337/dc07-9925.
COTE, A, PHILLIPS, A, HARRIS, K, SANDOR, G, PANAGIOTOPOULOS, C, & DEVLIN, A. (2015). Obesity and arterial stiffness in children: Systematic review and meta-analysis. *Arterioscler Thromb Vasc Biol, 35*(4)doi: 10.1161/ATVBAHA.114.305062.
COUMEL, P. (1993). Cardiac arrhythmias and the autonomic nervous system. *J Cardiovasc Electrophysiol, 4*(3)doi: 10.1111/j.1540-8167.1993.tb01235.x.
CRAIG, CL, MARSHALL, AL, SJOSTROM, M, BAUMAN, AE, BOOTH, ML, AINSWORTH, BE, et al. (2003). International physical activity questionnaire: 12-country reliability and validity. *Medicine & Science in Sport & Exercise, 35*(8), pp. 1381 - 1395.
CUENCA-GARCÍA, M, JAGO, R, SHIELD, J, & BURREN, C. (2012). How does physical activity and fitness influence glycaemic control in young people with type 1 diabetes? *Diabet Med, 29*(10)doi: 10.1111/j.1464-5491.2012.03740.x.
CUNHA, G, VAZ, M, GEREMIA, J, LEITES, G, BAPTISTA, R, LOPES, A, et al. (2016). Maturity status does not exert effects on aerobic fitness in soccer players after appropriate normalization for body size. *Pediatr Exerc Sci, 28*(3)doi: 10.1123/pes.2015-0133.
CZENCZEK-LEWANDOWSKA, E, LESZCZAK, J, BARAN, J, WERES, A, WYSZYŃSKA, J, LEWANDOWSKI, B, et al. (2019). Levels of physical activity in children and adolescents with type 1 diabetes in relation to the healthy comparators and to the method of insulin therapy used *Int j environ res public health* (Vol. 16).
CZENCZEK-LEWANDOWSKA, E, LESZCZAK, J, WERES, A, BARAN, J, WYSZYŃSKA, J, GRZEGORCZYK, J, et al. (2019). Sedentary behaviors in children and adolescents with type 1 diabetes, depending on the insulin therapy used. *Medicine, 98*(19)doi: 10.1097/md.0000000000015625.
D'SILVA, LA, DAVIES, RE, EMERY, SJ, & LEWIS, MJ. (2014). Influence of somatic state on cardiovascular measurements in pregnancy. *Physiol Meas, 35*(1), pp. 15-29. doi: 10.1088/0967-3334/35/1/15.
DA SILVA, C, PEREIRA, L, CARDOSO, J, MOORE, J, & NAKAMURA, F. (2014). The effect of physical training on heart rate variability in healthy children: A systematic review with meta-analysis. *Pediatr Exerc Sci, 26*(2)doi: 10.1123/pes.2013-0063.
DAHL-JØRGENSEN, K, LARSEN, J, & HANSSEN, K. (2005). Atherosclerosis in childhood and adolescent type 1 diabetes: Early disease, early treatment? *Diabetologia, 48*(8)doi: 10.1007/s00125-005-1832-1.
DALE, D, CORBIN, C, & DALE, K. (2000). Restricting opportunities to be active during school time: Do children compensate by increasing physical activity levels after school? *Res Q Exerc Sport, 71*(3)doi: 10.1080/02701367.2000.10608904.

DANNE, T, NIMRI, R, BATTELINO, T, BERGENSTAL, RM, CLOSE, KL, DEVRIES, JH, et al. (2017). International consensus on use of continuous glucose monitoring. *Diabetes Care, 40*(12), pp. 1631-1640. doi: 10.2337/dc17-1600.
DAVIS, PB, & KALINER, M. (1983). Autonomic nervous system abnormalities in cystic fibrosis. *J Chronic Dis, 36*(3), pp. 269-278.
DAVY, KP, DESOUZA, CA, JONES, PP, & SEALS, DR. (1998). Elevated heart rate variability in physically active young and older adult women. *Clin Sci, 94*(6), pp. 579-584.
DE ALMEIDA-MENDES, M, DA SILVA, I, RAMIRES, V, REICHERT, F, MARTINS, R, & TOMASI, E. (2018). Calibration of raw accelerometer data to measure physical activity: A systematic review. *Gait & posture, 61*, pp. 98-110. doi: 10.1016/j.gaitpost.2017.12.028.
DE JEU, R, SCHOT, R, GROEPENHOFF, H, & NINABER, A. (2018). Modification of inspired oxygen fraction does not change exercise oxygen uptake measured by jaeger® vyntus cpx; a validation study. *Eur Respir Jour, 52*doi: 10.1183/13993003.congress-2018.PA3400.
DE LIMA, VA, MASCARENHAS, LPG, DECIMO, JP, DE SOUZA, WC, MONTEIRO, ALS, LAHART, I, et al. (2017). Physical activity levels of adolescents with type 1 diabetes physical activity in t1d. *Pediatr Exerc Sci, 29*(2), pp. 213-219. doi: 10.1123/pes.2016-0199.
DE MEERSMAN, R, & STEIN, P. (2007). Vagal modulation and aging. *Biol Psychol, 74*(2)doi: 10.1016/j.biopsycho.2006.04.008.
DE-FERRANTI, S, DE BOER, I, FONSECA, V, FOX, C, GOLDEN, S, LAVIE, C, et al. (2014). Type 1 diabetes mellitus and cardiovascular disease: A scientific statement from the american heart association and american diabetes association. *Circulation, 130*(13)doi: 10.1161/CIR.0000000000000034.
DHINGRA, R, & VASAN, RS. (2012). Age as a cardiovascular risk factor. *Med Clin North Am, 96*(1), pp. 87-91. doi: 10.1016/j.mcna.2011.11.003.
DIABETES UK. (2016). Diabetes prevalence 2016 (november 2016). Retrieved Date from https://www.diabetes.org.uk/professionals/position-statements-reports/statistics/diabetes-prevalence-2016.
DIMMELER, S. (2011). Cardiovascular disease review series. *EMBO Mol Med, 3*(12), p 697. doi: 10.1002/emmm.201100182.
DISHMAN, RK, SALLIS, JF, & ORENSTEIN, DR. (1985). The determinants of physical activity and exercise. *Public Health Rep, 100*(2), pp. 158-171.
DOLLMAN, J. (2018). Social and environmental influences on physical activity behaviours. *Int J Environ Res Public Health, 15*(1)doi: 10.3390/ijerph15010169.
DOLLMAN, J, OKELY, A, HARDY, L, TIMPERIO, A, SALMON, J, & HILLS, A. (2009). A hitchhiker's guide to assessing young people's physical activity: Deciding what method to use. *J Sci Med Sport, 12*(5)doi: 10.1016/j.jsams.2008.09.007.
DUMITH, S, GIGANTE, D, DOMINGUES, M, & KOHL, H. (2011). Physical activity change during adolescence: A systematic review and a pooled analysis. *Int J Epidemiol, 40*(3)doi: 10.1093/ije/dyq272.
DUMUID, D, STANFORD, T, MARTIN-FERNÁNDEZ, J, PEDIŠIĆ, Ž, MAHER, C, LEWIS, L, et al. (2018). Compositional data analysis for physical activity, sedentary time and sleep research. *Stat Methods Med Res, 27*(12)doi: 10.1177/0962280217710835.

DUNSTAN, DW, THORP, AA, & HEALY, GN. (2011). Prolonged sitting: Is it a distinct coronary heart disease risk factor? *Curr Opin Cardiol, 26*(5), pp. 412-419. doi: 10.1097/HCO.0b013e3283496605.
EARNEST, CP, BLAIR, SN, & CHURCH, TS. (2010). Age attenuated response to aerobic conditioning in postmenopausal women. *Eur J Appl Physiol, 110*(1), pp. 75-82. doi: 10.1007/s00421-010-1472-0.
EARNEST, CP, WHARTON, RP, CHURCH, TS, & LUCIA, A. (2005). Reliability of the lode excalibur sport ergometer and applicability to computrainer electromagnetically braked cycling training device. *J Strength Cond Res, 19*(2), pp. 344-348. doi: 10.1519/r-15714.1.
EDMUNDS, S, ROCHE, D, & STRATTON, G. (2010). Levels and patterns of physical activity in children and adolescents with type 1 diabetes and associated metabolic and physiologic health outcomes. *J Phys Act Health, 7*(1)doi: 10.1123/jpah.7.1.68.
EDWARDS, NM, DANIELS, SR, CLAYTOR, RP, KHOURY, PR, DOLAN, LM, KIMBALL, TR, et al. (2012). Physical activity is independently associated with multiple measures of arterial stiffness in adolescents and young adults. *Metabolism, 61*(6), pp. 869-872. doi: 10.1016/j.metabol.2011.10.016.
EIJSVOGELS, TM, GEORGE, KP, & THOMPSON, PD. (2016). Cardiovascular benefits and risks across the physical activity continuum. *Curr Opin Cardiol, 31*(5), pp. 566-571. doi: 10.1097/hco.0000000000000321.
EKELUND, U, LUAN, J, SHERAR, L, ESLIGER, D, GRIEW, P, COOPER, A, et al. (2019). Moderate to vigorous physical activity and sedentary time and cardiometabolic risk factors in children and adolescents. *Jama, 307*(7), pp. 704-712. doi: 10.1001/jama.2012.156.
ELIASZIW, M, YOUNG, SL, WOODBURY, MG, & FRYDAY-FIELD, K. (1994). Statistical methodology for the concurrent assessment of interrater and intrarater reliability: Using goniometric measurements as an example. *Phys Ther, 74*(8), pp. 777-788. doi: 10.1093/ptj/74.8.777.
ENDES, S, SCHAFFNER, E, CAVIEZEL, S, DRATVA, J, AUTENRIETH, CS, WANNER, M, et al. (2016). Physical activity is associated with lower arterial stiffness in older adults: Results of the sapaldia 3 cohort study. *Eur J Epidemiol, 31*(3), pp. 275-285. doi: 10.1007/s10654-015-0076-8.
ESLIGER, DW, ROWLANDS, AV, HURST, TL, CATT, M, MURRAY, P, & ESTON, RG. (2011). Validation of the genea accelerometer. *Med Sci Sports Exerc, 43*(6), pp. 1085-1093. doi: 10.1249/MSS.0b013e31820513be.
EUROPEAN SOCIETY OF CARDIOLOGY, pae. (1996). Heart rate variability: Standards of measurement, physiological interpretation and clinical use. Task force of the european society of cardiology and the north american society of pacing and electrophysiology. *Circulation, 93*(5), pp. 1043-1065.
EVANS, M. (2016). Current methods of assessing blood glucose control in diabetes. [Reviews]. *Brit J Diabetes, 16*doi: https://bjd-abcd.com/bjdvd/index.php/bjd/article/view/133.
EVENSON, K, CATELLIER, D, GILL, K, ONDRAK, K, & MCMURRAY, R. (2008). Calibration of two objective measures of physical activity for children. [research-article]. *J Sports Sci, 26*(40)doi: Journal of Sports Sciences, Vol. 26, No. 14, December 2008, pp. 1557–1565.
FAIRCLOUGH, SJ, NOONAN, R, ROWLANDS, AV, VAN HEES, V, KNOWLES, Z, & BODDY, LM. (2016). Wear compliance and activity in

children wearing wrist- and hip-mounted accelerometers. *Med Sci Sports Exerc, 48*(2), pp. 245-253. doi: 10.1249/mss.0000000000000771.
FAIRCLOUGH, SJ, TAYLOR, S, ROWLANDS, AV, BODDY, LM, & NOONAN, RJ. (2019). Average acceleration and intensity gradient of primary school children and associations with indicators of health and well-being. *J Sports Sci, 37*(18), pp. 2159-2167. doi: 10.1080/02640414.2019.1624313.
FANTIN, F, MATTOCKS, A, BULPITT, C, BANYA, W, & RAJKUMAR, C. (2018). Is augmentation index a good measure of vascular stiffness in the elderly? *Age Ageing, 36*(1), pp. 43-48. doi: 10.1093/ageing/afl115.
FARABI, SS. (2016). Type 1 diabetes and sleep *Diabetes spectr* (Vol. 29, pp. 10-13).
FARAH, B, CHRISTOFARO, D, ANDRADE-LIMA, A, SARAIVA, B, GOMES-DE-BARROS, M, LUIZ-DO-PRADO, W, et al. (2020). Association between sedentary recreational time and cardiac autonomic modulation in adolescent boys: Cross-sectional study. [OriginalPaper]. *Sport Sci Health*, pp. 1-7. doi: doi:10.1007/s11332-020-00641-7.
FAROOQ, MA, PARKINSON, KN, ADAMSON, AJ, PEARCE, MS, REILLY, JK, HUGHES, AR, et al. (2018). Timing of the decline in physical activity in childhood and adolescence: Gateshead millennium cohort study. *Br J Sports Med, 52*(15), pp. 1002-1006. doi: 10.1136/bjsports-2016-096933.
FERGUSON, E, WRIGHT, N, REGAN, F, AGWU, J, WILLIAMS, E, SONI, A, et al. (2020). Variations in access to continuous glucose monitoring and flash glucose sensors for children and young people in england and wales: A national survey. *Arch Dis Child, 105*(6)doi: 10.1136/archdischild-2019-317800.
FONOLLEDA, M, MURILLO, M, VÁZQUEZ, F, BEL, J, & VIVES-PI, M. (2017). Remission phase in paediatric type 1 diabetes: New understanding and emerging biomarkers. *Horm Res Paediatr, 88*(5)doi: 10.1159/000479030.
FORD, E, & CASPERSEN, CJ. (2019). Sedentary behaviour and cardiovascular disease: A review of prospective studies. *Int J Epidemiol, 41*(5), pp. 1338-1353. doi: 10.1093/ije/dys078.
FRÉMEAUX, A, MALLAM, K, METCALF, B, HOSKING, J, VOSS, L, & WILKIN, T. (2011). The impact of school-time activity on total physical activity: The activitystat hypothesis (earlybird 46). *Int J Obes, 35*(10)doi: 10.1038/ijo.2011.52.
FROBERG, K, & ANDERSEN, L. (2005). Mini review: Physical activity and fitness and its relations to cardiovascular disease risk factors in children. [OriginalPaper]. *Int J Obesity, 29*(2)doi: doi:10.1038/sj.ijo.0803096.
FUJIWARA, H, NAKAJIMA, H, INOUE, F, KOSAKA, K, ASANO, H, & YOSHII, K. (2018). Arterial stiffness in junior high school students: Longitudinal observations. *Pediatr Int, 60*(2)doi: 10.1111/ped.13475.
FÜZÉKI, E, ENGEROFF, T, & BANZER, W. (2017). Health benefits of light-intensity physical activity: A systematic review of accelerometer data of the national health and nutrition examination survey (nhanes). *Sports Med, 47*(9)doi: 10.1007/s40279-017-0724-0.
GANDO, Y, YAMAMOTO, K, MURAKAMI, H, OHMORI, Y, KAWAKAMI, R, SANADA, K, et al. (2010). Longer time spent in light physical activity is associated with reduced arterial stiffness in older adults. *Hypertension, 56*(3), pp. 540-546. doi: 10.1161/hypertensionaha.110.156331.

GĄSIOR, JS, SACHA, J, JELEŃ, PJ, PAWŁOWSKI, M, WERNER, B, & DĄBROWSKI, MJ. (2015). Interaction between heart rate variability and heart rate in pediatric population. *Front Physiol, 6*(385)doi: 10.3389/fphys.2015.00385.
GASKILL, SE, RUBY, BC, WALKER, AJ, SANCHEZ, OA, SERFASS, RC, & LEON, AS. (2001). Validity and reliability of combining three methods to determine ventilatory threshold. *Med Sci Sports Exerc, 33*(11), pp. 1841-1848.
GAY, JL, BUCHNER, DM, SMITH, J, & HE, C. (2017). An examination of compensation effects in accelerometer-measured occupational and non-occupational physical activity *Prev med rep* (Vol. 8, pp. 55-59).
GERMANO-SOARES, A, ANDRADE-LIMA, A, MENÊSES, A, CORREIA, M, PARMENTER, B, TASSITANO, R, et al. (2018). Association of time spent in physical activities and sedentary behaviors with carotid-femoral pulse wave velocity: A systematic review and meta-analysis. *Atherosclerosis, 269*doi: 10.1016/j.atherosclerosis.2018.01.009.
GLUKHOVA, M, FRID, M, & KOTELIANSKY, V. (1991). Phenotypic changes of human aortic smooth muscle cells during development and in the adult vessel. *Am J Physiol, 261*(4 Suppl)doi: 10.1152/ajpheart.1991.261.4.78.
GOMERSALL, S, ROWLANDS, A, ENGLISH, C, MAHER, C, & OLDS, T. (2013a). The activitystat hypothesis: The concept, the evidence and the methodologies. *Sports medicine (Auckland, N.Z.), 43*(2)doi: 10.1007/s40279-012-0008-7.
GOMERSALL, S, ROWLANDS, A, ENGLISH, C, MAHER, C, & OLDS, T. (2013b). The activitystat hypothesis: The concept, the evidence and the methodologies. *Sports Med, 43*(2)doi: 10.1007/s40279-012-0008-7.
GOMERSALL, SR, ROWLANDS, AV, ENGLISH, C, MAHER, C, & OLDS, TS. (2012). The activitystat hypothesis. [ReviewPaper]. *Sports Medicine, 43*(2), pp. 135-149. doi: doi:10.1007/s40279-012-0008-7.
GOMEZ-MARCOS, MA, RECIO-RODRIGUEZ, JI, PATINO-ALONSO, MC, AGUDO-CONDE, C, LASAOSA-MEDINA, L, RODRIGUEZ-SANCHEZ, E, et al. (2014). Relationship between objectively measured physical activity and vascular structure and function in adults. *Atherosclerosis, 234*(2), pp. 366-372. doi: 10.1016/j.atherosclerosis.2014.02.028.
GOODMAN, A, MACKETT, R, & PASKINS, J. (2011). Activity compensation and activity synergy in british 8-13 year olds. *Prev Med, 53*(4-5)doi: 10.1016/j.ypmed.2011.07.019.
GORDON-LARSEN, P, MCMURRAY, R, & POPKIN, B. (2000). Determinants of adolescent physical activity and inactivity patterns. *Pediatrics, 105*(6)doi: 10.1542/peds.105.6.e83.
GRAY, P, MURPHY, M, GALLAGHER, A, & SIMPSON, EEA. (2018). A qualitative investigation of physical activity compensation among older adults. *Br J Health Psychol, 23*(1), pp. 208-224. doi: 10.1111/bjhp.12282.
GREENBAUM, C. (2002). Insulin resistance in type 1 diabetes. *Diabetes Metab Res Rev, 18*(3)doi: 10.1002/dmrr.291.
GREENWALD, SE. (2007). Ageing of the conduit arteries. *J Pathol, 211*(2), pp. 157-172. doi: 10.1002/path.2101.
GROEPENHOFF, H, DE JEU, R, & SCHOT, R. (2017). Vyntus cpx compared to oxycon pro shows equal gas-exchange and ventilation during exercise. *Eur Respir J, 50*doi: 10.1183/1393003.congress-2017.PA3002.
GROSSMAN, P, KAREMAKER, J, & WIELING, W. (1991). Prediction of tonic parasympathetic cardiac control using respiratory sinus arrhythmia: The need for

respiratory control. *Psychophysiology, 28*(2)doi: 10.1111/j.1469-8986.1991.tb00412.x.
GROSSMAN, P, & TAYLOR, E. (2007). Toward understanding respiratory sinus arrhythmia: Relations to cardiac vagal tone, evolution and biobehavioral functions. *Biol Psychol, 74*(2)doi: 10.1016/j.biopsycho.2005.11.014.
GUTIN, B, HOWE, C, JOHNSON, MH, HUMPHRIES, MC, SNIEDER, H, & BARBEAU, P. (2005). Heart rate variability in adolescents: Relations to physical activity, fitness, and adiposity. *Med Sci Sports Exerc, 37*(11), pp. 1856-1863.
GUY, J, OGDEN, L, WADWA, RP, HAMMAN, RF, MAYER-DAVIS, EJ, LIESE, AD, et al. (2009). Lipid and lipoprotein profiles in youth with and without type 1 diabetes: The search for diabetes in youth case-control study *Diabetes care* (Vol. 32, pp. 416-420).
HAAPALA, EA, VÄISTÖ, J, VEIJALAINEN, A, LINTU, N, WIKLUND, P, WESTGATE, K, et al. (2016). Associations of objectively measured physical activity and sedentary time with arterial stiffness in pre-pubertal children. *Pediatr Exerc Sci, 29*(3), pp. 326-335.
HAAPALA, EA, VÄISTÖ, J, VEIJALAINEN, A, LINTU, N, WIKLUND, P, WESTGATE, K, et al. (2017). Associations of objectively measured physical activity and sedentary time with arterial stiffness in pre-pubertal children. *Pediatr Exerc Sci, 29*(3), pp. 326-335. doi: 10.1123/pes.2016-0168.
HADI, HA, CARR, CS, & AL SUWAIDI, J. (2005). Endothelial dysfunction: Cardiovascular risk factors, therapy, and outcome. *Vasc Health Risk Manag, 1*(3), pp. 183-198.
HÄGGLUND, H, UUSITALO, A, PELTONEN, JE, KOPONEN, AS, AHO, J, TIINANEN, S, et al. (2012). Cardiovascular autonomic nervous system function and aerobic capacity in type 1 diabetes. *Front Physiol, 3*doi: 10.3389/fphys.2012.00356.
HAGSTROMER, M, AINSWORTH, B, OJA, P, & SJOSTROM, M. (2010). Comparison of a subjective and an objective measure of physical activity in a population sample. *J Phys Act Health, 7*(4)doi: 10.1123/jpah.7.4.541.
HALLER, MJ, SAMYN, M, NICHOLS, WW, BRUSKO, T, WASSERFALL, C, SCHWARTZ, RF, et al. (2004). Radial artery tonometry demonstrates arterial stiffness in children with type 1 diabetes. *Diabetes Care, 27*(12), pp. 2911-2917.
HAMER, M, O'DONOVAN, G, & MURPHY, M. (2017). Physical inactivity and the economic and health burdens due to cardiovascular disease: Exercise as medicine. *Adv Exp Med Biol, 999*doi: 10.1007/978-981-10-4307-9_1.
HAMILTON, P, LOCKHART, C, QUINN, C, & MCVEIGH, G. (2007). Arterial stiffness: Clinical relevance, measurement and treatment. *Clin Sci, 113*(4)doi: 10.1042/CS20070080.
HÄNGGI, J, PHILLIPS, L, & ROWLANDS, A. (2013). Validation of the gt3x actigraph in children and comparison with the gt1m actigraph. *J Sci Med Sport, 16*(1)doi: 10.1016/j.jsams.2012.05.012.
HARRELL, JS, MCMURRAY, RG, BAGGETT, CD, PENNELL, ML, PEARCE, PF, & BANGDIWALA, SI. (2005). Energy costs of physical activities in children and adolescents. *Med Sci Sports Exerc, 37*(2), pp. 329-336.
HARRIS, MA. (2018). The relationship between physical inactivity and mental wellbeing: Findings from a gamification-based community-wide physical activity intervention. *Health Psychol Open, 5*(1)doi: 10.1177/2055102917753853.
HASKELL, WL, LEE, IM, PATE, RR, POWELL, KE, BLAIR, SN, FRANKLIN, BA, et al. (2007). Physical activity and public health: Updated recommendation

for adults from the american college of sports medicine and the american heart association. *Med Sci Sports Exerc, 39*(8), pp. 1423-1434. doi: 10.1249/mss.0b013e3180616b27.

HAWKINS, M, GABRIEL, K, COOPER, J, STORTI, K, SUTTON-TYRRELL, K, & KRISKA, A. (2014). The impact of change in physical activity on change in arterial stiffness in overweight or obese sedentary young adults:. [research-article]. *Vasc Med, 19*(4)doi: 10.1177_1358863X14536630.

HAZIR, T, & KOSAR, N. (2007). Assessment of gender differences in maximal anaerobic power by ratio scaling and allometric scaling. *Isokinet Exerc Sci, 15*(4), pp. 253-261. doi: 10.3233/IES-2007-0281.

HEALTH AND SOCIAL CARE INFORMATION CENTRE. (2008). *Joint health surveys unit. Health survey for england 2008*. Leeds, UK: http://www.hscic.gov.uk/catalogue/PUB00430/heal-surv-phys-acti-fitn-eng-2008-rep-v2.pdf. 5/7/19.

HEALY, G, DUNSTAN, D, SALMON, J, CERIN, E, SHAW, J, ZIMMET, P, et al. (2008). Breaks in sedentary time: Beneficial associations with metabolic risk. *Diabetes Care, 31*(4)doi: 10.2337/dc07-2046.

HEALY, GN, WIJNDAELE, K, DUNSTAN, DW, SHAW, JE, SALMON, J, ZIMMET, PZ, et al. (2008). Objectively measured sedentary time, physical activity, and metabolic risk: The australian diabetes, obesity and lifestyle study (ausdiab). *Diabetes Care, 31*(2), pp. 369-371. doi: 10.2337/dc07-1795.

HEINEMANN, L, & FRECKMANN, G. (2015). Quality of hba1c measurement in the practice: The german perspective. *J Diabetes Sci Technol, 9*(3), pp. 687-695. doi: 10.1177/1932296815572254.

HEINONEN, I, HELAJÄRVI, H, PAHKALA, K, HEINONEN, OJ, HIRVENSALO, M, PÄLVE, K, et al. (2013). Sedentary behaviours and obesity in adults: The cardiovascular risk in young finns study. *BMJ open, 3*(6)doi: 10.1136/bmjopen-2013-002901.

HELMERHORST, H, BRAGE, S, WARREN, J, BESSON, H, & EKELUND, U. (2012). A systematic review of reliability and objective criterion-related validity of physical activity questionnaires. *Int J Behav Nutr Phys Act, 9*doi: 10.1186/1479-5868-9-103.

HENSON, J, YATES, T, BIDDLE, S, EDWARDSON, C, KHUNTI, K, WILMOT, E, et al. (2013). Associations of objectively measured sedentary behaviour and physical activity with markers of cardiometabolic health. *Diabetologia, 56*(5)doi: 10.1007/s00125-013-2845-9.

HERBST, A, BACHRAN, R, KAPELLEN, T, & HOLL, RW. (2006). Effects of regular physical activity on control of glycemia in pediatric patients with type 1 diabetes mellitus. *Arch Pediatr Adolesc Med, 160*(6), pp. 573-577. doi: 10.1001/archpedi.160.6.573.

HERBST, A, KORDONOURI, O, SCHWAB, KO, SCHMIDT, F, & HOLL, RW. (2007). Impact of physical activity on cardiovascular risk factors in children with type 1 diabetes: A multicenter study of 23,251 patients. *Diabetes Care, 30*(8), pp. 2098-2100. doi: 10.2337/dc06-2636.

HERRMANN, S, BARREIRA, T, KANG, M, & AINSWORTH, B. (2013). How many hours are enough? Accelerometer wear time may provide bias in daily activity estimates. *J Phys Act Health, 10*(5)doi: 10.1123/jpah.10.5.742.

HERRMANN, S, BARREIRA, T, KANG, M, & AINSWORTH, B. (2014). Impact of accelerometer wear time on physical activity data: A nhanes semisimulation data approach. *Br J Sports Med, 48*(3)doi: 10.1136/bjsports-2012-091410.

HERZIG, D, ESER, P, RADTKE, T, WENGER, A, RUSTERHOLZ, T, WILHELM, M, et al. (2017). Relation of heart rate and its variability during sleep with age, physical activity, and body composition in young children. *Front Physiol, 8*(109)doi: 10.3389/fphys.2017.00109.

HEYMAN, E, TOUTAIN, C, DELAMARCHE, P, BERTHON, P, BRIARD, D, YOUSSEF, H, et al. (2007). Exercise training and cardiovascular risk factors in type 1 diabetic adolescent girls. *Pediatr Exerc Sci, 19*(4), pp. 408-419.

HIDDING, LM, CHINAPAW, MJM, VAN POPPEL, MNM, MOKKINK, LB, & ALTENBURG, TM. (2018). An updated systematic review of childhood physical activity questionnaires *Sports med* (Vol. 48, pp. 2797-2842).

HILDEBRAND, M, HANSEN, BH, VAN HEES, VT, & EKELUND, U. (2017). Evaluation of raw acceleration sedentary thresholds in children and adults. *Scand J Med Sci Sports, 27*(12), pp. 1814-1823. doi: 10.1111/sms.12795.

HILDEBRAND, M, VAN HEES, V, HANSEN, BH, & EKELUND, U. (2014). Age group comparability of raw accelerometer output from wrist- and hip-worn monitors. *Med Sci Sports Exerc, 46*(9), pp. 1816-1824. doi: 10.1249/mss.0000000000000289.

HILLS, AP, MOKHTAR, N, & BYRNE, NM. (2014). Assessment of physical activity and energy expenditure: An overview of objective measures. *Front Nutr, 1*doi: 10.3389/fnut.2014.00005.

HNATIUK, J, LAMB, K, RIDGERS, N, SALMON, J, & HESKETH, K. (2019). Changes in volume and bouts of physical activity and sedentary time across early childhood: A longitudinal study. [OriginalPaper]. *Int J Behav Nutr Phys. Act, 16*(1), pp. 1-9. doi: doi:10.1186/s12966-019-0805-6.

HOPKINS, W, MARSHALL, S, BATTERHAM, A, & HANIN, J. (2009). Progressive statistics for studies in sports medicine and exercise science. *Med Sci Sports Exerc, 41*(1)doi: 10.1249/MSS.0b013e31818cb278.

HORTA, L, SCHAAN, B, MORAES BIELEMANN, R, ÁVILA VIANNA, C, PETRUCCI GIGANTE, D, BARROS, F, et al. (2015). Objectively measured physical activity and sedentary-time are associated with arterial stiffness in brazilian young adults. *Atherosclerosis, 243*(1), pp. 148-154. doi: https://doi.org/10.1016/j.atherosclerosis.2015.09.005.

HOWARD, B, WINKLER, E, SETHI, P, CARSON, V, RIDGERS, N, SALMON, J, et al. (2015). Associations of low- and high-intensity light activity with cardiometabolic biomarkers. *Med Sci Sports Exerc, 47*(10)doi: 10.1249/MSS.0000000000000631.

HRON, K, FILZMOSER, P, & THOMPSON, K. (2012). Linear regression with compositional explanatory variables. [research-article]. *J Appl Stat, 39*(5), pp. 115-1128. doi: http://dx.doi.org/10.1080/02664763.2011.644268.

HU, MX, LAMERS, F, DE GEUS, EJ, & PENNINX, BW. (2017). Influences of lifestyle factors on cardiac autonomic nervous system activity over time. *Prev Med, 94*, pp. 12-19. doi: 10.1016/j.ypmed.2016.11.003.

HUGHSON, R, & SHOEMAKER, J. (2015). Autonomic responses to exercise: Deconditioning/inactivity. *Auton Neurosci, 188*doi: 10.1016/j.autneu.2014.10.012.

HURTER, L, FAIRCLOUGH, SJ, KNOWLES, ZR, PORCELLATO, LA, COOPER-RYAN, AM, & BODDY, LM. (2018). Establishing raw acceleration thresholds to classify sedentary and stationary behaviour in children. *Children, 5*(12)doi: 10.3390/children5120172.

IM, JA, LEE, JW, SHIM, JY, LEE, HR, & LEE, DC. (2007). Association between brachial-ankle pulse wave velocity and cardiovascular risk factors in healthy adolescents. *J Pediatr, 150*(3), pp. 247-251. doi: 10.1016/j.jpeds.2006.11.038.
INGALL, TJ, MCLEOD, JG, & O'BRIEN, PC. (1990). The effect of ageing on autonomic nervous system function. *Aust N Z J Med, 20*(4), pp. 570-577.
JAESCHKE, L, STEINBRECHER, A, JERAN, S, KONIGORSKI, S, & PISCHON, T. (2018). Variability and reliability study of overall physical activity and activity intensity levels using 24 h-accelerometry-assessed data. *BMC Public Health, 18*(1)doi: 10.1186/s12889-018-5415-8.
JAISWAL, M, DIVERS, J, URBINA, EM, DABELEA, D, BELL, RA, PETTITT, DJ, et al. (2018). Cardiovascular autonomic neuropathy in adolescents and young adults with type 1 and type 2 diabetes: The search for diabetes in youth cohort study. *Pediatr Diabetes, 19*(4), pp. 680-689. doi: 10.1111/pedi.12633.
JAISWAL, M, URBINA, E, WADWA, R, TALTON, J, D'AGOSTINO, R, HAMMAN, R, et al. (2013). Reduced heart rate variability among youth with type 1 diabetes. *Diabetes Care*doi: 10.2337/dc12-0463.
JAISWAL, M, URBINA, EM, WADWA, RP, TALTON, JW, D'AGOSTINO, RB, HAMMAN, RF, et al. (2013). Reduced heart rate variability is associated with increased arterial stiffness in youth with type 1 diabetes: The search cvd study *Diabetes care* (Vol. 36, pp. 2351-2358).
JAKOVLJEVIC, DG. (2018). Physical activity and cardiovascular aging: Physiological and molecular insights. *Exp Gerontol, 109*, pp. 67-74. doi: 10.1016/j.exger.2017.05.016.
JANSSEN, I, & LEBLANC, AG. (2010). Systematic review of the health benefits of physical activity and fitness in school-aged children and youth. *Int J Behav Nutr Phys Act, 7*, p 40. doi: 1479-5868-7-40 [pii]
10.1186/1479-5868-7-40.
JARCZOK, MN, JARCZOK, M, MAUSS, D, KOENIG, J, LI, J, HERR, RM, et al. (2013). Autonomic nervous system activity and workplace stressors--a systematic review. *Neurosci Biobehav Rev, 37*(8), pp. 1810-1823. doi: 10.1016/j.neubiorev.2013.07.004.
JEBB, A, & TAY, L. (2016). Introduction to time series analysis for organizational research: Methods for longitudinal analyses. [research-article]. *Organ Res Methods, 20*(1)doi: 10.1177_1094428116668035.
JEFFERIS, B, PARSONS, T, SARTINI, C, ASH, S, LENNON, L, PAPACOSTA, O, et al. (2019). Objectively measured physical activity, sedentary behaviour and all-cause mortality in older men: Does volume of activity matter more than pattern of accumulation? *Brit J Sport Med, 53*(1013-1020)doi: 10.1136/bjsports-2017-098733.
JENSEN-URSTAD, K, STORCK, N, BOUVIER, F, ERICSON, M, LINDBLAD, L, & JENSEN-URSTAD, M. (1997). Heart rate variability in healthy subjects is related to age and gender. *Acta Physiol Scand, 160*(3)doi: 10.1046/j.1365-201X.1997.00142.x.
JETTÉ, M, SIDNEY, K, & BLÜMCHEN, G. (1990). Metabolic equivalents (mets) in exercise testing, exercise prescription, and evaluation of functional capacity. *Clin Cardiol, 13*(8)doi: 10.1002/clc.4960130809.
JIANG, J. (2007). *Linear and generalized linear mixed models and their applications | springerlink*: Name Springer, New York, NY.
JOHNSON, C, BAUGH, R, WILSON, C, & BURNS, J. (2001). Age related changes in the tunica media of the vertebral artery: Implications for the assessment of

vessels injured by trauma. *J Clin Pathol, 54*(2), pp. 139-145. doi: 10.1136/jcp.54.2.139.
JUONALA, M, MAGNUSSEN, C, BERENSON, G, VENN, A, BURNS, T, SABIN, M, et al. (2011). Childhood adiposity, adult adiposity, and cardiovascular risk factors. *N Engl J Med, 365*(20)doi: 10.1056/NEJMoa1010112.
KAMINSKY, L, ARENA, R, & MYERS, J. (2015). Reference standards for cardiorespiratory fitness measured with cardiopulmonary exercise testing: Data from the fitness registry and the importance of exercise national database. *Mayo Clinic proceedings, 90*(11)doi: 10.1016/j.mayocp.2015.07.026.
KANTARAS, P. (2018). *The reliability of the vyntus cpx.* (T.E.I. of Crete, School of Agriculture, Food and Nutrition (STeGTET), Department of Nutrition and Dietetics.
KARAS, M, BAI, J, STRĄCZKIEWICZ, M, HAREZLAK, J, GLYNN, N, HARRIS, T, et al. (2019). Accelerometry data in health research: Challenges and opportunities. *Stat Biosci, 11*(2)doi: 10.1007/s12561-018-9227-2.
KEADLE, SK, CONROY, DE, BUMAN, MP, DUNSTAN, DW, & MATTHEWS, CE. (2017). Targeting reductions in sitting time to increase physical activity and improve health. *Med Sci Sports Exerc, 49*(8), pp. 1572-1582. doi: 10.1249/mss.0000000000001257.
KEMBER, G, FENTON, G, ARMOUR, J, & KALYANIWALLA, N. (2001). Competition model for aperiodic stochastic resonance in a fitzhugh-nagumo model of cardiac sensory neurons. *Phys Rev E Stat Nonlin Soft Matter Phys, 63*(4 Pt 1)doi: 10.1103/PhysRevE.63.041911.
KEMBER, G, FENTON, G, COLLIER, K, & ARMOUR, J. (2000). Aperiodic stochastic resonance in a hysteretic population of cardiac neurons. *Phys Rev E Stat Phys Plasmas Fluids Relat Interdiscip Topics, 61*(2)doi: 10.1103/physreve.61.1816.
KENNEDY, A, NIRANTHARAKUMAR, K, CHIMEN, M, PANG, TT, HEMMING, K, ANDREWS, RC, et al. (2013). Does exercise improve glycaemic control in type 1 diabetes? A systematic review and meta-analysis *Plos one* (Vol. 8).
KERR, J, MARINAC, CR, ELLIS, K, GODBOLE, S, HIPP, A, GLANZ, K, et al. (2017). Comparison of accelerometry methods for estimating physical activity. *Med Sci Sports Exerc, 49*(3), pp. 617-624. doi: 10.1249/mss.0000000000001124.
KLEIGER, RE, STEIN, PK, & BIGGER, JT, Jr. (2005). Heart rate variability: Measurement and clinical utility. *Ann Noninvasive Electrocardiol, 10*(1), pp. 88-101. doi: 10.1111/j.1542-474X.2005.10101.x.
KNOWLES, JW, & ASHLEY, EA. (2018). Cardiovascular disease: The rise of the genetic risk score. *PLoS Med, 15*(3)doi: 10.1371/journal.pmed.1002546.
KOHL, H. (2001). Physical activity and cardiovascular disease: Evidence for a dose response. *Med Sci Sports Exerc, 33*(6 Suppl)doi: 10.1097/00005768-200106001-00017.
KÖNIGSTEIN, K, KLENK, C, APPENZELLER-HERZOG, C, HINRICHS, T, & SCHMIDT-TRUCKSÄSS, A. (2020). Impact of sedentary behavior on large artery structure and function in children and adolescents: A systematic review. *Eur J Pediatr, 179*(1)doi: 10.1007/s00431-019-03497-3.
KOSTER, A, CASEROTTI, P, PATEL, KV, MATTHEWS, CE, BERRIGAN, D, VAN DOMELEN, DR, et al. (2012). Association of sedentary time with mortality independent of moderate to vigorous physical activity. *PLoS One, 7*(6), p e37696. doi: 10.1371/journal.pone.0037696.

KOZIEŁ, SM, & MALINA, RM. (2018). Modified maturity offset prediction equations: Validation in independent longitudinal samples of boys and girls *Sports med* (Vol. 48, pp. 221-236).
KRACHT, D, SHROFF, R, BAIG, S, DOYON, A, JACOBI, C, ZELLER, R, et al. (2011). Validating a new oscillometric device for aortic pulse wave velocity measurements in children and adolescents. *Am J Hypertens, 24*(12), pp. 1294-1299. doi: 10.1038/ajh.2011.147.
KRISTENSEN, P, KORSHOLM, L, MØLLER, N, WEDDERKOPP, N, ANDERSEN, L, & FROBERG, K. (2008). Sources of variation in habitual physical activity of children and adolescents: The european youth heart study. *Scand J Med Sci Sports, 18*(3)doi: 10.1111/j.1600-0838.2007.00668.x.
KROMENACKER, B, SANOVA, A, MARCUS, F, ALLEN, J, & LANE, R. (2018). Vagal mediation of low-frequency heart rate variability during slow yogic breathing. *Psychosom Med, 80*(6)doi: 10.1097/PSY.0000000000000603.
KWON, S, JANZ, KF, BURNS, TL, & LEVY, SM. (2011). Association between light-intensity physical activity and adiposity in childhood. *Pediatr Exerc Sci, 23*(2), pp. 218-229.
LACHAT, C, OTCHERE, S, ROBERFROID, D, ABDULAI, A, SERET, F, MILESEVIC, J, et al. (2013). Diet and physical activity for the prevention of noncommunicable diseases in low- and middle-income countries: A systematic policy review. *PLoS medicine, 10*(6)doi: 10.1371/journal.pmed.1001465.
LACOLLEY, P, REGNAULT, V, SEGERS, P, & LAURENT, S. (2017). Vascular smooth muscle cells and arterial stiffening: Relevance in development, aging, and disease. *Physiol Rev, 97*(4)doi: 10.1152/physrev.00003.2017.
LAKATTA, EG, & LEVY, D. (2003). Arterial and cardiac aging: Major shareholders in cardiovascular disease enterprises: Part i: Aging arteries: A "set up" for vascular disease. *Circulation, 107*(1), pp. 139-146. doi: 10.1161/01.cir.0000048892.83521.58.
LANDT, KW, CAMPAIGNE, BN, JAMES, FW, & SPERLING, MA. (1985). Effects of exercise training on insulin sensitivity in adolescents with type i diabetes. *Diabetes Care, 8*(5), pp. 461-465.
LANGSTED, A, FREIBERG, JJ, & NORDESTGAARD, BG. (2008). Fasting and nonfasting lipid levels: Influence of normal food intake on lipids, lipoproteins, apolipoproteins, and cardiovascular risk prediction. *Circulation, 118*(20), pp. 2047-2056. doi: 10.1161/circulationaha.108.804146.
LARKIN, M, BACKLUND, J, P, C, M, B, B, S, CANADY, J, et al. (2010). Disparity in management of diabetes and coronary heart disease risk factors by sex in dcct/edic. *Diabet Med, 27*(4)doi: 10.1111/j.1464-5491.2010.02972.x.
LAROUCHE, R. (2014). Physical inactivity in developing countries. *CMAJ, 186*(14), p 1092. doi: 10.1503/cmaj.114-0071.
LASCAR, N, KENNEDY, A, JACKSON, N, DALEY, A, DOWSWELL, G, THOMPSON, D, et al. (2013). Exercise to preserve beta cell function in recent-onset type 1 diabetes mellitus (extod)--a study protocol for a pilot randomized controlled trial. *Trials, 14*, p 180. doi: 10.1186/1745-6215-14-180.
LAURENT, P, MARENCO, P, CASTAGNA, O, SMULYAN, H, BLACHER, J, & SAFAR, ME. (2011). Differences in central systolic blood pressure and aortic stiffness between aerobically trained and sedentary individuals. *J Am Soc Hypertens, 5*(2), pp. 85-93. doi: 10.1016/j.jash.2011.01.003.

LAURENT, S, BOUTOUYRIE, P, & LACOLLEY, P. (2005). Structural and genetic bases of arterial stiffness. *Hypertens, 45*(6)doi: 10.1161/01.HYP.0000164580.39991.3d.

LAURENT, S, COCKCROFT, J, VAN BORTEL, L, BOUTOUYRIE, P, GIANNATTASIO, C, HAYOZ, D, et al. (2006). Expert consensus document on arterial stiffness: Methodological issues and clinical applications. *Eur Heart J, 27*(21), pp. 2588-2605. doi: 10.1093/eurheartj/ehl254.

LAURSEN, ASD, HANSEN, ALS, WIINBERG, N, BRAGE, S, SANDBÆK, A, LAURITZEN, T, et al. (2015). Higher physical activity is associated with lower aortic stiffness but not with central blood pressure: The addition-pro study. *Medicine, 94*(5)doi: 10.1097/md.0000000000000485.

LECLAIR, E, DE KERDANET, M, RIDDELL, M, & HEYMAN, E. (2013). Type 1 diabetes and physical activity in children and adolescents. *Diabetes Metab*, pp. 1-10. doi: 10.4172/2155-6156.S10-004.

LEE, IM, & SHIROMA, EJ. (2014). Using accelerometers to measure physical activity in large-scale epidemiologic studies: Issues and challenges. *Br J Sports Med, 48*(3), pp. 197-201. doi: 10.1136/bjsports-2013-093154.

LEE, IM, SHIROMA, EJ, LOBELO, F, PUSKA, P, BLAIR, SN, & KATZMARZYK, PT. (2012). Impact of physical inactivity on the world's major non-communicable diseases. *Lancet, 380*(9838), pp. 219-229. doi: 10.1016/s0140-6736(12)61031-9.

LEMOGOUM, D, FLORES, G, VAN DEN ABEELE, W, CIARKA, A, LEEMAN, M, DEGAUTE, J, et al. (2004). Validity of pulse pressure and augmentation index as surrogate measures of arterial stiffness during beta-adrenergic stimulation. *J Hypertens, 22*(3)doi: 10.1097/00004872-200403000-00013.

LESSIANI, G, SANTILLI, F, BOCCATONDA, A, IODICE, P, LIANI, R, TRIPALDI, R, et al. (2016). Arterial stiffness and sedentary lifestyle: Role of oxidative stress. *Vascul Pharmacol, 79*, pp. 1-5. doi: 10.1016/j.vph.2015.05.017.

LI, C, BEECH, B, CRUME, T, D'AGOSTINO, R, DABELEA, D, KAAR, J, et al. (2015a). Longitudinal association between television watching and computer use and risk markers in diabetes in the search for diabetes in youth study. *Pediatric diabetes, 16*(5)doi: 10.1111/pedi.12163.

LI, C, BEECH, B, CRUME, T, D'AGOSTINO, R, DABELEA, D, KAAR, J, et al. (2015b). Longitudinal association between television watching and computer use and risk markers in diabetes in the search for diabetes in youth study. *Pediatr Diabetes, 16*(5)doi: 10.1111/pedi.12163.

LIATIS, S, ALEXIADOU, K, TSIAKOU, A, MAKRILAKIS, K, KATSILAMBROS, N, & TENTOLOURIS, N. (2011). Cardiac autonomic function correlates with arterial stiffness in the early stage of type 1 diabetes. *Exp Diabetes Res, 2011*doi: 10.1155/2011/957901.

LIESE, A, MA, X, MAAHS, D, M, & TRILK, J, L. (2013). Physical activity, sedentary behaviors, physical fitness, and their relation to health outcomes in youth with type 1 and type 2 diabetes: A review of the epidemiologic literature - sciencedirect. *J Sport Health Sci, 2*(1), pp. 21-38.

LIVINGSTONE, MB, ROBSON, PJ, WALLACE, JM, & MCKINLEY, MC. (2003). How active are we? Levels of routine physical activity in children and adults. *Proc Nutr Soc, 62*(3), pp. 681-701. doi: 10.1079/pns2003291.

LONDON, G, & COHN, J. (2002). Prognostic application of arterial stiffness: Task forces. *Am J Hypertens, 15*(8)doi: 10.1016/s0895-7061(02)02966-7.

LOPRINZI, PD, & CARDINAL, BJ. (2011). Measuring children's physical activity and sedentary behaviours. *Journal of Exercise Science & Fitness, 9*(1), pp. 15 - 23.
LOPRINZI, PD, LEE, H, & CARDINAL, BJ. (2014). Daily movement patterns and biological markers among adults in the united states. *Prev Med, 60*, pp. 128-130. doi: 10.1016/j.ypmed.2013.12.017.
LOWE, A, HARRISON, W, EL-AKLOUK, E, RUYGROK, P, & AL-JUMAILY, A. (2009). Non-invasive model-based estimation of aortic pulse pressure using suprasystolic brachial pressure waveforms. *J Biomech, 42*(13)doi: 10.1016/j.jbiomech.2009.05.029.
LOYEN, A, VAN HECKE, L, VERLOIGNE, M, HENDRIKSEN, I, LAKERVELD, J, STEENE-JOHANNESSEN, J, et al. (2016). Variation in population levels of physical activity in european adults according to cross-european studies: A systematic literature review within dedipac. *Int J Behav Nutr Phys Act, 13*(72)doi: 10.1186/s12966-016-0398-2.
LYNCH, BA, KAUFMAN, TK, RAJJO, TI, MOHAMMED, K, KUMAR, S, MURAD, MH, et al. (2019). Accuracy of accelerometers for measuring physical activity and levels of sedentary behavior in children: A systematic review. *J Prim Care Community Health, 10*doi: 10.1177/2150132719874252.
LYNCH, K, CORBIN, C, & SIDMAN, C. (2009). Testing compensation: Does recreational basketball impact adult activity levels? *J Phys Act Health, 6*(3)doi: 10.1123/jpah.6.3.321.
MACKINTOSH, K, MONTOYE, A, PFEIFFER, K, & MCNARRY, M. (2016). Investigating optimal accelerometer placement for energy expenditure prediction in children using a machine learning approach. *Physiol Meas, 37*(10)doi: 10.1088/0967-3334/37/10/1728.
MADDISON, R, JIANG, Y, FOLEY, L, SCRAGG, R, DIREITO, A, & OLDS, T. (2016). The association between the activity profile and cardiovascular risk. *J Sci Med Sport, 19*(8), pp. 605-610. doi: 10.1016/j.jsams.2015.08.001.
MAGNUSSEN, CG, & SMITH, KJ. (2016). Pediatric blood pressure and adult preclinical markers of cardiovascular disease. *Clin Med Insights Blood Disord, 9*, pp. 1-8. doi: 10.4137/cmbd.s18887.
MÄKI-PETÄJÄ, KM, BARRETT, SM, EVANS, SV, CHERIYAN, J, MCENIERY, CM, & WILKINSON, IB. (2016). The role of the autonomic nervous system in the regulation of aortic stiffness. *Hypertension, 68*(5), pp. 1290-1297. doi: 10.1161/hypertensionaha.116.08035.
MANCIA, G, & GRASSI, G. (2014). The autonomic nervous system and hypertension. *Circ Res, 114*(11), pp. 1804-1814. doi: 10.1161/circresaha.114.302524.
MASSA, G, GYS, I, OP'T EYNDT, A, BEVILACQUA, E, WIJNANDS, A, DECLERCQ, P, et al. (2018). Evaluation of the freestyle® libre flash glucose monitoring system in children and adolescents with type 1 diabetes. *Horm Res Paediatr, 89*(3)doi: 10.1159/000487361.
MATEU-FIGUERAS, G, PAWLOWSKY-GLAHN, V, & EGOZCUE, J. (2011). The principles of working on coordinates. In V. Pawlowsky-Glahn & A. Buccianti (Eds.), *Compositional data analysis: Theory and application*.
MATTHEWS, C, AINSWORTH, B, THOMPSON, R, & BASSETT, D. (2002). Sources of variance in daily physical activity levels as measured by an accelerometer. *Med Sci Sports Exerc, 34*(8)doi: 10.1097/00005768-200208000-00021.

MATTHEWS, C, KEADLE, S, TROIANO, R, KAHLE, L, KOSTER, A, BRYCHTA, R, et al. (2016). Accelerometer-measured dose-response for physical activity, sedentary time, and mortality in us adults. *Am J Clin Nutr, 104*(5)doi: 10.3945/ajcn.116.135129.

MATTHEWS, CE, CHEN, KY, FREEDSON, PS, BUCHOWSKI, MS, BEECH, BM, PATE, RR, et al. (2008). Amount of time spent in sedentary behaviors in the united states, 2003-2004. *Am J Epidemiol, 167*(7), pp. 875-881. doi: 10.1093/aje/kwm390.

MATTHEWS, CE, HAGSTRÖMER, M, POBER, DM, & BOWLES, HR. (2012). Best practices for using physical activity monitors in population-based research. *Med Sci Sports Exerc, 44*(1 Suppl 1), pp. S68-76. doi: 10.1249/MSS.0b013e3182399e5b.

MATTOCKS, C, NESS, A, LEARY, S, TILLING, K, BLAIR, SN, SHIELD, J, et al. (2008). Use of accelerometers in a large field-based study of children: Protocols, design issues, and effects on precision. [Article]. *J Phys Act Health, 5*, pp. S98-S111.

MCENIERY, C, YASMIN, N, HALL, I, QASEM, A, WILKINSON, I, & COCKCROFT, J. (2005). Normal vascular aging: Differential effects on wave reflection and aortic pulse wave velocity: The anglo-cardiff collaborative trial (acct). *J Am Coll Cardiol, 46*(9)doi: 10.1016/j.jacc.2005.07.037.

MCLELLAN, G, ARTHUR, R, & BUCHAN, D. (2018). Wear compliance, sedentary behaviour and activity in free-living children from hip-and wrist-mounted actigraph gt3x+ accelerometers. *J Sports Sci, 36*(21)doi: 10.1080/02640414.2018.1461322.

MCNARRY, M, MACKINTOSH, K, & STOEDEFALKE, K. (2014). Longitudinal investigation of training status and cardiopulmonary responses in pre- and early-pubertal children. *Eur J Appl Physiol, 114*(8)doi: 10.1007/s00421-014-2890-1.

MENAI, M, VAN HEES, VT, ELBAZ, A, KIVIMAKI, M, SINGH-MANOUX, A, & SABIA, S. (2017). *Accelerometer assessed moderate-to-vigorous physical activity and successful ageing: Results from the whitehall ii study* 2045-2322 (Electronic)). http://dx.doi.org/10.1038/srep45772.

MENDES MDE, A, DA SILVA, I, RAMIRES, V, REICHERT, F, MARTINS, R, FERREIRA, R, et al. (2018). Metabolic equivalent of task (mets) thresholds as an indicator of physical activity intensity *Plos one* (Vol. 13).

MICHALISZYN, SF, & FAULKNER, MS. (2010). Physical activity and sedentary behavior in adolescents with type 1 diabetes. *Res Nurs Health, 33*(5), pp. 441-449. doi: 10.1002/nur.20393.

MIGUELES, J, CADENAS-SANCHEZ, C, ROWLANDS, A, HENRIKSSON, P, SHIROMA, E, ACOSTA, F, et al. (2019). Comparability of accelerometer signal aggregation metrics across placements and dominant wrist cut points for the assessment of physical activity in adults. [OriginalPaper]. *Scientific Reports, 9*(1), pp. 1-12. doi: doi:10.1038/s41598-019-54267-y.

MIGUELES, JH, CADENAS-SANCHEZ, C, EKELUND, U, DELISLE NYSTRÖM, C, MORA-GONZALEZ, J, LÖF, M, et al. (2017). Accelerometer data collection and processing criteria to assess physical activity and other outcomes: A systematic review and practical considerations. *Sports Med, 47*(9), pp. 1821-1845. doi: 10.1007/s40279-017-0716-0.

MILLER, M. (2009). Dyslipidemia and cardiovascular risk: The importance of early prevention *Qjm* (Vol. 102, pp. 657-667).

MIRAKHUR, A, & WALSHAW, MJ. (2003). Autonomic dysfunction in cystic fibrosis. *J R Soc Med, 96*(Suppl 43), pp. 11-17.
MIRWALD, R, BAXTER-JONES, A, BAILEY, D, & BEUNEN, G. (2002). An assessment of maturity from anthropometric measurements. *Med Sci Sports Exerc*(34), pp. 689-694.
MITCHELL, GF, PARISE, H, BENJAMIN, EJ, LARSON, MG, KEYES, MJ, VITA, JA, et al. (2004). Changes in arterial stiffness and wave reflection with advancing age in healthy men and women: The framingham heart study. *Hypertension, 43*(6), pp. 1239-1245. doi: 10.1161/01.HYP.0000128420.01881.aa.
MOCNIK, M, NIKOLIC, S, & MARCUN, N. (2018). Arterial compliance measurement in overweight and hypertensive children | springerlink. *Indian J Pediatr, 83*(6), pp. 510-516. doi: 10.1007/s12098-015-1965-2.
MONTOYE, AH, PIVARNIK, JM, MUDD, LM, BISWAS, S, & PFEIFFER, KA. (2016). Validation and comparison of accelerometers worn on the hip, thigh, and wrists for measuring physical activity and sedentary behavior. *AIMS Public Health, 3*(2), pp. 298-312. doi: 10.3934/publichealth.2016.2.298.
MONZON, A, MCDONOUGH, R, MELTZER, L, & PATTON, S. (2019). Sleep and type 1 diabetes in children and adolescents: Proposed theoretical model and clinical implications. *Pediatric Diabetes, 20*(1)doi: 10.1111/pedi.12797.
MOODITHAYA, S, & AVADHANY, ST. (2012). Gender differences in age-related changes in cardiac autonomic nervous function. *J Aging Res, 2012*doi: 10.1155/2012/679345.
MÜLLER, J, OBERHOFFER, R, BARTA, C, HULPKE-WETTE, M, & HAGER, A. (2013). Oscillometric carotid to femoral pulse wave velocity estimated with the vicorder device. *J Clin Hypertens, 15*(3)doi: 10.1111/jch.12045.
MUNDWILER, J, SCHÜPBACH, U, DIETERLE, T, LEUPPI, JD, SCHMIDT-TRUCKSÄSS, A, WOLFER, DP, et al. (2017). Association of occupational and leisure-time physical activity with aerobic capacity in a working population. *PLoS One, 12*(1)doi: 10.1371/journal.pone.0168683.
MYERS, J, MCAULEY, P, LAVIE, C, DESPRES, J, ARENA, R, & KOKKINOS, P. (2015). Physical activity and cardiorespiratory fitness as major markers of cardiovascular risk: Their independent and interwoven importance to health status. *Prog Cardiovasc Dis, 57*(4)doi: 10.1016/j.pcad.2014.09.011.
NADEAU, KJ, REGENSTEINER, JG, BAUER, TA, BROWN, MS, DOROSZ, JL, HULL, A, et al. (2010). Insulin resistance in adolescents with type 1 diabetes and its relationship to cardiovascular function. *J Clin Endocrinol Metab, 95*(2), pp. 513-521. doi: 10.1210/jc.2009-1756.
NAGAI, N, HAMADA, T, KIMURA, T, & MORITANI, T. (2004). Moderate physical exercise increases cardiac autonomic nervous system activity in children with low heart rate variability | springerlink. *Child Nerv Syst, 20*(4), pp. 209-214. doi: 10.1007/s00381-004-0915-5.
NARENDRAN, P, JACKSON, N, DALEY, A, THOMPSON, D, STOKES, K, GREENFIELD, S, et al. (2017). Exercise to preserve β-cell function in recent-onset type 1 diabetes mellitus (extod) - a randomized controlled pilot trial. *Diabet Med, 34*(11)doi: 10.1111/dme.13439.
NATHAN, DM, KUENEN, J, BORG, R, ZHENG, H, SCHOENFELD, D, & HEINE, RJ. (2008). Translating the a1c assay into estimated average glucose values. *Diabetes Care, 31*(8), pp. 1473-1478. doi: 10.2337/dc08-0545.
NATIONAL HEALTH SERVICE DIGITAL. (2020). *Statistics on obesity, physical activity and diet, england 2020*. England: https://digital.nhs.uk/data-and-

information/publications/statistical/statistics-on-obesity-physical-activity-and-diet/england-2020/part-5-adult-physical-activity-copy.
NELSON, ME, REJESKI, WJ, BLAIR, SN, DUNCAN, PW, JUDGE, JO, KING, AC, et al. (2007). Physical activity and public health in older adults: Recommendation from the american college of sports medicine and the american heart association. *Med Sci Sports Exerc, 39*(8), pp. 1435-1445. doi: 10.1249/mss.0b013e3180616aa2.
NETTLEFOLD, L, MCKAY, H, NAYLOR, P, BREDIN, S, & WARBURTON, D. (2012). The relationship between objectively measured physical activity, sedentary time, and vascular health in children. *Am J Hypertens, 25*(8)doi: 10.1038/ajh.2012.68.
NETTLEFOLD, L, MCKAY, H, NAYLOR, P, BREDIN, S, & WARBURTON, D. (2019). The relationship between objectively measured physical activity, sedentary time, and vascular health in children. *Am J of Hypertens, 25*(8), pp. 914-919. doi: 10.1038/ajh.2012.68.
NEVILL, A, BATE, S, & HOLDER, R. (2005). Modeling physiological and anthropometric variables known to vary with body size and other confounding variables. *Am J Phys Anthropol, Suppl 41*doi: 10.1002/ajpa.20356.
NGUYEN, T, OBEID, J, WALKER, RG, KRAUSE, MP, HAWKE, TJ, MCASSEY, K, et al. (2015). Fitness and physical activity in youth with type 1 diabetes mellitus in good or poor glycemic control. *Pediatr Diabetes, 16*(1), pp. 48-57. doi: 10.1111/pedi.12117.
NICE. (2015). *Diabetes (type 1 and type 2) in children and young people: Diagnosis and management*. London: http://dx.doi.org/.
NOH, J, KIM, E, SEO, H, & KIM, SG. (2016). Independent association between glycated hemoglobin and arterial stiffness in healthy men. *J Diabetes Investig, 7*(2), pp. 241-246. doi: 10.1111/jdi.12389.
NOLAN, J, BATIN, P, ANDREWS, R, LINDSAY, S, BROOKSBY, P, MULLEN, M, et al. (1998). Prospective study of heart rate variability and mortality in chronic heart failure. *Circulation*(98), pp. 1510-1516. doi: 10.1161/01.CIR.98.15.1510.
NOOIJEN, CFJ, DEL POZO-CRUZ, B, NYBERG, G, SANDERS, T, GALANTI, MR, & FORSELL, Y. (2018). Are changes in occupational physical activity level compensated by changes in exercise behavior? *Eur J Pub Health, 28*(5), pp. 940-943. doi: 10.1093/eurpub/cky007.
NORDESTGAARD, BG. (2017). A test in context: Lipid profile, fasting versus nonfasting. *J Am Coll Cardiol, 70*(13), pp. 1637-1646. doi: 10.1016/j.jacc.2017.08.006.
NÚÑEZ, F, MARTÍNEZ-COSTA, C, SÁNCHEZ-ZAHONERO, J, MORATA, J, CHORRO, F, & BRINES, J. (2010). Carotid artery stiffness as an early marker of vascular lesions in children and adolescents with cardiovascular risk factors. *Revista espanola de cardiologia, 63*(11)doi: 10.1016/s1885-5857(10)70250-4.
NUTTALL, FQ. (2015). Body mass index: Obesity, bmi, and health: A critical review. *Nutr Today, 50*(3), pp. 117-128. doi: 10.1097/nt.0000000000000092.
O'CONNELL, SE, GRIFFITHS, PL, & CLEMES, SA. (2014). Seasonal variation in physical activity, sedentary behaviour and sleep in a sample of uk adults. *Ann Hum Biol, 41*(1), pp. 1-8. doi: 10.3109/03014460.2013.827737.
O'ROURKE, M, PAUCA, A, & JIANG, X. (2001). Pulse wave analysis. *Br J Clin Pharmacol, 51*(6)doi: 10.1046/j.0306-5251.2001.01400.x.

OBERMANNOVA, B, PETRUZELKOVA, L, SULAKOVA, T, & SUMNIK, Z. (2017). Hba1c but not diabetes duration predicts increased arterial stiffness in adolescents with poorly controlled type 1 diabetes. *Pediatric Diabetes, 18*(4)doi: 10.1111/pedi.12385.

OBERT, P, MANDIGOUT, S, VINET, A, NOTTIN, S, N'GUYEN, L, & LECOQ, A. (2005). Relationships between left ventricular morphology, diastolic function and oxygen carrying capacity and maximal oxygen uptake in children. *Int J Sports Med, 26*(2)doi: 10.1055/s-2004-817857.

OFFICE OF DISEASE PREVENTION AND HEALTH PROMOTION. (2008). *2008 physical activity guidelines - health.Gov*. https://health.gov/paguidelines/2008/.

OGOLA, BO, ZIMMERMAN, MA, CLARK, GL, ABSHIRE, CM, GENTRY, KM, MILLER, KS, et al. (2018). New insights into arterial stiffening: Does sex matter? *Am J Physiol Heart Circ Physiol, 315*(5), pp. H1073-1087. doi: 10.1152/ajpheart.00132.2018.

OLDS, T, WAKE, M, PATTON, G, RIDLEY, K, WATERS, E, WILLIAMS, J, et al. (2009). How do school-day activity patterns differ with age and gender across adolescence? *J Adolesc Health, 44*(1)doi: 10.1016/j.jadohealth.2008.05.003.

OLIVEIRA, R, BARKER, A, WILKINSON, K, ABBOTT, R, & WILLIAMS, C. (2017). Is cardiac autonomic function associated with cardiorespiratory fitness and physical activity in children and adolescents? A systematic review of cross-sectional studies. *Int J Cardiol, 236*doi: 10.1016/j.ijcard.2017.02.022.

OLIVEIRA, R, BARKER, A, & WILLIAMS, C. (2017). Cardiac autonomic function, cardiovascular risk and physical activity in adolescents. *Int J Sport Med, 39*, pp. 89-96. doi: 10.1055/s-0043-118850.

OLIVER, J, & WEBB, D. (2003). Noninvasive assessment of arterial stiffness and risk of atherosclerotic events. [review-article]. *Arterioscler Thromb Vasc Biol, 23*(4)doi: 10.1161/01.ATV.0000060460.52916.D6.

ORI, Z, MONIR, G, WEISS, J, SAYHOUNI, X, & SINGER, DH. (1992). Heart rate variability. Frequency domain analysis. *Cardiol Clin, 10*(3), pp. 499-537.

ORME, M, WIJNDAELE, K, SHARP, S, WESTGATE, K, EKELUND, U, & BRAGE, S. (2014). Combined influence of epoch length, cut-point and bout duration on accelerometry-derived physical activity. [OriginalPaper]. *Int J Behav Nutr Phys Act, 11*(1), pp. 1-8. doi: doi:10.1186/1479-5868-11-34.

OWEN, N, HEALY, GN, MATTHEWS, CE, & DUNSTAN, DW. (2010). Too much sitting: The population health science of sedentary behavior. *Exerc Sport Sci Rev, 38*(3), pp. 105-113. doi: 10.1097/JES.0b013e3181e373a2.

PALATINI, P, & JULIUS, S. (2009). The role of cardiac autonomic function in hypertension and cardiovascular disease. *Curr Hypertens Rep, 11*(3)doi: 10.1007/s11906-009-0035-4.

PANDIT, DS, KHADILKAR, AV, CHIPLONKAR, SA, KHADILKAR, VV, & KINARE, AS. (2014). Arterial stiffness in obese children: Role of adiposity and physical activity. *Indian J Endocrinol Metab, 18*(1), pp. 70-76. doi: 10.4103/2230-8210.126565.

PAPAIOANNOU, V, PNEUMATIKOS, I, & MAGLAVERAS, N. (2013). Association of heart rate variability and inflammatory response in patients with cardiovascular diseases: Current strengths and limitations. *Front Physiol, 4*doi: 10.3389/fphys.2013.00174.

PARASHAR, R, AMIR, M, PAKHARE, A, RATHI, P, & CHAUDHARY, L. (2016). Age related changes in autonomic functions. *J Clin Diagn Res, 10*(3), pp. CC11-15. doi: 10.7860/jcdr/2016/16889.7497.
PARIKH, JD, HOLLINGSWORTH, KG, KUNADIAN, V, BLAMIRE, A, & MACGOWAN, GA. (2016). Measurement of pulse wave velocity in normal ageing: Comparison of vicorder and magnetic resonance phase contrast imaging. *BMC Cardiovasc Disord, 16*(50)doi: 10.1186/s12872-016-0224-4.
PARK, S, & LAKATTA, EG. (2012). Role of inflammation in the pathogenesis of arterial stiffness. *Yonsei Med J, 53*(2), pp. 258-261. doi: 10.3349/ymj.2012.53.2.258.
PARK, W, PARK, HY, LIM, K, & PARK, J. (2017). The role of habitual physical activity on arterial stiffness in elderly individuals: A systematic review and meta-analysis *J exerc nutrition biochem* (Vol. 21, pp. 16-21).
PARSONS, TJ, SARTINI, C, ELLINS, EA, HALCOX, JPJ, SMITH, KE, ASH, S, et al. (2016). Objectively measured physical activity, sedentary time and subclinical vascular disease: Cross-sectional study in older british men. *Prev Med, 89*, pp. 194-199. doi: 10.1016/j.ypmed.2016.05.031.
PAVEY, TG, GOMERSALL, SR, CLARK, BK, & BROWN, WJ. (2016). The validity of the geneactiv wrist-worn accelerometer for measuring adult sedentary time in free living. *J Sci Med Sport, 19*(5), pp. 395-399. doi: 10.1016/j.jsams.2015.04.007.
PAWLOWSKY-GLAHN, V, EGOZCUE, J, & TOLOSANA-DELGADO, R. (2015). *Modelling and analysis of compositional data* Chichester, UK: John Wiley & Sons.
PEARSON, K. (1896). Mathematical contributions to the theory of evolution.--on a form of spurious correlation which may arise when indices are used in the measurement of organs. *Proc R Soc Lond, 60*, pp. 489-498.
PENG, X, HALDAR, S, DESHPANDE, S, IRANI, K, & KASS, D. (2003). Wall stiffness suppresses akt/enos and cytoprotection in pulse-perfused endothelium. *Hypertens, 41*(2)doi: 10.1161/01.hyp.0000049624.99844.3d.
PERCHARD, R, & AMIN, R. (2015). Childhood-onset type 1 diabetes and cardiovascular disease. *Diabetes Management, 5*(3), pp. 215 –227. doi: 10.2217/DMT.14.61.
PEREIRA, S, GOMES, TN, BORGES, A, SANTOS, D, SOUZA, M, DOS SANTOS, FK, et al. (2015). Variability and stability in daily moderate-to-vigorous physical activity among 10 year old children *Int j environ res public health* (Vol. 12, pp. 9248-9263).
PHILLIPS, L, PARFITT, G, & ROWLANDS, A. (2013). Calibration of the genea accelerometer for assessment of physical activity intensity in children. *J Sci Med Sport, 16*(2)doi: 10.1016/j.jsams.2012.05.013.
PHILPOTT, J, HOUGHTON, K, & LUKE, A. (2018). Physical activity recommendations for children with specific chronic health conditions: Juvenile idiopathic arthritis, hemophilia, asthma and cystic fibrosis. *Paediatr Child Health, 15*(4), pp. 213-218. doi: 10.1093/pch/15.4.213.
PIVOVAROV, JA, TAPLIN, CE, & RIDDELL, MC. (2015). Current perspectives on physical activity and exercise for youth with diabetes. *Pediatr Diabetes, 16*(4), pp. 242-255. doi: 10.1111/pedi.12272.
PLASQUI, G, & WESTERTERP, KR. (2007). Physical activity assessment with accelerometers: An evaluation against doubly labeled water. *Obesity, 15*(10), pp. 2371-2379. doi: 10.1038/oby.2007.281.

POEHLMAN, E, GORAN, M, GARDNER, A, ADES, P, ARCIERO, P, KATZMAN-ROOKS, S, et al. (1993). Determinants of decline in resting metabolic rate in aging females. *The American journal of physiology, 264*(3 Pt 1)doi: 10.1152/ajpendo.1993.264.3.E450.

POITRAS, V, GRAY, C, BORGHESE, M, CARSON, V, CHAPUT, J, JANSSEN, I, et al. (2016). Systematic review of the relationships between objectively measured physical activity and health indicators in school-aged children and youth. *Appl Physiol Nutr Metab, 41*(6 Suppl 3)doi: 10.1139/apnm-2015-0663.

POLONSKY, W, ANDERSON, B, LOHRER, P, APONTE, J, JACOBSON, A, & COLE, C. (1994). Insulin omission in women with iddm. *Diabetes Care, 17*(10)doi: 10.2337/diacare.17.10.1178.

PORTER, AK, MATTHEWS, KJ, SALVO, D, & KOHL, HW, 3rd. (2017). Associations of physical activity, sedentary time, and screen time with cardiovascular fitness in united states adolescents: Results from the nhanes national youth fitness survey. *J Phys Act Health, 14*(7), pp. 506-512. doi: 10.1123/jpah.2016-0165.

POULIOU, T, SERA, F, GRIFFITHS, L, JOSHI, H, GERACI, M, CORTINA-BORJA, M, et al. (2015). Environmental influences on children's physical activity. *J Epidemiol Community Health, 69*(1), pp. 77-85. doi: 10.1136/jech-2014-204287.

POWELL, C, CARSON, BP, DOWD, KP, & DONNELLY, AE. (2017). Simultaneous validation of five activity monitors for use in adult populations. *Scand J Med Sci Sports, 27*(12), pp. 1881-1892. doi: 10.1111/sms.12813.

PRASAD, D, & DAS, B. (2009). Physical inactivity: A cardiovascular risk factor. *Indian J Med Sci, 63*(1)doi: 10.4103/0019-5359.49082.

PRENNER, S, & CHIRINOS, J. (2015). Arterial stiffness in diabetes mellitus. *Atherosclerosis, 238*(2)doi: 10.1016/j.atherosclerosis.2014.12.023.

PUBLIC HEALTH ENGLAND. (2014). Everybody active, every day: Framework for physical activity. Retrieved Date Accessed, 2020 from https://www.gov.uk/government/publications/everybody-active-every-day-a-framework-to-embed-physical-activity-into-daily-life.

PUMPRLA, J, HOWORKA, K, GROVES, D, CHESTER, M, & NOLAN, J. (2002). Functional assessment of heart rate variability: Physiological basis and practical applications. *Int J Cardiol, 84*(1), pp. 1-14.

RAITAKARI, O, PORKKA, K, TAIMELA, S, TELAMA, R, RÄSÄNEN, L, & VIIKARI, J. (1994). Effects of persistent physical activity and inactivity on coronary risk factors in children and young adults. The cardiovascular risk in young finns study. *Am J Epidemiol, 140*(3)doi: 10.1093/oxfordjournals.aje.a117239.

REFERENCE VALUES FOR ARTERIAL STIFFNESS COLLABORATION. (2010). Determinants of pulse wave velocity in healthy people and in the presence of cardiovascular risk factors: 'Establishing normal and reference values'. *Eur Heart J, 31*(19), pp. 2338-2350. doi: 10.1093/eurheartj/ehq165.

REINHARD, U, MULLER, PH, & SCHMULLING, RM. (1979). Determination of anaerobic threshold by the ventilation equivalent in normal individuals. *Respiration, 38*(1), pp. 36-42. doi: 10.1159/000194056.

RENNIE, KL, HEMINGWAY, H, KUMARI, M, BRUNNER, E, MALIK, M, & MARMOT, M. (2003). Effects of moderate and vigorous physical activity on heart rate variability in a british study of civil servants. *Am J Epidemiol, 158*(2), pp. 135-143.

REUSZ, GS, CSEPREKAL, O, TEMMAR, M, KIS, E, CHERIF, AB, THALEB, A, et al. (2010). Reference values of pulse wave velocity in healthy children and teenagers. *Hypertension, 56*(2), pp. 217-224. doi: 10.1161/hypertensionaha.110.152686.

RHEE, M, LEE, H, & PARK, J. (2008). Measurements of arterial stiffness: Methodological aspects. *Kor Circu J, 38*(7), pp. 343-350.

RIDDELL, M, GALLEN, I, SMART, C, TAPLIN, C, ADOLFSSON, P, LUMB, A, et al. (2017). Exercise management in type 1 diabetes: A consensus statement. *Lancet Diabetes Endo, 5*(5), pp. 377-390.

RIDGERS, ND, TIMPERIO, A, CERIN, E, & SALMON, J. (2014). Compensation of physical activity and sedentary time in primary school children. *Med Sci Sports Exerc, 46*(8), pp. 1564-1569. doi: 10.1249/mss.0000000000000275.

RIEBE, D, FRANKLIN, B, A, THOMPSON, P, D, GARBER, C, E, WHITEFIELD, G, P, MAGAL, M, et al. (2015). Updating acsm's recommendations for exercise preparticipation health screening. *Med Sci Sport Exer*doi: DOI: 10.1249/MSS.0000000000000664.

RIED-LARSEN, M, GRØNTVED, A, MØLLER, N, LARSEN, K, FROBERG, K, & ANDERSEN, L. (2014). Associations between objectively measured physical activity intensity in childhood and measures of subclinical cardiovascular disease in adolescence: Prospective observations from the european youth heart study. *Br J Sports Med, 48*(20)doi: 10.1136/bjsports-2012-091958.

RIPPE, JM. (2019). Lifestyle strategies for risk factor reduction, prevention, and treatment of cardiovascular disease. *Am J Lifestyle Med, 13*(2), pp. 204-212. doi: 10.1177/1559827618812395.

ROBINSON, S. (1938). Experimental studies of physical fitness in relation to age. [OriginalPaper]. *Arbeitsphysiologie, 10*(3), pp. 251-323. doi: doi:10.1007/BF02011412.

RODRÍGUEZ, G, MORENO, L, BLAY, M, BLAY, V, FLETA, J, SARRÍA, A, et al. (2005). Body fat measurement in adolescents: Comparison of skinfold thickness equations with dual-energy x-ray absorptiometry. *Eur J Clin Nutr, 59*(10)doi: 10.1038/sj.ejcn.1602226.

ROMAN, M, DEVEREUX, R, SCHWARTZ, J, LOCKSHIN, M, PAGET, S, DAVIS, A, et al. (2005a). Arterial stiffness in chronic inflammatory diseases. *Hypertens, 46*(1)doi: 10.1161/01.HYP.0000168055.89955.db.

ROMAN, M, DEVEREUX, R, SCHWARTZ, J, LOCKSHIN, M, PAGET, S, DAVIS, A, et al. (2005b). Arterial stiffness in chronic inflammatory diseases. *Hypertension, 46*(1)doi: 10.1161/01.HYP.0000168055.89955.db.

ROSENBERGER, ME, BUMAN, MP, HASKELL, WL, MCCONNELL, MV, & CARSTENSEN, LL. (2016). 24 hours of sleep, sedentary behavior, and physical activity with nine wearable devices. *Med Sci Sports Exerc, 48*(3), pp. 457-465. doi: 10.1249/mss.0000000000000778.

ROSSI, P, FRANCÈS, Y, KINGWELL, B, & AHIMASTOS, A. (2011). Gender differences in artery wall biomechanical properties throughout life. *J Hypertens, 29*(6)doi: 10.1097/HJH.0b013e328344da5e.

ROUTLEDGE, FS, CAMPBELL, TS, MCFETRIDGE-DURDLE, JA, & BACON, SL. (2010). Improvements in heart rate variability with exercise therapy *Can j cardiol* (Vol. 26, pp. 303-312).

ROWLAND, T. (1998). The biological basis of physical activity. *Med Sci Sports Exerc, 30*(3)doi: 10.1097/00005768-199803000-00009.

ROWLANDS, A, DAWKINS, N, MAYLOR, B, EDWARDSON, C, FAIRCLOUGH, S, DAVIES, M, et al. (2019). Enhancing the value of accelerometer-assessed physical activity: Meaningful visual comparisons of data-driven translational accelerometer metrics. [BriefCommunication]. *Sports Medicine - Open, 5*(1), pp. 1-11. doi: doi:10.1186/s40798-019-0225-9.

ROWLANDS, A, GOMERSALL, S, TUDOR-LOCKE, C, BASSETT, D, KANG, M, FRAYSSE, F, et al. (2015). Introducing novel approaches for examining the variability of individuals' physical activity. *J Sports Sci, 33*(5)doi: 10.1080/02640414.2014.951067.

ROWLANDS, A, PILGRIM, E, & ESTON, R. (2009). Seasonal changes in children's physical activity: An examination of group changes, intra-individual variability and consistency in activity pattern across season. *Ann Hum Biol, 36*(4)doi: 10.1080/03014460902824220.

ROWLANDS, A, RENNIE, K, KOZARSKI, R, STANLEY, R, ESTON, R, PARFITT, G, et al. (2014). Children's physical activity assessed with wrist- and hip-worn accelerometers. *Med Sci Sports Exerc, 46*(12)doi: 10.1249/MSS.0000000000000365.

ROWLANDS, AV. (2018). Moving forward with accelerometer-assessed physical activity: Two strategies to ensure meaningful, interpretable, and comparable measures. *Pediatr Exerc Sci, 30*(4), pp. 450-456. doi: 10.1123/pes.2018-0201.

ROWLANDS, AV, EDWARDSON, CL, DAVIES, MJ, KHUNTI, K, HARRINGTON, DM, & YATES, T. (2018). Beyond cut points: Accelerometer metrics that capture the physical activity profile. *Med Sci Sports Exerc, 50*(6), pp. 1323-1332. doi: 10.1249/mss.0000000000001561.

ROWLANDS, AV, & ESTON, RG. (2007). The measurement and interpretation of children's physical activity. *J Sports Sci Med, 6*(3), pp. 270-276.

ROYAL COLLEGE OF PAEDIATRICS AND CHILD HEALTH. (2018). *National paediatric diabetes audit report 2016-17: care processes and outcomes*. https://www.rcpch.ac.uk/sites/default/files/2018-07/npda_annual_report_2016_-_2017_april_2018_final_updated_3.pdf. 15/11/2019.

RUNACRES, A, BEZODIS, NE, MACKINTOSH, KA, & MCNARRY, MA. (2019). The reliability of force-velocity-power profiling during over-ground sprinting in children and adolescents. *J Sports Sci, 37*(18), pp. 2131-2137. doi: 10.1080/02640414.2019.1622316.

SAFAR, M, ASMAR, R, BENETOS, A, BLACHER, J, BOUTOUYRIE, P, LACOLLEY, P, et al. (2018). Interaction between hypertension and arterial stiffness. *Hypertens, 72*(4)doi: 10.1161/HYPERTENSIONAHA.118.11212.

SAFAR, M, CZERNICHOW, S, & BLACHER, J. (2006). Obesity, arterial stiffness, and cardiovascular risk. *J Am Soc Nephrol, 17*(4 Suppl 2)doi: 10.1681/ASN.2005121321.

SAINT-MAURICE, PF, KIM, Y, WELK, GJ, & GAESSER, GA. (2016). Kids are not little adults: What met threshold captures sedentary behavior in children? *Eur J Appl Physiol, 116*(1), pp. 29-38. doi: 10.1007/s00421-015-3238-1.

SAKURAGI, S, ABHAYARATNA, K, GRAVENMAKER, K, O'REILLY, C, SRIKUSALANUKUL, W, BUDGE, M, et al. (2009). Influence of adiposity and physical activity on arterial stiffness in healthy children: The lifestyle of our kids study. *Hypertension, 53*(4)doi: 10.1161/HYPERTENSIONAHA.108.123364.

SALAHUDDIN, L, CHO, J, JEONG, M, & KIM, D. (2007). Ultra short term analysis of heart rate variability for monitoring mental stress in mobile settings. *Conf Proc IEEE Eng Med Biol Soc, 2007*doi: 10.1109/IEMBS.2007.4353378.

SALLIS, J, & SAELENS, B. (2000). Assessment of physical activity by self-report: Status, limitations, and future directions. *Res Q Exerc Sport, 71*(2 Suppl).
SALMON, J. (2010). Novel strategies to promote children's physical activities and reduce sedentary behavior. *J Phys Act Health, 7 Suppl 3*doi: 10.1123/jpah.7.s3.s299.
SAMMITO, S, & BOCKELMANN, I. (2016). Options and limitations of heart rate measurement and analysis of heart rate variability by mobile devices: A systematic review. *Herzschrittmacherther Elektrophysiol, 27*(1), pp. 38-45. doi: 10.1007/s00399-016-0419-5.
SAMUELSSON, U, ANDERZÉN, J, GUDBJÖRNSDOTTIR, S, STEINECK, I, ÅKESSON, K, & HANBERGER, L. (2016). Teenage girls with type 1 diabetes have poorer metabolic control than boys and face more complications in early adulthood. *J Diabetes Complications, 30*(5)doi: 10.1016/j.jdiacomp.2016.02.007.
SANDERS, J, WARK, P, WINFREE, K, FALLAHZADEH, R, FERNÁNDEZ, C, HENRIKSEN, A, et al. (2018). Using fitness trackers and smartwatches to measure physical activity in research: Analysis of consumer wrist-worn wearables. *J Med Internet Res, 20*(3)doi: 10.2196/jmir.9157.
SANDERS, T, CLIFF, D, & LONSDALE, C. (2014). Measuring adolescent boys' physical activity: Bout length and the influence of accelerometer epoch length. *PLoS One, 9*(3)doi: 10.1371/journal.pone.0092040.
SARDINHA, LB, ANDERSEN, LB, ANDERSSEN, SA, QUITERIO, AL, ORNELAS, R, FROBERG, K, et al. (2008). Objectively measured time spent sedentary is associated with insulin resistance independent of overall and central body fat in 9- to 10-year-old portuguese children. *Diabetes Care, 31*(3), pp. 569-575. doi: 10.2337/dc07-1286.
SASAKI, J, JÚNIOR, J, MENEGUCI, J, TRIBESS, S, MAROCOLO JÚNIOR, M, STABELINI NETO, A, et al. (2018). Number of days required for reliably estimating physical activity and sedentary behaviour from accelerometer data in older adults. *J Sports Sci, 36*(14)doi: 10.1080/02640414.2017.1403527.
SAUNDERS, T, CHAPUT, J, & TREMBLAY, M. (2014). Sedentary behaviour as an emerging risk factor for cardiometabolic diseases in children and youth. *Can J Diabetes, 38*(1), pp. 53-61. doi: 10.1016/j.jcjd.2013.08.266.
SAVANT, JD, FURTH, SL, & MEYERS, KE. (2014). Arterial stiffness in children: Pediatric measurement and considerations. *Pulse (Basel), 2*(1-4), pp. 69-80. doi: 10.1159/000374095.
SCHOFIELD, J, HO, J, & SORAN, H. (2019). Cardiovascular risk in type 1 diabetes mellitus. *Diabetes Ther, 10*(3), pp. 773-789. doi: 10.1007/s13300-019-0612-8.
SCOTT, J, ROWLANDS, A, CLIFF, D, MORGAN, P, PLOTNIKOFF, R, & LUBANS, D. (2017). Comparability and feasibility of wrist- and hip-worn accelerometers in free-living adolescents. *J Sci Med Sport, 20*(12)doi: 10.1016/j.jsams.2017.04.017.
SEALS, D, WALKER, A, PIERCE, G, & LESNIEWSKI, L. (2009). Habitual exercise and vascular aging. *J Physiol, 587*(23)doi: https://doi.org/10.1113/jphysiol.2009.178822.
SEDENTARY BEHAVIOUR RESEARCH NETWORK. (2012). Letter to the editor: Standardized use of the terms "sedentary" and "sedentary behaviours". *Appl Physiol Nutr Metab, 37*(3), pp. 540-542. doi: 10.1139/h2012-024.
SELL, H, ECKEL, J, & DIETZE-SCHROEDER, D. (2006). Pathways leading to muscle insulin resistance--the muscle--fat connection. *Arch Physiol Biochem, 112*(2), pp. 105-113. doi: 10.1080/13813450600711540.

SHAFFER, F, & GINSBERG, JP. (2017). An overview of heart rate variability metrics and norms. *Front Public Health, 5*doi: 10.3389/fpubh.2017.00258.
SHAFFER, F, MCCRATY, R, & ZERR, C. (2014). A healthy heart is not a metronome: An integrative review of the heart's anatomy and heart rate variability. *Front Psychol, 5*doi: 10.3389/fpsyg.2014.01040.
SHAH, AS, WADWA, RP, DABELEA, D, HAMMAN, RF, D'AGOSTINO, R, Jr., MARCOVINA, S, et al. (2015). Arterial stiffness in adolescents and young adults with and without type 1 diabetes: The search cvd study. *Pediatr Diabetes, 16*(5), pp. 367-374. doi: 10.1111/pedi.12279.
SHANG, B, DUAN, Y, HUANG, W, & BREHM, W. (2018). Fluctuation – a common but neglected pattern of physical activity behaviour: An exploratory review of studies in recent 20 years. [review]. *Eur J Sport Sci, 18*(2), pp. 266-278. doi: 10.1080/17461391.2017.1417486.
SHEPHARD, R. (2017). The objective monitoring of physical activity : Progress in preventive medicine. *Prog Prev Med, 2*(2), p e0007. doi: 10.1097/pp9.0000000000000007.
SHEPHARD, R, & VUILLEMIN, A. (2003). Limits to the measurement of habitual physical activity by questionnaires. *Br J Sports Med, 37*(3), pp. 197-206. doi: 10.1136/bjsm.37.3.197.
SHIRWANY, NA, & ZOU, M. (2010). Arterial stiffness: A brief review. *Acta Pharmacol Sin, 31*(10), pp. 1267-1276. doi: 10.1038/aps.2010.123.
SILSBURY, Z, GOLDSMITH, R, & RUSHTON, A. (2015). Systematic review of the measurement properties of self-report physical activity questionnaires in healthy adult populations. *BMJ open*doi: 10.1136/bmjopen-2015-008430.
SILVA, DAS, NAGHAVI, M, DUNCAN, BB, SCHMIDT, MI, DE SOUZA MDE, FM, & MALTA, DC. (2019). Physical inactivity as risk factor for mortality by diabetes mellitus in brazil in 1990, 2006, and 2016 *Diabetol metab syndr* (Vol. 11).
SILVETTI, M, DRAGO, F, & RAGONESE, P. (2001). Heart rate variability in healthy children and adolescents is partially related to age and gender. *Int J Cardiol, 81*(2-3)doi: 10.1016/s0167-5273(01)00537-x.
SIMPERINGHAM, K, CRONIN, J, PEARSON, S, & ROSS, A. (2019). Reliability of horizontal force-velocity-power profiling during short sprint-running accelerations using radar technology. *Sports Biomech, 18*(1)doi: 10.1080/14763141.2017.1386707.
SIRARD, JR, & PATE, RR. (2001). Physical activity assessment in children and adolescents. *Sports Medicine, 31*(6), pp. 439 - 454.
SKRAPARI, I, TENTOLOURIS, N, PERREA, D, BAKOYIANNIS, C, PAPAZAFIROPOULOU, A, & KATSILAMBROS, N. (2007). Baroreflex sensitivity in obesity: Relationship with cardiac autonomic nervous system activity. *Obesity, 15*(7), pp. 1685-1693. doi: 10.1038/oby.2007.201.
SLAUGHTER, M, LOHMAN, T, BOILEAU, R, HORSWILL, C, STILLMAN, R, VAN LOAN, M, et al. (1988). Skinfold equations for estimation of body fatness in children and youth. *Hum Biol, 60*(5).
SNELL-BERGEON, JK, & NADEAU, K. (2012). Cardiovascular disease risk in young people with type 1 diabetes. *J Cardiovasc Transl Res, 5*(4), pp. 446-462. doi: 10.1007/s12265-012-9363-x.
SOEDAMAH-MUTHU, S, FULLER, J, MULNIER, H, RALEIGH, V, LAWRENSON, R, & COLHOUN, H. (2006). High risk of cardiovascular disease in patients with type 1 diabetes in the u.K.: A cohort study using the general

practice research database. *Diabetes Care, 29*(4)doi: 10.2337/diacare.29.04.06.dc05-1433.
SPORT ENGLAND. (2018). *Active-lives-children-survey-academic-year-17-18*. https://www.sportengland.org/media/13698/active-lives-children-survey-academic-year-17-18.pdf. 27/9/19.
STEFELOVÁ, N, DYGRÝN, J, HRON, K, GÁBA, A, RUBÍN, L, & PALAREA-ALBALADEJO, J. (2018). Robust compositional analysis of physical activity and sedentary behaviour data. *Int J Environ Res Public Health, 15*(10)doi: 10.3390/ijerph15102248.
STEIN, P, & REDDY, A. (2005). Non-linear heart rate variability and risk stratification in cardiovascular disease. *Indian Pacing Electrophysiol J, 5*(3).
STEWART, A, MARFELL-JONES, M, OLDS, T, & RIDDER, H. (2011). *International standards for anthropometric assessment* NZ: Lower Hutt.
STONE, MR, ROWLANDS, AV, MIDDLEBROOKE, AR, JAWIS, MN, & ESTON, RG. (2009). The pattern of physical activity in relation to health outcomes in boys. *Int J Pediatr Obes, 4*(4), pp. 306-315. doi: 10.3109/17477160902846179.
STONER, L, FAULKNER, J, WESTRUPP, N, & LAMBRICK, D. (2015). Sexual differences in central arterial wave reflection are evident in prepubescent children. *J Hypertens, 33*(2)doi: 10.1097/HJH.0000000000000399.
STONER, L, YOUNG, J, & FRYER, S. (2012). Assessments of arterial stiffness and endothelial function using pulse wave analysis. *Int J Vasc Med, 2012*doi: https://doi.org/10.1155/2012/903107.
SWINDELL, N, REES, P, FOGELHOLM, M, DRUMMEN, M, MACDONALD, I, MARTINEZ, J, et al. (2020). Compositional analysis of the associations between 24-h movement behaviours and cardio-metabolic risk factors in overweight and obese adults with pre-diabetes from the preview study: Cross-sectional baseline analysis. *Int J Behav Nutr Phys Act, 17*(1)doi: 10.1186/s12966-020-00936-5.
TANAKA, H, DESOUZA, C, & SEALS, D. (1998). Absence of age-related increase in central arterial stiffness in physically active women. [research-article]. *Arterio Thromb Vasc Bio, 18*, pp. 127-132. doi: 0008.
TANAKA, H, & SAFAR, M. (2019). Influence of lifestyle modification on arterial stiffness and wave reflections. *Am J Hypertens, 18*(1), pp. 137-144. doi: 10.1016/j.amjhyper.2004.07.008.
TARVAINEN, MP, NISKANEN, JP, LIPPONEN, JA, RANTA-AHO, PO, & KARJALAINEN, PA. (2014). Kubios hrv--heart rate variability analysis software. *Comp Meth Prog Bio, 113*(1), pp. 210-220. doi: 10.1016/j.cmpb.2013.07.024.
TAYLOR, J, CARR, D, MYERS, C, & ECKBERG, D. (1998). Mechanisms underlying very-low-frequency rr-interval oscillations in humans. *Circulation, 98*(6)doi: 10.1161/01.cir.98.6.547.
TELFORD, RM, TELFORD, RD, CUNNINGHAM, RB, COCHRANE, T, DAVEY, R, & WADDINGTON, G. (2013). Longitudinal patterns of physical activity in children aged 8 to 12 years: The look study. *Int J Behav Nutr Phys Act, 10*(81)doi: 10.1186/1479-5868-10-81.
TELFORD, RM, TELFORD, RD, OLIVE, LS, COCHRANE, T, & DAVEY, R. (2016). Why are girls less physically active than boys? Findings from the look longitudinal study. *PLoS One, 11*(3)doi: 10.1371/journal.pone.0150041.
TEN HARKEL, A, TAKKEN, T, VAN OSCH-GEVERS, M, & HELBING, W. (2011). Normal values for cardiopulmonary exercise testing in children. *Eur J Cardiovasc Prev Rehabil, 18*(1)doi: 10.1097/HJR.0b013e32833cca4d.

TERLEMEZ, S, BULUT, Y, UNUVAR, T, TOKGOZ, Y, ERYILMAZ, U, & CELIK, B. (2016). Evaluation of arterial stiffness in children with type 1 diabetes using the oscillometric method. *J Diabetes Complications, 30*(5), pp. 864-867. doi: 10.1016/j.jdiacomp.2016.03.012.

TEYCHENNE, M, STEPHENS, LD, COSTIGAN, SA, OLSTAD, DL, STUBBS, B, & TURNER, AI. (2019). The association between sedentary behaviour and indicators of stress: A systematic review. *BMC Public Health, 19*doi: 10.1186/s12889-019-7717-x.

THAYER, JF, & LANE, RD. (2007). The role of vagal function in the risk for cardiovascular disease and mortality. *Biol Psychol, 74*(2), pp. 224-242. doi: 10.1016/j.biopsycho.2005.11.013.

THAYER, JF, YAMAMOTO, SS, & BROSSCHOT, JF. (2010). The relationship of autonomic imbalance, heart rate variability and cardiovascular disease risk factors. *Int J Cardiol, 141*(2), pp. 122-131. doi: 10.1016/j.ijcard.2009.09.543.

THEILADE, S, LAJER, M, PERSSON, F, JOERGENSEN, C, & ROSSING, P. (2013). Arterial stiffness is associated with cardiovascular, renal, retinal, and autonomic disease in type 1 diabetes. *Diabetes Care, 36*(3), pp. 715-721. doi: 10.2337/dc12-0850.

THIJSSEN, D, CARTER, S, & GREEN, D. (2016). Arterial structure and function in vascular ageing: Are you as old as your arteries? *J Physiol, 594*(8)doi: 10.1113/JP270597.

THIVEL, D, TREMBLAY, A, GENIN, PM, PANAHI, S, RIVIÈRE, D, & DUCLOS, M. (2018). Physical activity, inactivity, and sedentary behaviors: Definitions and implications in occupational health. *Front Public Health, 6*doi: 10.3389/fpubh.2018.00288.

THORP, A, OWEN, N, NEUHAUS, M, & DUNSTAN, D. (2011). Sedentary behaviors and subsequent health outcomes in adults a systematic review of longitudinal studies, 1996-2011. *Am J Prev Med, 41*(2)doi: 10.1016/j.amepre.2011.05.004.

THOSAR, S, BIELKO, S, MATHER, K, JOHNSTON, J, & WALLACE, J. (2015). Effect of prolonged sitting and breaks in sitting time on endothelial function. *Med Sci Sports Exerc, 47*(4)doi: 10.1249/MSS.0000000000000479.

THOSAR, SS, JOHNSON, BD, JOHNSTON, JD, & WALLACE, JP. (2012). Sitting and endothelial dysfunction: The role of shear stress *Med sci monit* (Vol. 18, pp. RA173-180).

THURN, D, DOYON, A, SÖZERI, B, BAYAZIT, A, CANPOLAT, N, DUZOVA, A, et al. (2019). Aortic pulse wave velocity in healthy children and adolescents: Reference values for the vicorder device and modifying factors. *Am J Hypertens, 28*(12), pp. 1480-1488. doi: 10.1093/ajh/hpv048.

TREMBLAY, M, AUBERT, S, BARNES, J, SAUNDERS, T, CARSON, V, LATIMER-CHEUNG, A, et al. (2017). Sedentary behavior research network (sbrn) - terminology consensus project process and outcome. *Int J Behav Nutr Phys Act, 14*(1)doi: 10.1186/s12966-017-0525-8.

TRIGONA, B, AGGOUN, Y, MAGGIO, A, MARTIN, XE, MARCHAND, LM, BEGHETTI, M, et al. (2010). Preclinical noninvasive markers of atherosclerosis in children and adolescents with type 1 diabetes are influenced by physical activity. *J Pediatr, 157*(4), pp. 533-539. doi: 10.1016/j.jpeds.2010.04.023.

TROIANO, RP, MCCLAIN, JJ, BRYCHTA, RJ, & CHEN, KY. (2014). Evolution of accelerometer methods for physical activity research. *Br J Sports Med, 48*(13), pp. 1019-1023. doi: 10.1136/bjsports-2014-093546.

TROST, S. (2007). State of the art reviews : Measurement of physical activity in children and adolescents. *Am J Lifestyle Med, 1*(4), pp. 299-314. doi: 10.1177/1559827607301686.
TROST, S, LOPRINZI, P, MOORE, R, & PFEIFFER, K. (2011). Comparison of accelerometer cut points for predicting activity intensity in youth. *Med Sci Sport Exerc, 43*(7)doi: 10.1249/MSS.0b013e318206476e.
TROST, S, PATE, R, FREEDSON, P, SALLIS, J, & TAYLOR, W. (2000). Using objective physical activity measures with youth: How many days of monitoring are needed? *Med Sci Sports Exerc, 32*(2).
TULLY, C, ARONOW, L, MACKEY, E, & STREISAND, R. (2016). Physical activity in youth with type 1 diabetes: A review. *Curr Diab Rep, 16*(9), p 85. doi: 10.1007/s11892-016-0779-6.
URBINA, E, ISOM, S, BELL, R, BOWLBY, D, D'AGOSTINO, R, DANIELS, S, et al. (2019). Burden of cardiovascular risk factors over time and arterial stiffness in youth with type 1 diabetes mellitus: The search for diabetes in youth study. *J Am Heart Assoc, 8*(13)doi: 10.1161/JAHA.118.010150.
VAISMAN, N, PENCHARZ, P, COREY, M, CANNY, G, & HAHN, E. (1987). Energy expenditure of patients with cystic fibrosis. *J Pediatr, 111*(4)doi: 10.1016/s0022-3476(87)80107-5.
VÄISTÖ, J, HAAPALA, E, VIITASALO, A, SCHNURR, T, KILPELÄINEN, T, KARJALAINEN, P, et al. (2019). Longitudinal associations of physical activity and sedentary time with cardiometabolic risk factors in children. *Scand J Med Sci Sports, 29*(1)doi: 10.1111/sms.13315.
VALERIO, G, SPAGNUOLO, MI, LOMBARDI, F, SPADARO, R, SIANO, M, & FRANZESE, A. (2007). Physical activity and sports participation in children and adolescents with type 1 diabetes mellitus. *Nutr Metab Cardiovasc Dis, 17*(5), pp. 376-382. doi: 10.1016/j.numecd.2005.10.012.
VAN BORTEL, L, LAURENT, S, BOUTOUYRIE, P, CHOWIENCZYK, P, CRUICKSHANK, J, DE BACKER, T, et al. (2018). Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens, 30*(3), pp. 445-448. doi: 10.1097/HJH.0b013e32834fa8b0.
VAN BORTEL, LM, DUPREZ, D, STARMANS-KOOL, MJ, SAFAR, ME, GIANNATTASIO, C, COCKCROFT, J, et al. (2002). Clinical applications of arterial stiffness, task force iii: Recommendations for user procedures. *Am J Hypertens, 15*(5), pp. 445-452. doi: 10.1016/s0895-7061(01)02326-3.
VAN BORTEL, LM, LAURENT, S, BOUTOUYRIE, P, CHOWIENCZYK, P, CRUICKSHANK, JK, DE BACKER, T, et al. (2012). Expert consensus document on the measurement of aortic stiffness in daily practice using carotid-femoral pulse wave velocity. *J Hypertens, 30*(3), pp. 445-448. doi: 10.1097/HJH.0b013e32834fa8b0.
VAN HEES, VT, GORZELNIAK, L, DEAN LEON, EC, EDER, M, PIAS, M, TAHERIAN, S, et al. (2013). Separating movement and gravity components in an acceleration signal and implications for the assessment of human daily physical activity. *PLoS One, 8*(4), p e61691. doi: 10.1371/journal.pone.0061691.
VAN HEES, VT, GORZELNIAK, L, DEAN LEÓN, EC, EDER, M, PIAS, M, TAHERIAN, S, et al. (2013). Separating movement and gravity components in an acceleration signal and implications for the assessment of human daily physical activity *Plos one* (Vol. 8).

VAN HEES, VT, SABIA, S, ANDERSON, KN, DENTON, SJ, OLIVER, J, CATT, M, et al. (2015). A novel, open access method to assess sleep duration using a wrist-worn accelerometer *Plos one* (Vol. 10).
VANDELANOTTE, C, SHORT, C, ROCKLOFF, M, DI MILLIA, L, RONAN, K, HAPPELL, B, et al. (2015). How do different occupational factors influence total, occupational, and leisure-time physical activity? *J Phys Act Health, 12*(2)doi: 10.1123/jpah.2013-0098.
VANHELST, J, VIDAL, F, DRUMEZ, E, BÉGHIN, L, BAUDELET, J, COOPMAN, S, et al. (2019). Comparison and validation of accelerometer wear time and non-wear time algorithms for assessing physical activity levels in children and adolescents. [OriginalPaper]. *BMC Med Res Methodol, 19*(1), pp. 1-10. doi: doi:10.1186/s12874-019-0712-1.
VASANKARI, V, HUSU, P, VÄHA-YPYÄ, H, SUNI, J, TOKOLA, K, HALONEN, J, et al. (2017). Association of objectively measured sedentary behaviour and physical activity with cardiovascular disease risk. *Eur J Prev Cardiol, 24*(12)doi: 10.1177/2047487317711048.
VASTAGH, I, HORVÁTH, T, NAGY, G, VARGA, T, JUHÁSZ, E, JUHÁSZ, V, et al. (2010). Evolution and predictors of morphological and functional arterial changes in the course of type 1 diabetes mellitus. *Diabetes Metab Res Rev, 26*(8)doi: 10.1002/dmrr.1133.
VEIJALAINEN, A, HAAPALA, EA, VÄISTÖ, J, LEPPÄNEN, M, LINTU, N, TOMPURI, T, et al. (2019). Associations of physical activity, sedentary time, and cardiorespiratory fitness with heart rate variability in 6- to 9-year-old children: The panic study. [OriginalPaper]. *Eur J App Physiol, 119*(11), pp. 2487-2498. doi: doi:10.1007/s00421-019-04231-5.
VEIJALAINEN, A, TOMPURI, T, HAAPALA, E, VIITASALO, A, LINTU, N, VÄISTÖ, J, et al. (2016). Associations of cardiorespiratory fitness, physical activity, and adiposity with arterial stiffness in children. *Scand J Med Sci Sports, 26*(8)doi: 10.1111/sms.12523.
VERROTTI, A, PREZIOSO, G, SCATTONI, R, & CHIARELLI, F. (2014). Autonomic neuropathy in diabetes mellitus. *Front Endocrinol (Lausanne), 5*doi: 10.3389/fendo.2014.00205.
VINIK, A, ERBAS, T, & CASELLINI, C. (2013). Diabetic cardiac autonomic neuropathy, inflammation and cardiovascular disease. *J Diabetes Investig, 4*(1)doi: 10.1111/jdi.12042.
VINIK, AI, MASER, RE, MITCHELL, BD, & FREEMAN, R. (2003). Diabetic autonomic neuropathy. *Diabetes Care, 26*(5), pp. 1553-1579.
VINIK, AI, & ZIEGLER, D. (2007). Diabetic cardiovascular autonomic neuropathy. *Circulation, 115*(3), pp. 387-397. doi: 10.1161/circulationaha.106.634949.
VIRANI, S, ALONSO, A, BENJAMIN, E, BITTENCOURT, M, CALLAWAY, C, CARSON, A, et al. (2020). Heart disease and stroke statistics-2020 update: A report from the american heart association. *Circulation, 141*(9)doi: 10.1161/CIR.0000000000000757.
WADWA, RP, URBINA, EM, ANDERSON, AM, HAMMAN, RF, DOLAN, LM, RODRIGUEZ, BL, et al. (2010). Measures of arterial stiffness in youth with type 1 and type 2 diabetes: The search for diabetes in youth study *Diabetes care* (Vol. 33, pp. 881-886).
WANNAMETHEE, SG, & SHAPER, AG. (2001). Physical activity in the prevention of cardiovascular disease: An epidemiological perspective. *Sports Med, 31*(2), pp. 101-114. doi: 10.2165/00007256-200131020-00003.

WARBURTON, DE, NICOL, CW, & BREDIN, SS. (2006). Health benefits of physical activity: The evidence *Cmaj* (Vol. 174, pp. 801-809).
WARREN, TY, BARRY, V, HOOKER, SP, SUI, X, CHURCH, TS, & BLAIR, SN. (2010). Sedentary behaviors increase risk of cardiovascular disease mortality in men. *Med Sci Sports Exerc, 42*(5), pp. 879-885. doi: 10.1249/MSS.0b013e3181c3aa7e.
WATKINSON, C, VAN SLUIJS, EM, SUTTON, S, HARDEMAN, W, CORDER, K, & GRIFFIN, SJ. (2010). Overestimation of physical activity level is associated with lower bmi: A cross-sectional analysis. *Int J Behav Nutr Phys Act, 7*, p 68. doi: 10.1186/1479-5868-7-68.
WATSON, KB, CARLSON, S, CARROLL, DD, & FULTON, J. (2014). Comparison of accelerometer cut points to estimate physical activity in u.S. Adults. *J Sports Sci, 32*(7), pp. 660-669. doi: 10.1080/02640414.2013.847278.
WELLS, G, BEATON, D, SHEA, B, BOERS, M, SIMON, L, STRAND, V, et al. (2001a). Minimal clinically important differences: Review of methods. *The Journal of rheumatology, 28*(2).
WELLS, G, BEATON, D, SHEA, B, BOERS, M, SIMON, L, STRAND, V, et al. (2001b). Minimal clinically important differences: Review of methods. *J Rheumatol, 28*(2).
WELSMAN, J, & ARMSTRONG, N. (2019). Interpreting aerobic fitness in youth: The fallacy of ratio scaling. *Pediatr Exerc Sci, 31*(2)doi: 10.1123/pes.2018-0141.
WHIPP, BJ, DAVIS, JA, TORRES, F, & WASSERMAN, K. (1981). A test to determine parameters of aerobic function during exercise. *J Appl Physiol Respir Environ Exerc Physiol, 50*(1), pp. 217-221. doi: 10.1152/jappl.1981.50.1.217.
WHITE, T, WESTGATE, K, WAREHAM, NJ, & BRAGE, S. (2016). Estimation of physical activity energy expenditure during free-living from wrist accelerometry in uk adults *Plos one* (Vol. 11).
WHO, WHO. (2010a). *Global recommendations on physical activity for health* 978 92 4 159 997 9). https://apps.who.int/iris/bitstream/handle/10665/44399/9789241599979_eng.pdf jsessionid=9C2E799B0C043A93130CE3B57E7640A0?sequence=1.
WHO, WHO. (2010b). *Physical activity for health* (Text No. Geneva: https://www.ncbi.nlm.nih.gov/pubmed/.
WICKEL, E, & EISENMANN, J. (2007). Contribution of youth sport to total daily physical activity among 6- to 12-yr-old boys. *Med Sci Sports Exerc, 39*(9)doi: 10.1249/mss.0b013e318093f56a.
WICKSTRÖM, G, & BENDIX, T. (2000). The "hawthorne effect"--what did the original hawthorne studies actually show? *Scand J Work Environ Health, 26*(4).
WIJNDAELE, K, WHITE, T, ANDERSEN, L, BUGGE, A, KOLLE, E, NORTHSTONE, K, et al. (2019). Substituting prolonged sedentary time and cardiovascular risk in children and youth: A meta-analysis within the international children's accelerometry database (icad). [OriginalPaper]. *Int J Behav Nutr Phys Act, 16*(1), pp. 1-10. doi: doi:10.1186/s12966-019-0858-6.
WILKIN, T, MALLAM, K, METCALF, B, JEFFERY, A, & VOSS, L. (2006). Variation in physical activity lies with the child, not his environment: Evidence for an 'activitystat' in young children (earlybird 16). [OriginalPaper]. *Int J of Obes, 30*(7), pp. 1050-1055. doi: doi:10.1038/sj.ijo.0803331.
WILKINSON, I, & COCKCROFT, J. (2007). Cholesterol, lipids and arterial stiffness. *Adv Cardiol, 44*doi: 10.1159/000096747.

WILKINSON, I, MCENIERY, C, BOUTOUYRIE, P, SEGERS, P, DONALD, A, & CHOWIENCZYK, P. (2019). Artery society guidelines for validation of non-invasive haemodynamic measurement devices: Part 1, arterial pulse wave velocity. *Artery Research, 4*(2), pp. 34-40. doi: 10.1016/j.artres.2010.03.001.

WILKINSON, IB, MACCALLUM, H, FLINT, L, COCKCROFT, JR, NEWBY, DE, & WEBB, DJ. (2000). The influence of heart rate on augmentation index and central arterial pressure in humans. *J Physiol, 525*(Pt 1), pp. 263-270. doi: 10.1111/j.1469-7793.2000.t01-1-00263.x.

WILLERSON, J, & RIDKER, P. (2004). Inflammation as a cardiovascular risk factor. *Circulation, 109*(21 Suppl 1)doi: 10.1161/01.CIR.0000129535.04194.38.

WILLIAMS, C, & LOPES, P. (2002). The influence of ventilatory control on heart rate variability in children. *J Sports Sci, 20*(5)doi: 10.1080/026404102317366663.

WILLIAMS, P. (2001). Physical fitness and activity as separate heart disease risk factors: A meta-analysis. *Med Sci Sports Exerc, 33*(5)doi: 10.1097/00005768-200105000-00012.

WILMOT, EG, EDWARDSON, CL, ACHANA, FA, DAVIES, MJ, GORELY, T, GRAY, LJ, et al. (2012). Sedentary time in adults and the association with diabetes, cardiovascular disease and death: Systematic review and meta-analysis. *Diabetologia, 55*(11), pp. 2895-2905. doi: 10.1007/s00125-012-2677-z.

YAMAMOTO, Y, HUGHSON, RL, & PETERSON, JC. (1991). Autonomic control of heart rate during exercise studied by heart rate variability spectral analysis. *J Appl Physiol, 71*(3), pp. 1136-1142. doi: 10.1152/jappl.1991.71.3.1136.

YARDLEY, J, MOLLARD, R, MACINTOSH, A, MACMILLAN, F, WICKLOW, B, BERARD, L, et al. (2013). Vigorous intensity exercise for glycemic control in patients with type 1 diabetes. *Can J Diabetes, 37*(6)doi: 10.1016/j.jcjd.2013.08.269.

YOONG, S, CHAI, L, WILLIAMS, C, WIGGERS, J, FINCH, M, & WOLFENDEN, L. (2016). Systematic review and meta-analysis of interventions targeting sleep and their impact on child body mass index, diet, and physical activity. *Obesity, 24*(5)doi: 10.1002/oby.21459.

ZIEMAN, SJ, MELENOVSKY, V, & KASS, DA. (2005). Mechanisms, pathophysiology, and therapy of arterial stiffness. *Arterioscler Thromb Vasc Biol, 25*(5), pp. 932-943. doi: 10.1161/01.atv.0000160548.78317.29.

ZULFIQAR, U, JURIVICH, D, GAO, W, & SINGER, D. (2010). Relation of high heart rate variability to healthy longevity. *Am J Cardiol, 105*(8)doi: 10.1016/j.amjcard.2009.12.022.

Chapter 10

Appendices

Chapter 10: Appendices

Appendix A – Participant Information

Chapter 4 (Study 1) – Parent/Guardian Information Sheet (In School)

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

PARENT / GUARDIAN INFORMATION SHEET
(Version 1.1, Date: 01/06/2018)

Project Title:
Swansea University Schools Research Week

Contact Details:

[redacted]

1. Invitation Paragraph
Thank you for taking the time to read this information sheet which gives details about our study and hopefully provides you with the information you need to help your son/daughter decide if they want to take part. It is important to say that whether they take part is entirely up to you and your child and that it doesn't matter for other studies if you both decide not to participate.

2. What is the purpose of the study?
The purpose of this study is to examine the effects of physical activity (any movement that requires more energy than rest) and participating in sport has on young people's health. We want to investigate specifically the reasons why being physically active and engaging in sport during growth make us healthier as these are currently poorly understood.

3. Why has my child been chosen?
Your child has been asked if they would like to participate because they are between the ages of 8 – 18 years old and go to a school in the Swansea area. If they decide to take part, they can withdraw at any point without giving any reason.

4. What will happen to my child if they take part?
Your child will be invited to take part in this research during the school day where they will have the opportunity to learn more about the research process and why we carry out research. At the beginning of the day, they will have a short talk about what is going to happen during the session, where they will have the opportunity to ask any questions they may have. For the rest of the day, your child will have the opportunity to participate in a range of research projects going on within the department. The research projects include, a maximal running test, a fundamental movement skills assessment, a basic assessment of their lung and heart function, measures of their height and weight and optional physical activity monitoring for 7 days.

For the running exercise, we will ask your child to run between two cones 30m apart as fast as they can while we record their speed with a speed gun (similar to the ones used by the police to track the speed of cars). They will be asked to do these 3 times, with a minimum of 2 minutes rest in-between each sprint to allow them to recover fully.

When we look at heart function we will ask your child to perform three short tests to measure how your child's heart is functioning during rest. Firstly, we will take a blood pressure and a further analysis of the blood flow out of the heart using the same cuff. Next, we will use a cuff on the thigh and a sensor on the neck to see how fast the blood is travelling between these two points. We will repeat these tests three times to ensure measurement accuracy. Finally, we will put a heart rate belt on your child's front and a watch on their wrist to record their heart rate, while they change their breathing rate and complete the movements of moving from lying down to standing and back again. For lung function we will ask your child to breathe out through a mouthpiece connected to a machine called a peak flow meter, which will show us how hard they are breathing out and their lung capacity. Please note that the techniques used to assess heart and lung function are being used for research purposes only and therefore not able to diagnose any underlying conditions that your child may have, be at risk of, or assess any concerns you may have.

For the fundamental movement exercise we will ask your child to perform 13 skills that they will already often perform as part of P.E .lessons and everyday activities, these will include running, catching a ball, jumping, throwing a ball. We will attach 7 watch like units called accelerometers on various locations, these will allow us to see how your child body moves during these skills. It is hoped that the information we can gather during the completion of these skills will allow us to illustrate how to coach and improve these skills for teachers.

In addition to these measures we will also ask your child some questions, in the form of three questionnaires, how well they feel they perform in certain activities, how they value certain aspects of their life and the activities they enjoy doing in their spare time. For these questions, there are no right or wrong answers we are just interested in the activity's children are engaging with in their spare time and their perception of their ability in sports and other activities.

At the end of the research day you and your child will have the option to be involved within the physical activity monitoring aspect of this study. What this would involve is your child wearing an accelerometer on their hip for 7 days. If they choose to wear the activity monitor we will ask them to fill in a diary detailing if they took the monitor off, and for how long. Upon completion of the 7-day period, we ask you as a parent / guardian to also take responsibility to ensure that your son / daughter returns the activity monitor to their teacher, or the relevant member of staff, at school for its return to the research team.

When all the activity monitors have been returned, with your and your child's permission, the primary researcher record your child's latest academic achievement. We record this to assess if there may be a link between your child's movement development and their academic development.

Finally, further opportunity to take part in additional activities and other research projects will be offered at the end of the research day. Taking part in these additional activities will involve coming in to the sports science laboratories at Swansea University during the school half term at a time convenient to you. More detailed participant information for either opportunity will be passed to you if you or your child express further interest.

5. What are the possible disadvantages of taking part?

Some of the activities will involve your child completing strenuous running exercise, which will make them feel out of breath, but they will recover quickly when they stop. During these activities your child can stop at any time if they feel uncomfortable, and there will always be at least one researcher present to make sure you are safe. Your child may think that the activity monitor feels odd to begin with, but they will soon forget it is even there. When we look at their heart function, we will use a lightweight strap on the neck and a blood pressure cuff on their thigh measure the speed of blood flow. This test might make them feel uncomfortable, but they have the option to stop at any point.

6. What are the possible benefits of taking part?

Your child will have the opportunity to be a part of a one-off study examining the reasons why physical activity and participating in sport is beneficial to health throughout childhood. Additionally, it will allow them to see a different area of the sciences which they may not have had the opportunity to participate in / thought about before.

7. Will my child's taking part in the study be kept confidential?

Yes, when your child starts the study we will give them a unique ID code, so no one can identify them from their data. All their personal information will be stored on a password protected computer and only members of the research team will be able to access their information.

8. What if I have any questions?

If you have any questions, please don't hesitate to contact us on the details provided at the top of this sheet. If you have concerns regarding the study but don't want to talk to us directly, please talk to [redacted] who is the chair of the research ethics committee where this study was approved.

If after reading this information sheet and you are happy for you child to participate within this study, please complete the consent form and pre-screening questionnaire, either on the [redacted] school website or on paper form below. We will ask for your permission for your son / daughter to take part within the research day and ask you to fill in a short pre-screening questionnaire to ensure they are fit and able to take part within the exercise involved within this research day.

Please note: Your son / daughter will **not be able to take part** unless you complete this form. Also, if you are consenting for more than one child, please fill in **separate individual forms, one for each child**.

Chapter 4 (Study 1)– Parent/Guardian Information Sheet (Laboratory visit)

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

PARENT/ GUARDIAN INFORMATION SHEET
(*Version 1.0:* Date: 18/09/2018**)**

Project Title:

[redacted] Physical Activity and Physical Education Research Project.

Primary Investigators:

[redacted]

Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy for your child to take part. It is important to say at this point that the decision to take part is entirely up to you and that your child will not be at a disadvantage for future studies should you decide for them not to participate.

What is the purpose of the study?
The purpose of the study is to investigate the assessment of fundamental movement skills proficiency in children using objective measures. Secondly, to ascertain whether the skill proficiency of the children changes as they grow, and their physical activity habits and parameters of health status change.

Why has your child been chosen?
Your child has been asked if they would like to take part because they are 8-18 years old and free of any physical or neurological conditions that affect the way they move. However, this does not mean your child has to take part in the study. This is voluntary and you have the right to withdraw them from the study at any time.

What will happen to your child if they take part?
If you decide for your child to take part they will be asked to complete the fundamental movement skill assessment, together with the physical activity monitoring at 5 points across the study. We will measure their sitting and standing height, weight and waist circumference, before asking them to complete a handedness questionnaire for us to work out their dominant hand. Following this, we will give your child 7 monitors to wear, one on each wrist, hip and ankle and one on the chest. They will wear the

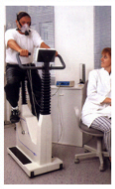
monitors whilst they complete 13 fundamental movement skills. Before performing the skills, a demonstration will be given to your child by the researcher. After this, your child will be asked to perform each skill three times while they are observed by the researchers and video recorded.

The skills we will ask your child to complete are: run, gallop, skip, hop, horizontal jump, slide, two-handed strike of a stationary ball, one hand forehand strike of self-bounced ball, one hand stationary dribble, two hand catch, kick a stationary ball, overhand throw and underhand throw.

Also, your child will then be asked to do an incremental cycling test which starts very easy and gets harder, like pedalling up a hill. The test is stopped when they can't keep going. The test lasts approximately 10 minutes. Whilst the final stages of this test are uncomfortable, the discomfort is very short and they will recover within minutes of completing the test. The exercise is no harder that they will do in training!

During these tests they will be asked to:

- Wear a face mask so we can measure the air that they breathe in and out. This mask does not make breathing any harder and they can talk through it and remove it at any time if they feel uncomfortable about wearing it.
- Have 3 small electrodes placed on the upper body so we can see how the heart works during exercise. These electrodes are just like sticky plasters.
- Have a small device stuck to their leg to measure how oxygen is used in the muscles.



After this, they will have a little cool down. We will then look at heart function we will ask your child to perform three short tests to measure how your child's heart is functioning during rest. Firstly, we will take a blood pressure and a further analysis of the blood flow out of the heart using the same cuff. Next, we will use a cuff on the thigh and a sensor on the neck to see how fast the blood is travelling between these two points. We will repeat these tests three times to ensure measurement accuracy. Finally, we will put a heart rate belt on your child's front and a watch on their wrist to record their heart rate, while they change their breathing rate and complete the movements of moving from lying down to standing and back again.

Following on from their participation in the movement assessment, children will be asked to wear a physical activity monitor for 7 consecutive days. They will also be asked to keep an activity log to record when they remove the accelerometer. Handing out and collecting the accelerometers will take approximately 1 hour.

What are the possible disadvantages of taking part?

There aren't any significant risks or discomforts associated with the study. If your child follows our instructions which will ensure that they are appropriately warmed up for the activity, then the risks will be minimized. The cycle will be hard work but they will recover quickly, and there is a reduced risk of injury from the activity (as in any Physical Education class), trained first aiders on hand to deal with any injuries should they occur.

What are the possible benefits of taking part?

Your child might find it interesting to see how we assess movement proficiency and how this leads to unique visualization tools!

Do they have to take part in this study?

Their participation in this study is completely voluntary and you are free to withdraw them at any time, for any reason, without penalty or prejudice from the investigator and/or research assistants. They will not be treated differently if at any time you wish to withdraw them from the study. Please feel free to ask any questions of the investigator and/or research assistants before signing this form and at any time during the study.

Can their involvement in the study end early?

If you provide permission for your child take part in the study, you still have the right to decide at any time that you no longer wish them to continue to take part.

Who will see the information that is collected?

All information gathered will be stored on password protected hard drives using unique participant ID codes. The original copy aligning your child's participant ID code and identifying information will be stored in a locked office at Swansea University. Their information will be combined with information from other children taking part in the study. When we write about the study to share it with other researchers, we will write about the combined information we have gathered. Individuals will not be identified in these written materials. We may publish the results of this study; however, we will keep all names and other identifying information private.

What if I have questions?

This study has been approved by Council of Engineering Research Ethics Committee and if you have specific concerns or if you have questions about the study, you can contact the study's principal investigator, [redacted]
Should you have any concerns regarding an ethical aspect of this study please contact [redacted] College of Engineering Research Ethics Committee, [redacted]

Thank you for your time and we look forward to your response!

Chapter 4 (Study 1) – Participant Information Sheet (In School Research)

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

CHILD INFORMATION SHEET (8 – 12 years)
(Version 1.1, Date: 01/06/2018)

Project Title:
Swansea University Schools Research Week

Contact Details:

[redacted]

1. Invitation Paragraph

Thank you for reading this information sheet which tells you all about what we are doing. We would like to ask you to come to Swansea University with your school so that you can learn more about science, sport, and physical activity. It is important to say that taking part is up to you and it doesn't matter if you don't want to.

2. What is the purpose of the study?

Physical activity, which includes all the walking, running, playing and sports you do every day, is a big part of our lives. We want to know more about it and how it can affect us. Being active and taking part in sport can help to make us healthy. We would like to know about how this works in young people like you. We hope to do this by asking you to take part in our project looking at movement, physical activity, and how this affects your health.

3. Why have I been chosen?

You have been asked if you like to take part because you are between the ages of 8 and 12 years old and go to a school in Swansea. If you decide to take part, you can stop at any time without any problems and we won't try to change your mind.

4. What will happen to me if I take part?

Before you take part in the project, the researchers will come in to one of your assemblies and talk to you about the project. During the talk we will go through what is involved and you will have the chance to ask questions. For your research session, you will take part in different activities and learn more about what projects we do and why we do them. The projects you will take part in include measuring your height and weight, a couple of short questionnaires, a sprinting exercise, a skills and movement session, and a session looking at how your heart and lungs works.

For the running exercise, we will ask you to run between two cones, as fast as you can, while we record your speed. You will do these 3 times with a little time to rest before each run. For the measurement station we will take your height, sitting height, waist circumference and weight. On the same station you will be invited to fill in a questionnaire which will ask you how you feel about different parts of your life.

When we look at your heart we will ask you to perform three short tests to measure how your heart works. Firstly, we will ask to take your blood pressure, where we will place a blue strap just above your elbow. It will inflate and get a bit tight for about 10-15 seconds and then deflate again. Next, we will use the same cuff on your leg and a sensor on your neck to see how fast your blood travels around your body. We will do these tests three times, so we can make sure it is the same. Finally, we will put three markers on your front (a bit like plasters) to record your heart rate, while we ask you to change your breathing and stand up.

For your lung function we will ask you to breathe out into a tube which will show us how hard you are breathing out and how much air is in your lungs. On the same station we will ask you to answer some questions about what you do when you are not at school or doing other activities. There is no right or wrong answer, we would just like to know what activities you like doing.

For the fundamental movement exercise, we will ask you to perform 13 skills that you will already often perform as part of your P.E. and everyday activities, these will include running, catching a ball, jumping, throwing a ball. We will attach 7 watch like units called accelerometers to you, these will allow us to see how your body moves during these skills. It is hoped that the information we can gather during the completion of these skills will allow us to illustrate how to coach and improve these skills for your teachers. On the same station you will also be asked to fill in a quick questionnaire about how well you think you can do certain activities.

After the research session we will come back into your school and have a chat at the end about what you learned during the day. We will also ask you if you would like to wear an accelerometer for 7 days, which will be worn on your hip, and measures the amount of activity you do! If you choose to wear the monitor, we will ask you to fill in a diary to let us know if, and when you took it off. Once 7 days are over, you will be asked to hand these to your teacher at school, so we can pick them up and see how much physical activity you did. When all the activity monitors have been returned, with your permission, the researchers will record your latest grades. We are doing this to look at whether your grades may be linked to any of the measures we took on the research day.

5. What are the possible disadvantages of taking part?

Some of the activities involve doing exercise such as running which will get your heart pumping and make you out of breath but when you stop you will recover quickly. During these activities you can stop at any time if you feel uncomfortable and there will always be a researcher there to make sure you are ok. Your activity monitor might feel weird to begin with, but you will soon forget they are even there. When we look at how your heart works we will use a Velcro strap around your leg and neck to see how fast your blood flows. This test might make you feel a bit uncomfortable, but you can stop the test at any time.

6. What are the possible benefits of taking part?

You will have a fun time with us, learning more about physical activity and sport and why it is so important for young people. You will also get the chance to use equipment that only high-level athletes usually get the chance to use!

7. Will my taking part in the study be kept confidential?

Yes, when you come to Swansea you will be given a one-off ID code, so no one knows who you are from your results. All your personal information will be stored on a computer with a password known only by us so only we will be able to see your information.

8. What if I have any questions?

If you have any questions, now or in the future, please ring or email us using the details at the top of this sheet. If you don't want to talk to us but want to talk to someone, please talk to [redacted] who is the head of the research ethics committee where this study was approved.

Chapter 4 (Study 1) – Participant Information Sheet (Laboratory Visit)

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

ADOLESCENT INFORMATION SHEET (13 - 18 years)
(Version 1.1, Date: 01/06/2018)

Project Title:
Swansea University Schools Research Week
Contact Details:

[redacted]

1. Invitation Paragraph
Thank you for reading this information sheet which tells you all about what we are doing. We would like to ask you to come to Swansea University with your school so that you can learn more about science, sport, and physical activity. It is important to say that taking part is up to you and it doesn't matter if you don't want to.

2. What is the purpose of the study?
Physical activity, which includes walking, running, playing sport or any movement that requires energy, plays a big part in everyday life. We want to investigate the reasons why being physically active and doing sport keeps us healthy as we grow and mature. We hope to investigate this by asking you to take part in our research project looking at fundamental movement skills, physical activity and how this affects your health.

3. Why have I been chosen?
You have been asked if you like to take part because you are between the ages of 13 and 18 years old and go to a secondary school in the Swansea area. If you decide to take part, you can withdraw from the study at any time without any problems.

4. What will happen to me if I take part?
Before the research session takes place, we will come into an assembly and talk about the research projects that you are going to have the opportunity to take part in. During and after the assembly you will have the chance to ask any questions you may have regarding any of the projects.

For your research session, you will take it turns to participate in and learn about the different research projects going on in the department. The research projects that you will have the chance to take part in include measuring your height and weight, a couple of short questionnaires, a short sprint, a fundamental movement skills session, and a session looking at how your heart and lungs work. You will each get a chance to try or at least learn about each of these projects throughout the day.

For the running exercise, we will ask you to run between two cones 30m apart as fast as you can while we record your speed with a speed gun (like the police use to track the speed of cars). You will be asked to do these 3 times, with a minimum of 2 minutes rest in-between each sprint to allow you to

we record your speed with a speed gun (like the police use to track the speed of cars). You will be asked to do these 3 times, with a minimum of 2 minutes rest in-between each sprint to allow you to recover fully.

When we look at your heart we will ask you to perform three short tests to measure how your heart works. Firstly, we will ask to take your blood pressure, where we will place a blue strap just above your elbow. It will inflate and get a bit tight for about 10-15 seconds and then deflate again. Next, we will use the same cuff on your leg and a sensor on your neck to see how fast your blood travels around your body. We will do these tests three times so we can make sure it is the same. Finally, we will put three markers on your front (a bit like plasters) to record your heart rate, while we ask you to change your breathing and stand up.

For your lung function we will ask you to breathe out through a mouthpiece which will show us how hard you are breathing out and what your lung capacity is. On the same station we will ask you to complete a few questions on the sort of activities you do in your spare time. There is no right or wrong answer we would just like to know the activities you enjoy doing.

For the fundamental movement exercise we will ask you to perform 13 skills that you will already often perform as part of your P.E. and everyday activities, these will include running, catching a ball, jumping, throwing a ball. We will attach 7 watch like units called accelerometers to you, these will allow us to see how your body moves during these skills. It is hoped that the information we can gather during the completion of these skills will allow us to illustrate how to coach and improve these skills for your teachers. On the same station you will also be asked to fill in a quick questionnaire about how well you think you can do certain activities.

For the measurement station we will take your height, sitting height, waist circumference and weight. You will also be invited to answer a short questionnaire about what you think about certain aspects of your life.

Finally, we will have a debrief at the end about the session you will be asked if you would like to be involved within the activity monitoring part of this study. If you choose to do so, you will be asked to wear the monitor for 7 days, and all it does is measure how much physical activity you do in a week! Whilst you wear it we will also ask you to fill in a diary to let us know if, and when you took it off. Once 7 days are over, you will be asked to give these to your teacher at school, so we can collect them and see how much physical activity you did When all the activity monitors have been returned, with your permission, the researchers will record your latest grades. We are doing this to look at whether your grades may be linked to any of the measures we took on the research day.

5. What are the possible disadvantages of taking part?

Some of the activities involve doing strenuous running exercises, these will make you feel out of breath but don't worry you will recover quickly once you stop. During these activities you can stop at any time if you feel uncomfortable, and there will always be at least one researcher there to make sure you are ok. The monitor we give you might feel weird to begin with, but you will soon forget they are even there. When we look at your heart function, we will use a lightweight strap on your neck and a blood pressure cuff on your thigh to see how fast your blood flows. This test might make you feel

uncomfortable, but you can stop the test at any time.

6. What are the possible benefits of taking part?

You will have the opportunity to be a part of a one-off study, so we can really start to understand the reasons why physical activity is so important for our health and well-being. Also, you will get the opportunity to use equipment usually only elite level athletes get the chance to use!

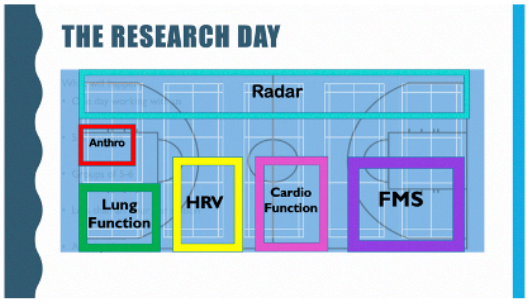
7. Will my taking part in the study be kept confidential?

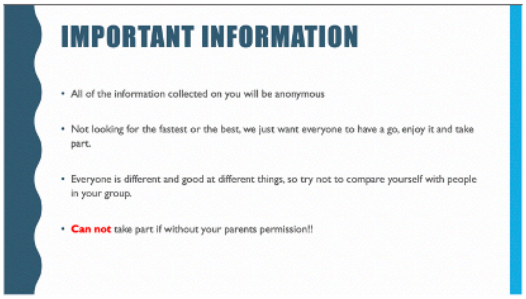
Yes, when you come to Swansea you will be given a one-off ID code, so no one knows who you are from your results. All of your personal information will be stored on a computer with a password known only by us so only we will be able to see your information.

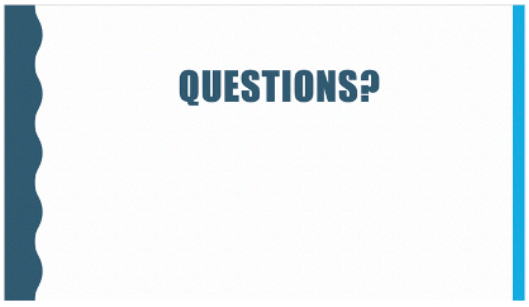
8. What if I have any questions?

If you have any questions, now or in the future, please ring or email us using the details at the top of this sheet. If you don't want to talk to us but want to talk to someone, please talk to [redacted] who is the head of the research ethics committee where this study was approved.

Chapter 4 (Study 1) – Participant information and Consent Assembly Slides for In School Research







Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

PARTICIPANT INFORMATION SHEET
(Version 1.0 20/09/18)

Project Title:

Investigating the influence of physical activity, sedentary time and sedentary behaviour on risk of cardiovascular disease

Contact Details:

[redacted]

1. Invitation Paragraph
We would like to invite you to participate in the above study being conducted by the Applied Sports, Technology, exercise and Medicine (A-STEM) Research Centre and College of Health and Human Sciences at Swansea University. Before you decide if you would like to take part, please take time to read the following information carefully. Ask us if there is anything you do not understand or if you would like further information, and then decide whether you wish to take part. It is entirely up to you whether you would like to participate or not and you can withdraw at any time without fear of penalty or consequence.

2. What is the purpose of the study?
The increasing sitting and screen time seen in children and adults in recent years has been closely linked to an increase in the risk of cardiovascular disease. Physical activity has been found to offset the increased risk associated with sitting time, however this physical activity level may be more than currently suggested. On average, 39% of adults in the UK, approximately 20 million people, do not meet the recommended 150 minutes of moderate to vigorous activity per week, and with the trend of screen use increasing this is a growing concern. Therefore, this study aims to further explore the relationship between physical activity, sedentary time and cardiovascular disease.

3. Why have I been chosen?
You have been invited to take part in this study as you are an adult aged between 18-75years old, are healthy and free from any known illness or injury that could prevent you from completing the exercises in this study.

4. What will happen to me if I take part?
If you decide to take part in this study, you will be asked to attend one session at Bay or Singleton Campus of Swansea University. The session will last approximately 2 hours and will involve you completing a questionnaire on your quality of life, a heart function test, a lung function test and a test of your fitness on a bike. We will then ask you to wear an activity monitor for 28 days, after which we will arrange to collect it.

Prior to any testing, we will run through the process and obtain written consent if you are happy to participate. We will then take your height, weight and assess your lung function. Lung function will be recorded using a device called a Spirometer which will require you to breathe forcefully through a mouth piece. Before commencing testing, we will ask you to complete a Health-Related Quality of Life Questionnaire, asking questions around your health, fitness and day to day life.

We will assess the function of your heart and circulation using blood pressure cuffs and specialised equipment; this should take less than 10 minutes. Two assessments will take place, the first with a cuff on your upper arm

and the second with a sensor on the neck and a cuff on the upper thigh. This testing will be carried out while you are lying down with your trunk slightly elevated, and we will ask you to remain silent and awake. After the blood pressure, we will use an electrocardiogram (ECG) to record your heart rate, which will take approximately 15 minutes. This will be done by applying 3 plaster-like pads to your upper body, then asking you to complete a series of breathing changes and movements (going from lying to sitting to standing and back to lying) to assess the changes in the control of your heart. If you become uncomfortable at any time, we will stop immediately.

The bike exercise will involve a three-minute warm up at a slow speed. After this, we will increase the resistance against the pedals gradually and ask you to keep going until you can not turn the pedals. This test will be like cycling up a hill, it will start easy but get gradually harder. This test will tell us how fit you are; it is hard work, but you will recover quickly once you finish and it is entirely up to you when you stop exercising. During the test, we will ask you to wear a breathing mask, for us to monitor your breathing, and an ECG, with sticky plaster-like electrodes on your upper body (these do not hurt and simply peel off after exercise), for us to monitor your heart rate.

Finally, we will ask you to wear a wrist worn activity monitor continuously for 28 days. The monitor is small, lightweight and waterproof; and will record any movements such as walking running, jumping, swimming etc. Whilst wearing the monitor you do not need to act or do anything differently, just carry on as you would normally each day. We will give you a diary to fill in the times you took the monitor off and your sleeping times. At the end of the 28 days we will arrange to collect the monitor.

5. What are the possible disadvantages of taking part?
The maximal testing will be difficult and tiring, however you will be supervised throughout and will have a sufficient warm up and cool down to minimize injury. If at any point this exercise become too difficult and you feel you want to stop, testing will stop, and we will not try to change your mind. Finally, the monitor worn on the wrist could become uncomfortable but taking a break from wearing it can help with this.

6. What are the possible benefits of taking part?
You will find out how much you move in a typical week, be part of some interesting new research, and help better understand the effects of sedentary time.

7. Will my taking part in the study be kept confidential?
Your participation in this study will be kept confidential and you will be given a unique number to maintain anonymity. Data will only be accessible to those with authorisation. The data will be collected and stored electronically, and it will be password protected.

8. What if I have any questions?
If you have any questions about this study, either now or in the future, please do not hesitate to contact one of the members of the research team using the details at the top of this document. The above project has been approved by the College of Engineering Research Ethics Committee at Swansea University. If you have any questions, complaints or concerns regarding the ethics of this research please contact [redacted] Chair of the College of Engineering Research Ethics Committee, Swansea University. [redacted]

Once again, we thank you for your time and look forward to your response.
We hope you will want to participate!

Chapters 5-7 (Studies 2-4) – Parental/Guardian Information Sheets (Healthy/Control Participants)

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

PARENT/GUARDIAN INFORMATION SHEET
(Version 1.0, Date: 16/01/2018)

Project Title:
Examining the relationship of physical activity and metabolic control with cardiovascular health in healthy children and adolescents

Contact Details:

[redacted]

1. Invitation Paragraph
Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy for your child to take part. If you are happy for them to take part, thank you. If you prefer them not to take part, this is not a problem and we thank you for thinking about it.

2. What is the purpose of the study?
We are often told that people should regularly participate in physical activity (walking, running, playing, etc.) because it gives them a range of health benefits. The aim of this study is to measure the amount your child moves in 1 month and how this can prevent health issues.

3. Why has your child been chosen?
Your child has been asked if they would like to take part because they are aged between 8 and 16 years of age, and is free from any injuries or other illnesses that might change how much they move or impact on how their blood sugar levels are controlled.

4. What will happen to your child if they take part?
You and your child will be asked to come to Swansea University or your child will attend a session during school time. During this session, an introduction to the study will be given, including what will be involved for your child over the course of the month. As part of this study we will need to know how physically mature your child is so we will ask them to look at a series of pictures and tick which picture is most like them. This will be done on their own and the results will not be shown to anyone except the researcher. If this process upsets your child too much, they can choose not to do it.

During the visit, we will carry out two assessments with your child. The first assessment is a specialized lying down blood pressure with a sensor on the side of the neck and a cuff on their thigh. The second assessment is monitoring your child's heart rate, with a monitor using three sensors attached to your child's chest. We will ask your child to go from lying to standing to sitting and then to do a special breathing exercise where they try to breathe out while they have their nose and mouth closed! During these assessments we will ask your child to remain silent and awake. If your child becomes uncomfortable at any time we will stop immediately.

For this visit we ask that you child does not drink any drink containing caffeine 12 hours before and that they do not do any strenuous exercise the day you come into clinic.

these assessments we will ask your child to remain silent and awake. If your child becomes uncomfortable at any time we will stop immediately.

For this visit we ask that you child does not drink any drink containing caffeine 12 hours before and that they do not do any strenuous exercise the day you come into clinic.

During this session, we will also take measurements of your child's height, weight and sitting height, then give your child a physical activity monitor to wear (Picture 1). This monitor will be worn like a watch on the right wrist (Picture 2) and must be worn at all times (24 hours a day). The monitor is very comfortable and will become unnoticeable once worn for an hour or two. The monitor is waterproof which means it can be worn in the shower/bath and during water based activities such as swimming.

Picture 1.

Picture 2.

After wearing the monitor for a month, we will arrange for the monitor to be returned along with the wear-time diary we will ask you to complete during the monitoring period. When your child is wearing the monitor, they do not need to act or do anything differently. We just want them to carry on with what they would normally do each day. The study and all the protocols within it are covered by Swansea University's indemnity policy.

5. What are the possible disadvantages of taking part?

Your child may think the monitors feel weird to start with but will soon forget the monitor is even there. They may also find filling in the diabetes/activity questionnaires annoying, however by doing so it will give us a better insight into the type of lifestyle your child leads.

6. What are the possible benefits of taking part?

You and your child will find out how much they move in one month and gain an insight into how the heart works.

7. Will my child taking part in the study be kept confidential?

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. Your child will be given a unique number so that no one knows who their results belong to. After the study is finished, all private information will be deleted.

8. What if my child or I have any questions?

If your child or you have any questions, please contact us on the details at the beginning of this sheet. If there are any problems, please feel free to contact us or [redacted] at Swansea University who are the sponsor for this projec[redacted]

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

CHILD PARTICIPANT (AGES 8 – 12 YEARS) INFORMATION SHEET
(Version 1.0, Date: 16/01/2018)

Project Title:
Examining the relationship of physical activity and metabolic control with cardiovascular health in healthy children and adolescents.

Contact Details:

[redacted]

1. Invitation
Thank you for being interested in our project. Please read this information sheet carefully and think about whether you would like to take part. If you do want to, that's great and thank you! If you don't, that's also totally fine! It won't change anything about how you are treated if you do or don't take part.

2. What is the study about?
We want to see how much children move in a month and see how your heart is working!

3. Why have I been chosen?
You have been asked if you would like to take part because you are aged between 8 and 12 years old and don't have any injuries or other illnesses that might change how much you move.

4. What will happen to me if I take part?
You will be asked to come to a session at Swansea University or your school. In this session we will talk about what we would like you to do, but you don't have to do anything you want to. We also need to know how mature you are so we will ask you to look at some pictures and tick which picture is most like you. You will do this on your own and no one else will see what you have ticked except for the researcher. There is no right or wrong answer and no one minds which picture you tick. If you don't want to do this bit, you don't have to.

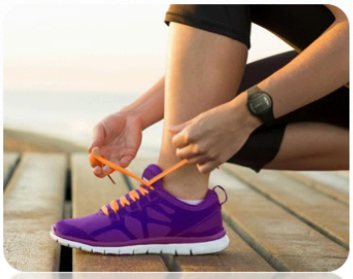
Next we will do two simple activities with you. First, while lying down, we will put a band on your neck and leg to see how your blood flows around your body. While you are lying down, we will put three sticky pads to your chest to see how your heart is beating. We will then ask you to sit up, then stand up and then sit back down! After this, we will get you to hold your nose and keep your mouth closed while you try to breathe out, like blowing up a balloon! These tests will not take too long to complete and if you feel uncomfortable at any time we will stop straight away.

while you try to breathe out, like blowing up a balloon! These tests will not take too long to complete and if you feel uncomfortable at any time we will stop straight away.

Before this visit we would like you not to drink any tea, coffee or sugary drinks and not to do any hard exercise!

We will then see how tall and heavy you are, and give you a monitor to wear, shown in Picture 1, which you will have to wear this on your right wrist, shown in picture 2. This monitor will record and show us how much you move every day. You will need to wear this monitor all day and when you go to sleep. The monitor is very comfortable and you won't notice you are wearing it once you have worn it for an hour or two. The monitor is waterproof which means you can wear it in the shower or bath and in pools if you go swimming.

Picture 1.



Picture 2.

After wearing the monitor for a month, we will sort out getting the monitor and the diaries you filled in back. When you are wearing these monitors, you do not need to do anything differently. We will also get some of the data that your care team regularly collect from your medical record, such as height and weight. We just want you to do whatever you would normally do each day.

5. What are the possible bad things about taking part?

You may think the monitors feel weird to start with but you will soon forget they are even there.

6. What are the possible good things about taking part?

You will find out how much you move in a month!

7. Who will know about my results?

All the information we collect from you will be completely private. No-one will know whose results they are as we will assign you a unique number.

8. What if I have any questions?

If you have any questions, please contact us on the details at the beginning of this sheet. You can also ask one of the researchers when you come in to visit the Clinic. If there are any problems, please feel free to contact us or [redacted] at Swansea University who are the sponsor for this project [redacted]; [redacted]

Chapters 5 -7(Studies 2-4) – Adolescent Participant Information Sheets

(Health/Control Participants)

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

ADOLESCENT (AGES 13 – 16 YEARS) INFORMATION SHEET
(Version 1.0, Date: 16/01/2018)

Project Title:
Examining the relationship of physical activity and metabolic control with cardiovascular health in healthy children and adolescents

Contact Details:

[redacted]

1. Invitation Paragraph
Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy to take part. If you are happy to take part, thank you. If you prefer not to take part, this is not a problem and we thank you for thinking about it.

2. What is the purpose of the study?
We are always being told that we don't do enough exercise, but how much exercise are we actually doing? The reason why we are doing this study is see how much people move in 1 month and how this can affect your heart.

3. Why have you been chosen?
You have been asked if you would like to take part because you are aged between 13 and 16 years old, and are free from any injuries or other illnesses that might change how much you move or impact on how your blood sugar levels are controlled.

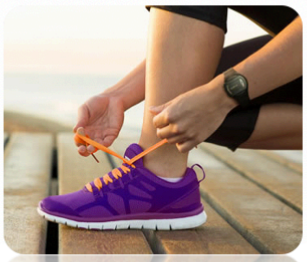
4. What will happen to you if they take part?
You will be asked to come to a session at Swansea University or your school. During this session you will be given an introduction to the study and told what you will need to do over the course of a month We also need to know how physically mature you are so we will ask you to look at a series of pictures and tick which picture is most like you. This will be done on your own and the results will not be shown to anyone except the researcher. There is no right or wrong answer and you will not be judged on the picture that you tick. If this process upsets you too much, you can choose not to do it.

Next, we will do two simple activities with you. First, while lying down, we will put a band on your neck and leg to see how your blood flows around your body. While you are lying down, we will put three sticky pads to your chest to see how your heart is beating. We will then ask you to sit up, then stand up and then sit back down! After this, we will get you to hold your nose and keep your mouth closed while you try to breathe out, like blowing up a balloon! These tests will not take too long to complete and if you feel uncomfortable at any time we will stop straight away.

For this visit, we ask that you do not drink anything with caffeine in it (tea, coffee, energy drinks or fizzy drinks) for 12 hours before you come in for your visit, and that you do not do strenuous exercise on the day you come in.

During this session we will also take measurements of your height, weight and sitting height, then give you a monitor that will record how much you move, shown in Picture 1. This monitor will have to be worn on the right wrist, shown in Picture 2. The monitor is very light and comfortable and you won't be able to notice it's on once you have worn it for an hour or two. You have to make sure that you wear this monitor all day and is not taken off. It is also very important that you wear the monitor also when you are sleeping. The monitor is waterproof which means you can wear it in the shower or bath and also in the pool if you want to go swimming.

Picture 1.



Picture 2

After wearing the monitor for a month, we will arrange to collect the monitor and diary you've filled in. When you are wearing these monitors, you do not need to act or do anything differently. We will also access routine data from your child's notes such as height and weight. We just want you to carry on with what you would normally do each day.

5. What are the possible disadvantages of taking part?

You may think the monitors feel weird to start with but they will soon forget they are even there. You may also find filling in the diabetes/diet/activity questionnaires annoying, but by filling them in you will be giving us a better look into the type of lifestyle you have.

6. What are the possible benefits of taking part?

You will find out how much you move in one month!

7. Will my taking part in the study be kept confidential?

All the information we collect about you will be kept completely private. Only people of the research team will be able to see it. You will be given a unique number so that no one knows who their results belong to. After the study is finished, all the information will be deleted.

8. What if I have any questions?

If you have any questions, please contact us on the details at the beginning of this sheet. If there are any problems, please feel free to contact us [redacted]t Swansea University who are the sponsor for this [redacted]

Chapters 5 and 7 (Studies 2 and 4) – Parent/Guardian Participant Information Sheets (Diabetic Participants)

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

PARENT/GUARDIAN INFORMATION SHEET
(Version 2.3, Date: 17/03/2017)

Project Title:
Examining the relationship of physical activity and metabolic control with cardiac risk in children and adolescents with type 1 diabetes mellitus.

Contact Details:
[redacted]

1. Invitation Paragraph
Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy for your child to take part. If you are happy for them to take part, thank you. If you prefer them not to take part, this is not a problem and we thank you for thinking about it. Your child's care will not be influenced if they do or do not decide to take part.

2. What is the purpose of the study?
We are often told that people, whether they have type 1 diabetes or not, should regularly participate in physical activity (walking, running, playing, etc.) because it gives them a range of health benefits. The aim of this study is to measure the amount your child moves in 1 month and how this can prevent health issues associated with the condition. Your child will also be given questionnaires to fill in regarding what types of foods they eat, the type of exercise they do, they amount of times they test their blood sugar levels each day, how many times a week they go hypo, etc. These results will give us a better overview of the type of lifestyle your child has. There are no right or wrong answers and your child's treatment will not be influenced by the results.

3. Why has your child been chosen?
Your child has been asked if they would like to take part because they are aged between 8 and 16 years of age, has type 1 diabetes, and is free from any injuries or other illnesses that might change how much they move or impact on how their blood sugar levels are controlled.

4. What will happen to your child if they take part?
You and your child will be asked to come to your normal Diabetes clinic on two occasions. On the first visit during your routine clinic visit, you will both be given an introduction to the study and told what your child will need to do over the course of a month. This induction session will include explanations of how to fill in the diabetes questionnaire, in addition to the blood glucose monitoring diaries. We also need to know how physically mature your child is so we will ask them to look at a series of pictures and tick which picture is most like them. This will be done on their own and the results will not be shown to anyone except the researcher. As with the questionnaires, there is no right or wrong answer and your child will not be judged on the picture that they tick. If this process upsets your child too much, they can choose not to do it.

During this first visit we will carry out two assessments with your child. The first assessment is a specialized lying down blood pressure with a sensor on the side of the neck and a cuff on their thigh. The second assessment is monitoring your child's heart rate, with a monitor using three sensors attached to your child's chest. We will ask your child to go from lying to standing to sitting and then to do a special breathing exercise where they try to breathe out while they have their nose and mouth closed! During these assessments we will ask your child to remain silent and awake. If your child becomes uncomfortable at any time we will stop immediately.

For this visit we ask that you child does not drink any drink containing caffeine 12 hours before and that they do not do any strenuous exercise the day you come into clinic.

During this initial visit, we will then give your child a physical activity monitor to wear (Picture 1). This monitor will be worn like a watch on the right wrist (Picture 2) and must be worn at all times (24 hours a day). The monitor is very comfortable and will become unnoticeable once worn for an hour or two. The monitor is waterproof which means it can be worn in the shower/bath and during water based activities such as swimming.

Picture 1.


Picture 2.

After wearing the monitor for a month, your child will come back to the clinic for a second time, where we will then take off the monitor and collect the questionnaires/diaries. When your child is wearing the monitor, they do not need to act or do anything differently. We just want them to carry on with what they would normally do each day. We will also access routine data from your child's notes such as height and weight. The study and all the protocols within it are covered by Swansea University's indemnity policy.

5. What are the possible disadvantages of taking part?

Your child may think the monitors feel weird to start with but will soon forget the monitor is even there. They may also find filling in the diabetes/activity questionnaires annoying, however by doing so it will give us a better insight into the type of lifestyle your child leads.

6. What are the possible benefits of taking part?

You and your child will find out how much they move in one month! They will also be given a valuable insight into how their lifestyle/diet has an effect on their diabetes.

7. Will my child taking part in the study be kept confidential?

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. Your child will be given a unique number so that no one knows who their results belong to. After the study is finished, all private information will be deleted.

All personal information collected will be kept completely confidential. That is, only members of the research team will have access to it. Your child will be given a unique number so that no one knows who their results belong to. After the study is finished, all private information will be deleted.

8. What if my child or I have any questions?

If your child or you have any questions, please contact us on the details at the beginning of this sheet. You can also ask one of the researchers when you come in to visit the Clinic. If there are any problems, please feel free to contact us or [redacted] Swansea University who are the sponsor for this project [redacted] Alternatively, you can contact the Cardiff and Vale University Health Board complaints department (details available at http://www.cardiffandvaleuhb.wales.nhs.uk/concerns-complaints).

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

CHILD PARTICIPANT (AGES 8 – 12 YEARS) INFORMATION SHEET
(Version 2.3, Date: 17/03/2017)

Project Title:
Examining the relationship of physical activity and metabolic control with cardiac risk in children and adolescents with type 1 diabetes mellitus.

Contact Details:
[redacted]

1. Invitation
Thank you for being interested in our project. Please read this information sheet carefully and think about whether you would like to take part. If you do want to, that's great and thank you! If you don't, that's also totally fine! It won't change anything about how you are treated if you do or don't take part.

2. What is the study about?
We want to see how much children with type 1 diabetes move in a month and see how your heart is working!

3. Why have I been chosen?
You have been asked if you would like to take part because you are aged between 8 and 12 years old with type 1 diabetes and don't have any injuries or other illnesses that might change how much you move.

4. What will happen to me if I take part?
You will be asked to come to your normal Diabetes clinic twice. The first time you go you will be shown how to fill in questions and write about what foods you eat, how much exercise you do, and some questions to do with your diabetes like how many times a day do you test your sugar levels. We also need to know how mature you are so we will ask you to look at some pictures and tick which picture is most like you. You will do this on your own and no one else will see what you have ticked except for the researcher. There is no right or wrong answer and no one minds which picture you tick. If you don't want to do this bit, you don't have to.

Next we will do two simple activities with you. First, while lying down, we will put a band on your neck and leg to see how your blood flows around your body. While you are lying down, we will put three sticky pads to your chest to see how your heart is beating. We will then ask you to sit up, then stand up and then sit back down! After this, we will get you to hold your nose and keep your mouth closed while you try to breathe out, like blowing up a balloon! These tests will not take too long to complete and if you feel uncomfortable at any time we will stop straight away.

Before this visit we would like you not to drink any tea, coffee or sugary drinks and not to do any hard exercise!

We will then give you a monitor to wear, shown in Picture 1, and you will have to wear this on your right wrist, shown in picture 2. This monitor will record and show us how much you move every day. You will need to wear this monitor all day and when you go to sleep. The monitor is very comfortable and you won't notice you are wearing it once you have worn it for an hour or two. The monitor is waterproof which means you can wear it in the shower or bath and in pools if you go swimming.

Picture 1.

Picture 2.

After wearing the monitor for a month, you will come back to the clinic for the second session where we will then take them off and collect the questionnaires/diaries you have filled in. When you are wearing these monitors, you do not need to do anything differently. We will also get some of the data that your care team regularly collect from your medical record, such as height and weight. We just want you to do whatever you would normally do each day.

5. What are the possible bad things about taking part?

You may think the monitors feel weird to start with but you will soon forget they are even. You might find filling in the diabetes/diet/activity questionnaires annoying, but by filling them in you will give us a better look into the way you lead your life.

6. What are the possible good things about taking part?

You will find out how much you move in a month!

7. Who will know about my results?

All the information we collect from you will be completely private. No-one will know whose results they are as we will assign you a unique number.

8. What if I have any questions?

If you have any questions, please contact us on the details at the beginning of this sheet. You can also ask one of the researchers when you come in to visit the Clinic. If there are any problems, please feel free to contact us or [redacted] at Swansea University who are the sponsor for this project [redacted] Alternatively, you can contact the Cardiff and Vale University Health Board complaints department (details available at http://www.cardiffandvaleuhb.wales.nhs.uk/concerns-complaints).

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)

ADOLESCENT (AGES 13 – 16 YEARS) INFORMATION SHEET
(Version 2.3, Date: 17/03/2017)

Project Title:
Examining the relationship of physical activity and metabolic control with cardiac risk in children and adolescents with type 1 diabetes mellitus.

Contact Details:
[redacted]

1. Invitation Paragraph
Thank you for being interested in our project. Please read this information sheet carefully and think about whether you are happy to take part. If you are happy to take part, thank you. If you prefer not to take part, this is not a problem and we thank you for thinking about it. Your care will not be influenced if you do or do not decide to take part.

2. What is the purpose of the study?
We are always being told that we don't do enough exercise, but how much exercise are we actually doing? The reason why we are doing this study is see how much people with type 1 diabetes move in 1 month and how this can affect your heart. We will also want you to answer questions and write about what foods you eat, what exercise you do, and questions about your diabetes likes how much times a day do you test your sugar levels.

3. Why have you been chosen?
You have been asked if you would like to take part because you are aged between 13 and 16 years old, have type 1 diabetes and are free from any injuries or other illnesses that might change how much you move or impact on how your blood sugar levels are controlled.

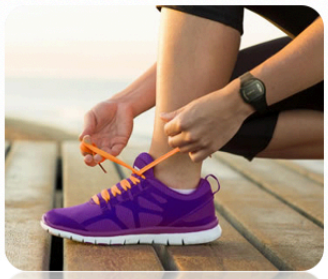
4. What will happen to you if they take part?
You will be asked to come to your normal Diabetes clinic twice. On the first visit you will be given an introduction to the study and told what you will need to do over the course of a month. This induction session will include explanations of how to fill the diabetes questionnaire, in addition to the diet and physical activity diaries. We also need to know how physically mature you are so we will ask you to look at a series of pictures and tick which picture is most like you. This will be done on your own and the results will not be shown to anyone except the researcher. There is no right or wrong answer and you will not be judged on the picture that you tick. If this process upsets you too much, you can choose not to do it.

Next, we will do two simple activities with you. First, while lying down, we will put a band on your neck and leg to see how your blood flows around your body. While you are lying down, we will put three sticky pads to your chest to see how your heart is beating. We will then ask you to sit up, then stand up and then sit back down! After this, we will get you to hold your nose and keep your mouth closed while you try to breathe out, like blowing up a balloon! These tests will not take too long to complete and if you feel uncomfortable at any time we will stop straight away.

For this visit, we ask that you do not drink anything with caffeine in it (tea, coffee, energy drinks or fizzy drinks) for 12 hours before you come in for your visit, and that you do not do strenuous exercise on the day you come in.

During this first visit we will also give you a monitor that will record how much you move, shown in Picture 1. This monitor will have to be worn on the right wrist, shown in Picture 2. The monitor is very light and comfortable and you won't be able to notice it's on once you have worn it for an hour or two. You have to make sure that you wear this monitor all day and is not taken off. It is also very important that you wear the monitor also when you are sleeping. The monitor is waterproof which means you can wear it in the shower or bath and also in the pool if you want to go swimming.

Picture 1.



Picture 2.

After wearing the monitor for a month, you will come back to the clinic for the second session where we will then take the monitor off and collect the questionnaires/diaries you've filled in. When you are wearing these monitors, you do not need to act or do anything differently. We will also access routine data from your child's notes such as height and weight. We just want you to carry on with what you would normally do each day.

5. What are the possible disadvantages of taking part?

You may think the monitors feel weird to start with but they will soon forget they are even there. You may also find filling in the diabetes/diet/activity questionnaires annoying, but by filling them in you will be giving us a better look into the type of lifestyle you have.

6. What are the possible benefits of taking part?

You will find out how much you move in one month!

7. Will my taking part in the study be kept confidential?

All the information we collect about you will be kept completely private. Only people of the research team will be able to see it. You will be given a unique number so that no one knows who their results belong to. After the study is finished, all the information will be deleted.

8. What if I have any questions?

If you have any questions, please contact us on the details at the beginning of this sheet. You can also ask one of the researchers when you come in to visit the Clinic. If there are any problems, please feel free to contact us or [redacted] at Swansea University who are the sponsor for this project [redacted]. Alternatively, you can contact the Cardiff and Vale University Health Board complaints department (details available at http://www.cardiffandvaleuhb.wales.nhs.uk/concerns-complaints).

Appendix B – Pre-Screening

Chapters 4-7 (Studies 1 – 4) – Paediatric Participant Pre-screening Questionnaire

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

PRE-SCREENING QUESTIONNAIRE

Name of child:

Your email address:

Does your child have, or has he / she ever experienced any of the following? Please Tick:

	YES	NO
High Blood Pressure		
Diabetes		
Chest pains brought on by physical exertion		
A bone, muscle or joint problem with arthritis		
Asthma or any other respiratory problems		
Any sustained / prolonged illnesses		
Is your child taking any medication?		

If you have answered YES to any of the questions above, or if there is anything else not mentioned above that you think the researchers should be aware of, then please provide more details in the text box below. If not applicable, then please enter N/A

If your child has any known allergies, has the researcher in charge of your session been made aware of medication you are taking and where to find this?

In the absence of a parent/guardian, I understand that my child is responsible for monitoring him or herself throughout any activity, and should any unusual symptoms occur, would ease participation and inform the instructor.

Video/Photography Consent

I understand that occasionally my child may appear in promotional photography/video clips of Swansea University and that material may be used by Swansea University websites and other promotional material.

Please tick here ☐ **if photographs are NOT permitted**

By signing this form, I the parent/guardian of the aforementioned child, affirm that I have read this form in its entirety; I have answered the questions accurately and to the best of my knowledge and will inform Swansea University of any future changes.

I the parent/guardian of the aforementioned child give permission for him/her to participant in Swansea University research sessions and understand that Swansea University researchers taking the exercise sessions cannot be liable for any loos of personal injury

Parent/guardian's signature: Date:

Please print name:

Researcher(s) signature: Date:

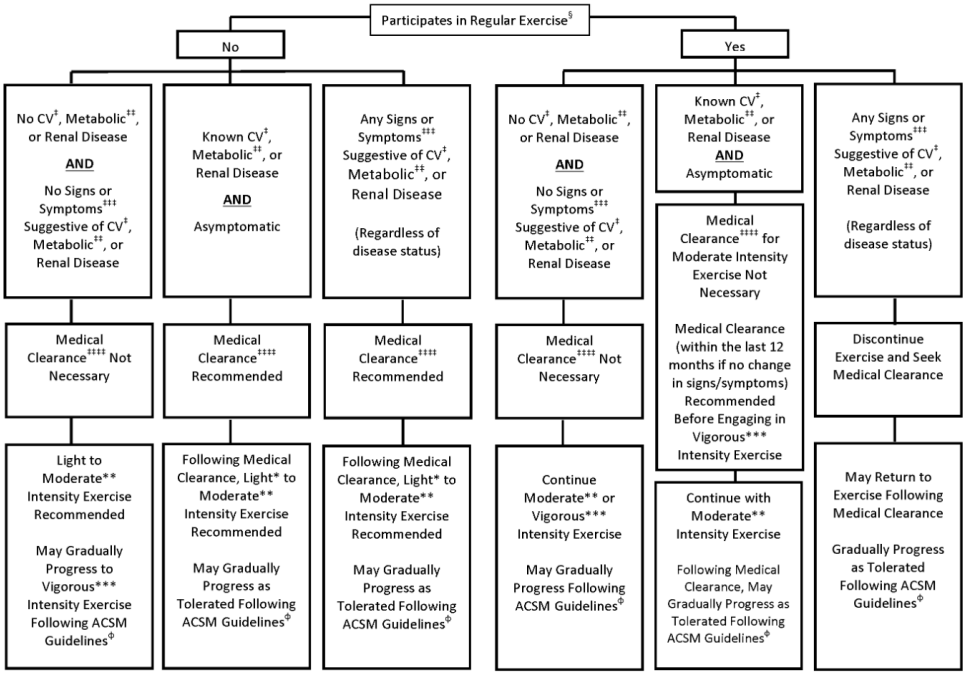


FIGURE 2—Exercise preparticipation health screening logic model for aerobic exercise participation.
§Exercise participation, performing planned, structured physical activity at least 30 min at moderate intensity on at least 3 d·wk^{-1} for at least the last 3 months.
***Light-intensity exercise, 30% to <40% HRR or $\dot{V}O_2R$, 2 to <3 METs, 9–11 RPE, an intensity that causes slight increases in HR and breathing.**
****Moderate-intensity exercise, 40% to <60% HRR or $\dot{V}O_2R$, 3 to <6 METs, 12–13 RPE, an intensity that causes noticeable increases in HR and breathing.**
*****Vigorous-intensity exercise ≥60% HRR or $\dot{V}O_2R$, ≥6 METs, ≥14 RPE, an intensity that causes substantial increases in HR and breathing.**
‡CVD, cardiac, peripheral vascular, or cerebrovascular disease.
‡‡Metabolic disease, type 1 and 2 diabetes mellitus.
‡‡‡Signs and symptoms, at rest or during activity; includes pain, discomfort in the chest, neck, jaw, arms, or other areas that may result from ischemia; shortness of breath at rest or with mild exertion; dizziness or syncope; orthopnea or paroxysmal nocturnal dyspnea; ankle edema; palpitations or tachycardia; intermittent claudication; known heart murmur; or unusual fatigue or shortness of breath with usual activities.
‡‡‡‡Medical clearance, approval from a health care professional to engage in exercise.
ΦACSM Guidelines, see *ACSM's Guidelines for Exercise Testing and Prescription, 9th edition*, 2014.

Appendix C – Informed Consent/Assent

Chapter 4 (Study 1) – Parental/Guardian Consent form

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

PARENT/GUARDIAN CONSENT FORM
(Version 1.1, Date: 01/06/2018)

Project Title:
Swansea University Research Engagement Week

Contact Details:

[redacted]

	Please initial box
1. I confirm that I have read and understood the information sheet dated 01/06/2018 (version number 1.1) for the above study and have had the opportunity to ask questions.	☐
2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason, without their medical care or legal rights being affected.	☐
3. I understand that sections of any of data obtained may be looked at by responsible individuals from the Swansea University or from regulatory authorities where it is relevant to my child taking part in research. I give permission for these individuals to have access to these records.	☐
4. I give permission for my child's academic records to be accessed by the primary researchers. This will not affect their education or affect their participation within the rest of the study.	☐
5. I understand that data collected on my child may be used in reports and academic publications in anonymous fashion	☐
6. I understand that the research techniques used in this study are for research purposes only and not for diagnosis of any condition	☐
7. I give permission for my child to be video recorded during the fundamental movement skills station for research analysis purposes only	☐
8. I agree for my child's physical activity levels to be monitored by an activity monitor for 7 days. If I agree to this, I also understand that it is my child's and my responsibility to ensure the return of the monitor by the end of the current half term.	☐
9. I agree to my child taking part in the above study.	

_____	_____	_____
Name of Parent	Date	Signature
_____	_____	_____
Name of child giving consent for	Date	Signature

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

CHILD ASSENT FORM
(Version 1.1, Date: 01/06/2018)

Project Title:
Swansea University Research Engagement Week

Contact Details:

[redacted]

Please initial box

1. I confirm that I was at the assent assembly / have read and understood the participant information sheet given to me (dated: 01/06/2018, version number 1.1) for this study and have had the opportunity to ask any questions ☐
2. I understand that taking part is my choice and that I can choose to stop taking part at any time, without giving a reason, and it won't affect my participation in other research studies in the future. ☐
3. I understand that information collected about me by the researchers will only be looked at by people who can do so. I am happy for them to have access to it ☐
4. I am happy for my latest grades to be looked at by the researchers and I understand that it will not affect my education or effect my participation within this study ☐
5. I understand that the information collected by the researchers may be used in their work and published, but the information will be anonymous. This means that the information will not have my name on it or any information that links it to me. ☐
6. I am happy to take part in the physical activity monitoring part of this study and wear an accelerometer for 7 days. I also understand that it is my responsibility to bring this back into school before the end of the current term. ☐
7. I agree to being video recorded whilst I perform the movement skills. ☐
8. I understand that the heart and lung function stations are for research only and cannot tell me if I have an illness or not ☐
9. I agree to take part in the above study.

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

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

ADOLESCENT ASSENT FORM
(Version 1.1, Date: 01/06/2018)

Project Title:
Swansea University Research Engagement Week

Contact Details:

[redacted]

Please initial box

10. I confirm that I have read and understood the information sheet dated 01/06/2018 (version number 1.1) for the above study and have had the opportunity to ask questions. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. ☐

11. I understand that sections of any of data obtained may be looked at by responsible individuals from the Swansea University or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to these records. ☐

12. I give permission for my academic records to be accessed by the primary researcher, for my latest academic achievement to be accessed. This will not affect your education or your ability to take part within this study. ☐

13. I understand that data I provide may be used in reports and academic publications in anonymous fashion ☐

6. I am happy to take part in the physical activity monitoring part of this study and wear an accelerometer for 7 days. I also understand that it is my responsibility to bring this back into school before the end of the current term ☐

7. I agree to being video recorded whilst I perform the movement skills ☐

8. I understand that the heart and lung function stations are for research only and cannot tell me if I have an illness or not ☐

14. I agree to take part in the above study. ☐

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

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

PARTICIPANT CONSENT FORM
(Version 1.3, Date: 15/10/18)

Project Title:
Investigating the influence of physical activity, sedentary time and sedentary behaviour on risk of cardiovascular disease

	Please initial box
1. I confirm that I have read and understood the information sheet dated 29/11/2017 (version number 1.1) for the above study and have had the opportunity to ask questions.	☐
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.	☐
3. I understand that sections of any of data obtained may be looked at by responsible individuals from the Swansea University or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to these records.	☐
4. I understand that data I provide may be used in reports and academic publications in anonymous fashion.	☐
5. I regularly take part in physical exercise at a comparable level of exertion to that which I will undertake during this study, and am fit to take part in this study	☐
6. I have no known cardiovascular (e.g. heart), metabolic (e.g. diabetes or pre-diabetes) or renal (e.g. kidney) disease.	☐
7. As far as I am aware, I have not experienced any signs or symptoms of cardiovascular (e.g. heart), metabolic (e.g. diabetes or pre-diabetes) or renal (e.g. kidney) disease.	☐
8. I agree to take part in the above study.	☐

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

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

PARENT/GUARDIAN CONSENT FORM

(Version 1.0, Date: 16/01/2018)

Project Title:

Examining the relationship of physical activity and metabolic control with cardiovascular health in healthy children and adolescents.

Contact Details:

[redacted]

Please initial box

1. I confirm that I have read and understood the information sheet dated 16/01/2018 (version number 1.0) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason and without their medical care, school work or legal rights being affected. ☐
3. I understand that the data obtained may be looked at by responsible individuals from the Swansea University or from regulatory authorities where it is relevant to my child taking part in research. ☐
4. I agree for my child to take part in the above study ☐

Name of Parent/Guardian	Date	Signature
Name of Person taking consent	Date	Signature
Researcher	Date	Signature

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

PARTICIPANT ASSENT FORM
(Version 1.0, Date: 16/01/2018)

Project Title:

Examining the relationship of physical activity and metabolic control with cardiovascular health in healthy children and adolescents

Contact Details:

[redacted]

Please initial box

1. I have read and understood the information sheet dated 16/01/2018 (version 1.0) for this study and have been able to ask any questions I have. ☐
2. I know that it is my choice to take part and that I am can stop doing so at any time, without giving any reason, and without any problems. ☐
3. I understand the information I give may be looked at by people at Swansea University. I am happy for these people to see my results. ☐
4. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature
Researcher	Date	Signature

Chapters 5 and 7 (Studies 2 and 4) – Parental/Guardian Consent Form

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

PARENT/GUARDIAN CONSENT FORM
(Version 2.1, Date: 17/03/2017)

Project Title:

Examining the relationship between physical activity and metabolic control in children and adolescents with type 1 diabetes mellitus.

Contact Details:

[redacted]

Please initial box

1. I confirm that I have read and understood the information sheet dated 30/11/2015 (version number 2.1) for the above study and have had the opportunity to ask questions. ☐
2. I understand that my child's participation is voluntary and that they are free to withdraw at any time, without giving any reason and without their medical care, school work or legal rights being affected. ☐
3. I understand that sections of medical history relating to your child's type 1 diabetes, in addition to any of the data obtained may be looked at by responsible individuals from the Swansea University or from regulatory authorities where it is relevant to my child taking part in research. I give permission for these individuals to have access to these records. ☐
4. I agree for my child to take part in the above study. ☐

Name of Parent/Guardian	Date	Signature
Name of Person taking consent	Date	Signature
Researcher	Date	Signature

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

PARTICIPANT ASSENT FORM
(Version 2.1, Date: 17/03/2017)

Project Title:

Examining the relationship between physical activity and metabolic control in children and adolescents with type 1 diabetes mellitus.

Contact Details:

[redacted]

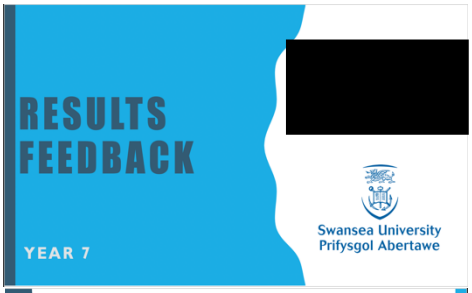
Please initial box

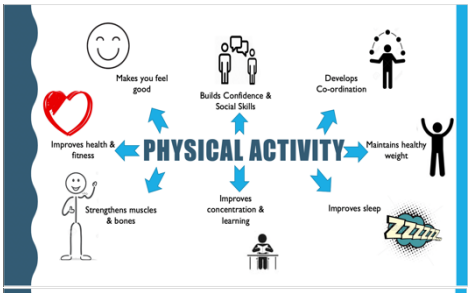
1. I have read and understood the information sheet dated 30/11/2015 (version 2.1) for this study and have been able to ask any questions I have. ☐
2. I know that it is my choice to take part and that I am can stop doing so at any time, without giving any reason, and without any problems. ☐
3. I understand that aspects of my medical history relating to my diabetes, in addition to some of the information I give may be looked at by people at Swansea University or the hospital. I am happy for these people to see my results. ☐
4. I agree to take part in the above study. ☐

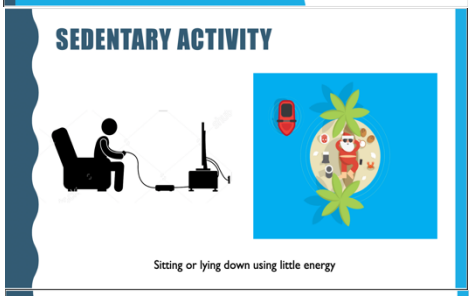
Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature
Researcher	Date	Signature

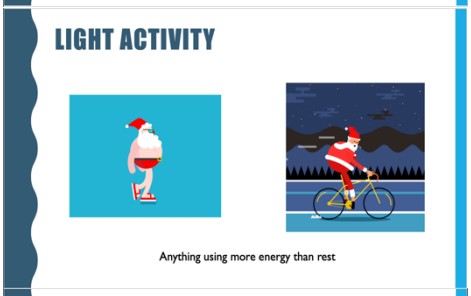
Appendix D – Engagement and Results Feedback

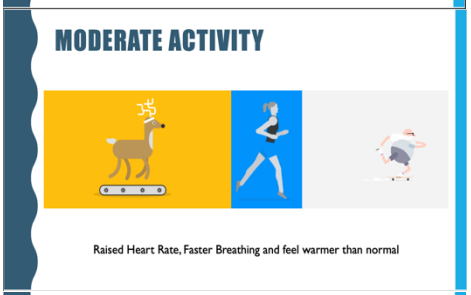
Chapter 4 (Study 1) – Engagement and Results Feedback Presentations

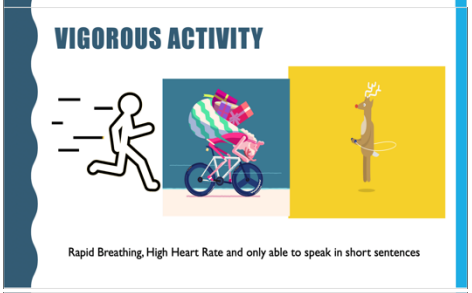


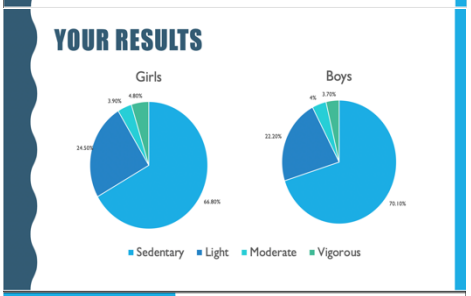






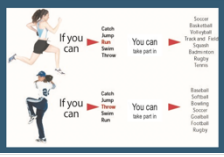




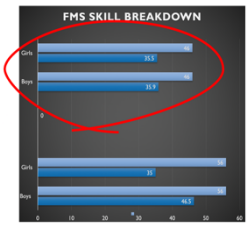


THE IMPORTANCE OF FMS

FMS → PHYSICAL ACTIVITY → SHORT AND LONG-TERM HEALTH



FMS SKILL BREAKDOWN



YEAR 7 RESULTS

LOCOMOTOR SKILLS

NO DIFFERENCE BETWEEN BOYS AND GIRLS

OBJECT CONTROL

HIGHER COMPETENCE IN BOYS

DIFFERENCE LESS THAN PREVIOUS STUDIES

IDENTIFYING THE WEAKER FMS

GIRLS

BOYS

IMPORTANT POINTS TO REMEMBER

- THESE SKILLS SHOULD BE MASTERED BY AGES 10 AND 11
- THESE SKILLS ARE DEVELOPED THROUGH PRACTICE
- YOUR TIME IN P.E. IS RESTRICTED
- TRY AND INVOLVE YOURSELF IN AS MUCH PHYSICAL ACTIVITY AS POSSIBLE

30m Sprint Times

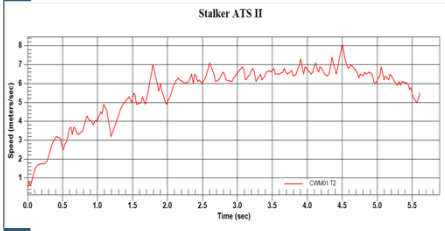
	Boys Average Time (s)	Girls Average Time (s)
30m Time (s)	6.22 seconds	6.29 seconds

Very close, there is only 0.07 seconds in it!

WHY ARE THEY SO CLOSE?

SPEED = STRIDE FREQUENCY X STEP LENGTH

Step length & Frequency



How else can we improve our sprint speed?

- Take part in P.E. and increase moderate to vigorous physical activity levels
  - Become more efficient
  - Running technique

QUESTIONS?

THANK YOU AND HAPPY CHRISTMAS

Swansea University Prifysgol Abertawe

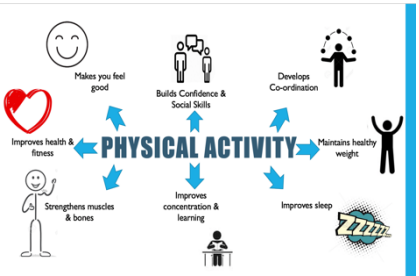
Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Canolfan Ymchwil Technoleg Chwaraeon Cymhwysol Ymarfer a Meddygaeth

RESULTS FEEDBACK

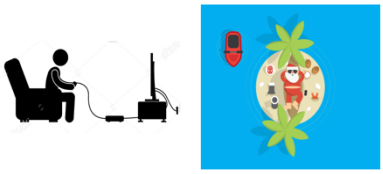
[redacted]

YEAR 7

Swansea University
Prifysgol Abertawe



SEDENTARY ACTIVITY



Sitting or lying down using little energy

LIGHT ACTIVITY

Anything using more energy than rest

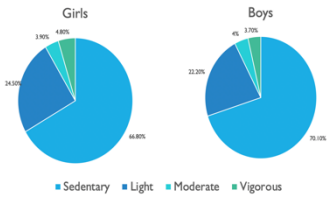
MODERATE ACTIVITY

Raised Heart Rate, Faster Breathing and feel warmer than normal

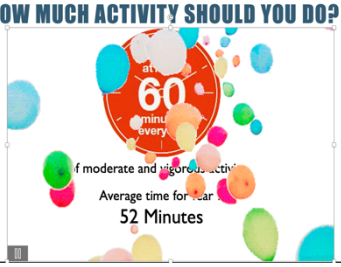
VIGOROUS ACTIVITY

Rapid Breathing, High Heart Rate and only able to speak in short sentences

YOUR RESULTS



HOW MUCH ACTIVITY SHOULD YOU DO?



IMPORTANT POINTS TO REMEMBER

- THE MORE WE MOVE THE MORE WE IMPROVE
- TAKE PART IN AS MANY DIFFERENT ACTIVITES AND SPORTS AS POSSIBLE
- EVERYBODY WILL BE GOOD AT DIFFERENT THINGS

REASONS TO BE ACTIVE

THE CIRCULATORY SYSTEM

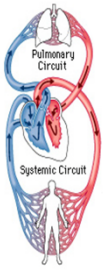
THE HEART BLOOD VESSELS BLOOD

THE HEART

Stroke Volume
Amount of blood pumped with every beat

50-80 ml average

Cardiac Output
Amount of blood pumped every minute

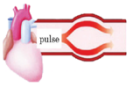


BLOOD VESSELS

Artery
Carries away from the heart to lungs or the body

Vein
Carries blood back to the heart ready to pick up more oxygen

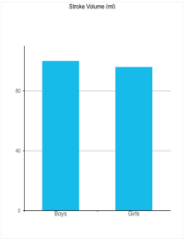
Capillary
Carries oxygen and nutrients to every cell in the body

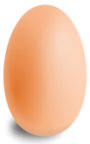


Pulse Wave Velocity
The speed pulses move through an artery

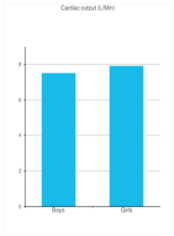
Metres per second (m/s)

RESULTS

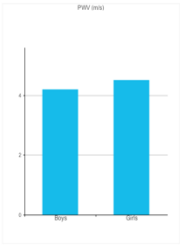




RESULTS

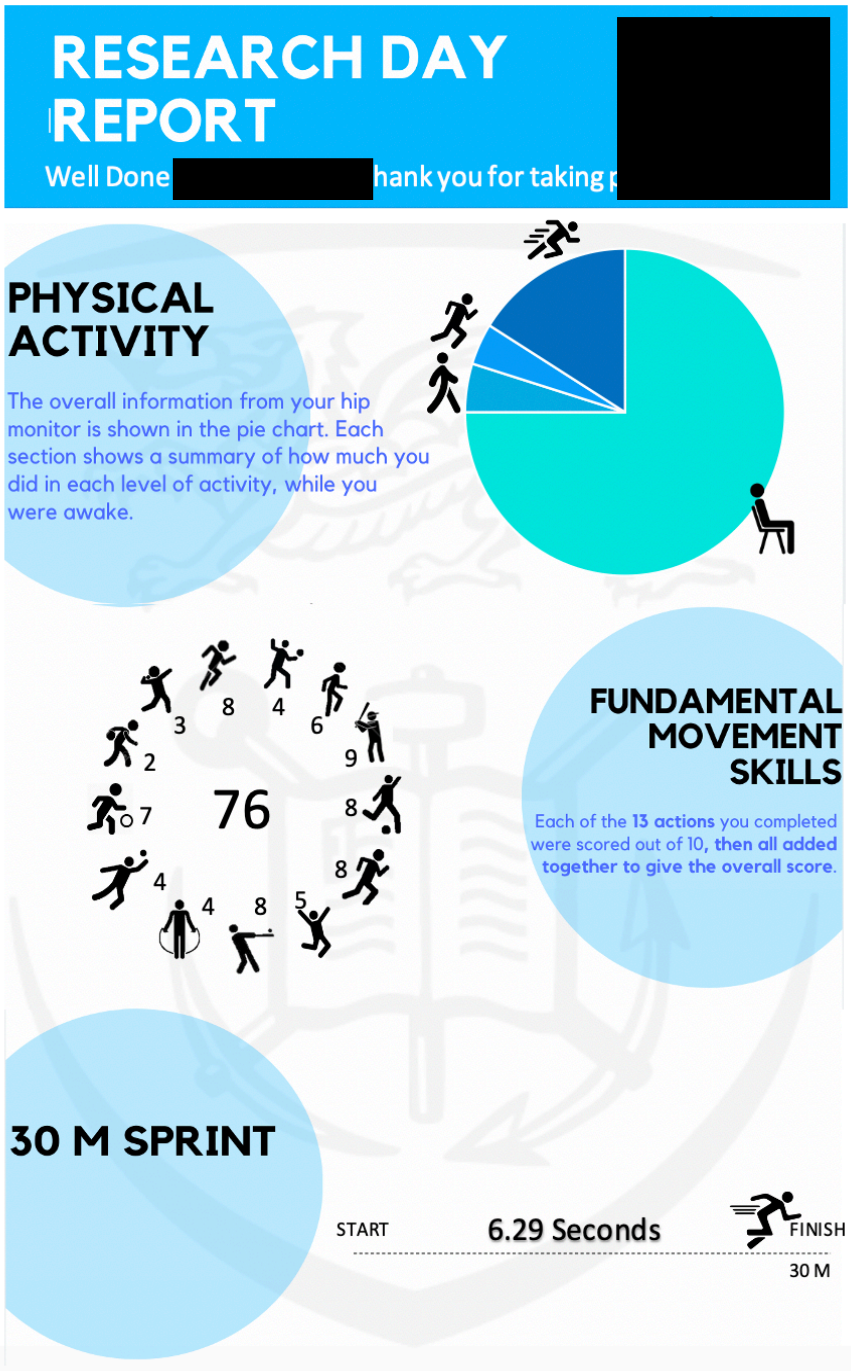


RESULTS



3 times as fast as a slow walk!

QUESTIONS?


RESEARCH DAY REPORT
Well Done [redacted] hank you for taking p [redacted]
PHYSICAL ACTIVITY
The overall information from your hip monitor is shown in the pie chart. Each section shows a summary of how much you did in each level of activity, while you were awake.
3
8
4
6
2
9
7
76
8
4
8
4
8
5
FUNDAMENTAL MOVEMENT SKILLS
Each of the 13 actions you completed were scored out of 10, then all added together to give the overall score.
30 M SPRINT
START
6.29 Seconds
FINISH
30 M

Swansea University
Prifysgol Abertawe

Applied Sports Technology Exercise and Medicine Research Centre (A-STEM)
Sport and Health Portfolio, College of Engineering

Study Feedback Report - [redacted]

Thank you for participating, we hope you enjoyed! Please see your results below. (These results are for research purposes, not for diagnosis. If you have any concerns, please contact your GP)

Parameter	Result	Explanation
BP (mmHg) SV (ml) CO (L/min) MAP (mmHg) Aix (%) PWV (m/Sec)	139/75 137 5.37 91.5 24 7.6	**Blood Pressure (BP)** - the measure of force your heart pumps blood around the body. The first number is the pressure when your heart pushes blood out, the second number is the resting pressure between beats. **Stroke Volume (SV)** - the volume of blood your heart heats with every pump. **Cardiac Output (CO)** - the volume of blood your heart beats per minute **Mean Arterial Pressure (MAP)** - the average pressure in your arteries during a heart cycle. **Augmentation Index (Aix)** - an indirect measure of arterial stiffness (this is only a research measure for indication) **Pulse Wave Velocity (PWV)** - the speed waves of blood from the heart travel through the circulatory system.
FVC (% of Pred) FEV1 (% of Pred)	6.33 (120) 5.08 (118)	**Forced Vital Capacity (FVC)** – the capacity of your lungs **Forced Expiratory Volume in 1 Second** – the amount of air you can expel from your lungs in 1 second
Absolute V02 (l/min) Relative V02 (ml/kg/min) GET (l/min) (% of V02)	4.95 60.00 3.76 (76.10)	Your **maximal aerobic capacity (V02)** is the volume of oxygen you effectively use, not just breathe in. Aerobic capacity is predominantly determined by genetics; however, this can be trained higher. **Gas exchange threshold (GET)** is the point at which you start producing more C02 than taking in oxygen, and therefore are in anaerobic exercise.

Average Day's Physical Activity