INTEGRATED MOVEMENT BEHAVIOURS IN CHILDREN WITH CHRONIC DISEASE

An Observational Case-Control Study

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Abstract

The prevalence of chronic diseases has increased in children and adolescents and physical inactivity, sedentary lifestyle and obesity have been identified as risk factors for earlier onset of chronic disease. Times spent in 24-hour movement behaviours have become important public health concerns because of their potential to impact on an individual's health.

The concept of 24-hour movement behaviours - comprising physical activity (PA), sedentary behaviour and sleep - is relatively new and quantifying the various movement behaviours with confidence is still a challenge. The adequacy of levels of 24-hour movement behaviors in children with chronic disease is unknown as is whether there are systematic differences between children with chronic disease and their healthy peers.

Aims: To examine the habitual amount of time spent in moderate to vigorous physical activity (MVPA) and sedentary time (ST) in children and adolescents with chronic disease and in children and adolescents with obesity; to compare measured MVPA against MVPA recommendations in children with chronic disease and their healthy peers and to investigate 24 hour-movement behaviours (PA, standing, sedentary and sleep behaviours – sleep; quantity and sleep quality) for 5-7 days in children with chronic childhood diseases and test whether there were differences between children with chronic disease and their healthy peers.

In systematic literature reviews (Chapters III and IV): the literature searching was focused on four key elements: children and/or adolescents, MVPA, ST and/or SB,

measured objectively by accelerometer, and common chronic disease (obesity, chronic cardiovascular disease, chronic respiratory disease, diabetes mellitus and malignancies). For each review, an extensive search was carried out in the five most relevant electronic databases: Medline, Cochrane library, EMBASE, SPORTDiscus and CINAHL from 2000. Study selection: Studies with accelerometer-measured MVPA and/or SB (at least 3 days and 6 hours/day) in children and adolescents (0-19 years) with cardiovascular disease, respiratory disease, diabetes, malignancy and obesity, studied while well and clinically stable. Study quality was assessed formally. Meta-analyses were planned for all outcomes. In the systematic review of MVPA and ST in children and adolescents with chronic disease, 25 studies were eligible, in four chronic disease categories: cardiovascular disease (7 studies), respiratory disease (7 studies), diabetes (8 studies), and malignancy (3 studies). Patient MVPA was generally below the recommended 60 min/day and ST was generally high regardless of the disease condition. Comparison with healthy controls suggested no marked differences. MVPA in children with chronic disease was not very much lower than in healthy control or comparison groups with the exception of children being treated for malignancy.

In the systematic review of MVPA and ST in children and adolescents with obesity, 26 studies were eligible (*n*=14,739 participants; *n*=3523 with obesity); 6/26 studies involved children aged 0 to 10 years and 18/26 involved adolescents aged 10.1 to19 years. In the participants with obesity, time spent in MVPA was consistently below the recommended 60 min/day, and ST was generally high regardless of the participant's age and sex. Comparison with controls suggested that the time spent in MVPA was significantly lower in children and adolescents with obesity, though

differences were relatively small. There were no marked differences in ST between obese study participants and their non-obese peers.

The primary data collection studies (Chapters V and VI) were based on an observational case-control study of 24-hour movement behaviours in children with common chronic diseases likely to disrupt these behaviours, and included 160 participants; 80 children with chronic disease; 20 with type 1 diabetes mellitus (T1DM), 20 with juvenile idiopathic arthritis (JIA), 20 with congenital heart disease (CHD), 20 with cystic fibrosis (CF). Patients were recruited from outpatient clinics at the Royal Hospital for Children, Glasgow. 80 healthy children were individually pair-matched for age, sex, and timing of measures. Habitual time spent in PA, standing, sedentary and sleep behaviours – sleep quantity – particularly sleep timing (sleep onset/offset), and sleep duration - and sleep quality) and step counts were all measured with the activPAL accelerometer/inclinometer over 7 days. Comparisons against recommendations were made and differences between the groups with chronic disease and controls examined. Mean time spent in PA and step counts per day were consistently lower in the children with chronic disease compared to healthy controls, reaching statistical significance only for the T1DM and CHD groups. Only 20/80 children with chronic disease and 29/80 controls met the daily step count recommendations. ST was consistently higher in children with chronic disease, though this reached significance only for the group with CF. Time spent asleep was slightly greater in the children with chronic disease, significant only for the group with JIA. Sleep disruption was consistently greater in those with chronic disease, reaching significance for groups with T1DM, CHD and CF.

When data from the groups of children with chronic disease and controls were combined, permitting a comparison of 80 vs 80 children respectively in the primary data collection studies, differences between children with chronic disease and healthy controls were more obvious when the children with chronic disease were compared as a single group with their healthy controls. The most important finding was that there were significant differences between children with chronic disease and healthy controls for ST, standing, PA and sleep. Those with chronic disease had greater time spent sedentary with significantly lower number of sedentary breaks, less standing time with slightly longer sleep time than their healthy controls. Time spent in PA was significantly lower (in both PA time and steps counts) in children with chronic disease compared to healthy controls.

The most obvious concerns in the present study arise from differences between patient and control groups with patient group showing greater ST, with consistently lower number of sitting bouts and lower PA levels than their healthy controls. However, differences between patient and control groups for the 24-h movement behaviours were generally quite small in the children studied and their biological significance of the differences is unclear. Finally, optimising levels of 24-hour movement behaviours should confer a number of benefits for child health, development, and wellbeing. There is a need for further research with a clinical focus on these behaviours in those with chronic disease.

Table of Contents

Chapter III Accelerometer Measured Levels of MVPA and ST in Children and Adolescents with Chronic Disease: a Systematic Review and Meta-Analysis

Chapter IV Comparison of Accelerometer Measured Levels of Physical Activity and Sedentary Behavior between Obese and Non-Obese Children and Adolescents: a Systematic Review

List of Tables

List of Figures

List of Publications

This thesis is based on the following publications and a number of poster presentations.

Publications:

1. Elmesmari R, Reilly JJ, Martin A, Paton JY. Accelerometer measured levels of moderate-to-vigorous intensity physical activity and sedentary time in children and adolescents with chronic disease: A systematic review and meta-analysis. PLoS One. 2017;12(6):e0179429.

2. Elmesmari R, Martin A, Reilly JJ, Paton JY. Comparison of accelerometer measured levels of physical activity and sedentary time between obese and non-obese children and adolescents: a systematic review. BMC Pediatr. 2018;18(1):106.

3. Elmesmari R, Reilly JJ, Paton JY. Objectively measured 24-hour movement behaviors in children with chronic disease: A case-control study. Manuscript submitted to PLoS One 2019.

Poster presentations:

1. Comparison of accelerometer measured levels of physical activity and sedentary behavior between children with chronic diseases and healthy peers: a systematic review and meta-analysis. Glasgow Paediatric research day, Glasgow, UK, 2016.

2. Comparison of accelerometer measured levels of physical activity and sedentary behavior between children with chronic diseases and healthy peers: a systematic review and meta-analysis. ICAMPAM conference. Maryland, USA. 2017

3. Comparison of accelerometer measured levels of physical activity and sedentary time between obese and non-obese children and adolescents: a systematic review. Glasgow Paediatric research day, Glasgow, UK, 2017.

4. Objectively Measured 24-Hour Movement Behaviors in Children with Chronic Disease: A Case-Control Study. ICAMPAM conference, in Maastricht, June 26 - 28, 2019.

5. Integrated movement behaviors in children with chronic disease and healthy peers: A case-control study. Glasgow Paediatric research day, Glasgow, UK, 2019.

6. Comparison of accelerometer measured of sleep behavior in children with chronic disease and healthy peers: A case-control study. Glasgow Paediatric research day, Glasgow, UK, 2019.

List of Abbreviations

ACR	American College of Rheumatology
BMI	Body mass index
CD	Chronic disease
CD	Cystic fibrosis
CHD	Congenital heart disease
cpm	Counts per minute
CRF	Cardiorespiratory fitness
CRP	C-reactive protein
ESR	Erythrocyte sedimentation rate
FEV1	Forced expiratory volume in 1 second
h	Hour
HC	Healthy control
ILAR	International League of Associations for Rheumatology
JADAS	Juvenile Arthritis Disease Activity Score
JIA	Juvenile Idiopathic Arthritis
LPA	Low physical activity
METs	Metabolic equivalents units
MVPA	Moderate-to-vigorous intensity physical activity
NICE	National Institute for Health and Care Excellence guideline
PA	Physical activity
SB	Sedentary behaviours
SBRN	Sedentary Behaviour Research Network
SD	Standard deviation
SDS	Standard deviation score
ST	Sedentary time
T1DM	Type 1 Diabetes Mellitus
T2DM	Type 2 Diabetes Mellitus
RF	Rheumatoid factor
UK	United Kingdom
US	United Status
VPA	Vigorous physical activity
WHO	World health organisation

Acknowledgement

I have been extremely privileged to able to carry out my postgraduate studies within Child Health Department, Queen Elizabeth University Hospital, at Glasgow University.

This thesis would not have been completed without the support and encouragement of my family, many friends and colleagues; and to all of them *I convey sincere thanks indeed.*

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Declaration

The work presented in this thesis represents original work carried out by the author within the School of Medicine, Dentistry and Nursing, Child Healthy, Queen Elizabeth University Hospital, College of Medicine, Veterinary and Life Sciences of the University of Glasgow. This thesis has not been submitted in any form to any other university.

Authors Declaration: Rabha A. T. Sulyman

Dedication

To my beloved family, who never stopped believing in me

CHAPTER I

GENERAL INTRODUCTION

1.1. Background

Over the past few decades, the importance of physical activity (PA- defined as any bodily movements) for maintain the health of the population has been increasingly recognised (1). The start of this recognition can be traced back to Morris *et al* in 1953, when they observed that both bus drivers and office workers who had prolonged periods of sitting were at a higher risk of coronary artery disease than more physically active workers like bus conductors and postmen (2).

Nowadays, the growth in electronic media along with dramatic environmental and social changes particularly in relation to modes of transportation has created sedentary lifestyles. This behavioural shift represents a move from traditional to more industrialised lifestyles and is characterised by having less opportunity for being physically active and much greater involvement at work or during leisure in activities that are more sedentary (3). Church et al reported a steady shift toward more sedentary occupations over the last 50 years in the United States (US), a trend probably seen in the rest of the western world. Adults spend more time sitting or reclining during waking hours (at work or home, watching television, or while driving a car (4)) and less time in physical activity. Further international evidence using the International Physical Activity Questionnaire (IPAQ) showed that adults typically spent ≥ 9 hours of their waking hours in sedentary behaviours (SB) and the prevalence of PA occupations has decreased from 48% in 1960 to 20% in 2008 (4)

Sedentary behaviour (SB) has been defined in the Sedentary Behaviour Research Network (SBRN) consensus as any waking behaviour characterised by energy expenditure ≤1.5 metabolic equivalents (METs) while sitting, reclining or lying (5))(6).

More recent studies using objective measurements (accelerometers) to measure the time spent in SB in adult population revealed that adults today typically spend about 55–70% of their waking hours sedentary (7, 8).

Studies of SB in children and young people showed that the majority of their discretionary time is also sedentary, associated with time spent consuming audio-visual media, such as watching television, using computer, and playing computer games (7). For instance, United States and Canadian children and adolescents are spending an average of 6-8 and 8.6 hours per day respectively being sedentary (7, 9, 10).

As a result of these studies and increasing evidence that SB is related to health outcomes separate from the decline in PA, SB in children has been receiving greater attention from researchers recently. Many complementary lines of evidence suggest sedentary lifestyles have a negative impact on health status (11, 12) with high levels of SB having been shown to increase the risk of obesity, to elevate metabolic risk profile in children and adolescent (13-15) and to be associated with obesity-related health problems, including type II diabetes, cardiovascular disease, certain cancers later in adulthood (8, 16-19).

Collectively, most studies on the influence of PA or SB on health outcomes in children have examined the influence of one behaviour in isolation from other behaviours (e.g. only PA and not the other 24 hour movement behaviours—SB, light physical activity (LPA) and sleep) and that may have restricted our understanding of how these behaviours might interact together and affect heath. Moreover, while there is no doubt that moderate-to-vigorous intensity physical activity (MVPA) provides many important health benefits in children (20), it is important to recognise that MVPA only accounts

for a small proportion (typically <5%) of the 24h day, even among active children and young people, while other movement behaviours fill almost 95 % of the 24h day. Typically, sleep (usually ~40%), SB (around ~40%) and LPA (around ~15%) make up the remaining 95% of the day (21), as summarised in Figure 1.1. Indeed, Chaput highlighted that focusing on one behaviour such as MVPA while ignoring other components of the 'integrated movement' spectrum limits our understanding of how these various 'activities' interact together to impact children's health (21).

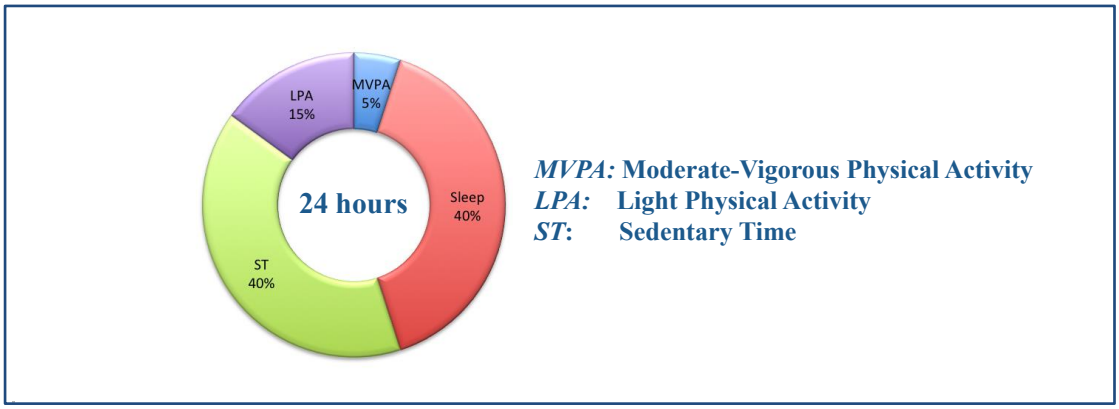


Figure 1.1: Estimated distribution of movement behaviours in children, adapted from Chaput et al (21)

This introductory chapter brings together information about integrated movement behaviours in healthy children before examining what is known about movement behaviours in children with common chronic disease. It begins by briefly reviewing the components of integrated movement behaviours in children, and then refers to how these behaviours have been measured, and current guidelines for them in children. It goes on to discuss some common chronic childhood diseases and what is known about movement behaviours in this context. By necessity much of the evidence describes each behaviour in isolation from other movement behaviours as that is what has been studied to date, rather than providing an integrated view of 24h movement behaviours in chronic disease.

1.2. Integrated Movement Behaviours in Healthy Children

The concept of integrated movement behaviours over the 24-hour period (referred to as "24-hour movement behaviours" throughout this thesis) is a new concept attracting growing interest. The idea is to study all of the 24-hour movement behaviours in combination, extending from sleep through to MVPA because having one "unhealthy" movement behaviour might moderate the health benefits of another (22). For example, the health benefits of MVPA might be reduced if children have poor sleep habits and/or engage in excessive time spent in SB and conversely, increased PA might promote better sleep and could well ameliorate the detrimental effects of insufficient sleep and/or extended periods of sedentary in some individuals.

There is some preliminary evidence available to support this. A Danish longitudinal study in of 785 aged 8-11 year investigated both independent and combined associations between all movement behaviours and risk of cardio-metabolic syndrome. They found that, low PA and short sleep duration were associated with increased risk of cardio-metabolic syndrome. Conversely, greater time spent in SB and more sleep disturbances were associated with increased risk cardio-metabolic syndrome. The study has shown that greater time spent sedentary with low PA and with short sleep duration was associated with higher risk of cardio-metabolic syndrome in children. It suggests that multiple movement behaviours may need to be targeted to improve cardio-metabolic risk markers in childhood (23).

1.2.1. Physical Activity

1.2.1.1. Definition

PA is defined as any “bodily movements” produced by skeletal muscles including activities undertaken while working, playing, carrying out household chores, travelling, and engaging in recreational pursuits (1) that requires energy expenditure more than 1.5 metabolic equivalent units (METs) (24) One MET is the energy cost of resting quietly, often defined in terms of oxygen uptake as 3.5 $mL \cdot kg^{-1} \cdot min^{-1}$ in adults (25). Resting energy expenditure is much higher in children than in adults but the same concept applies with one MET in childhood being equivalent to the energy expended at rest (1)) However, the term "physical activity" should not be confused with "exercise" (26), which is a subcategory of PA defined as planned, structured, repetitive bodily movement, and aims to improve or maintain one or more components of physical fitness, such as swimming, and yoga (1, 27).

PA is characterised and described in terms of frequency, duration, intensity and type. PA frequency is defined as the number of times an activity is performed in a particular period of time (28). PA duration refers to total amount of time spent in an activity, which could be either continuous or cumulative over a specified unit of time (29). PA intensity is defined as the energy expenditure during specific activity and is usually measured by METs. PA is commonly categorised into four levels according to the intensity: LPA is any activity that requires energy expenditure above 1.5 but less than 3.0 METs; in MVPA energy expenditure ranges between 3.0 to 6.0 METs; while vigorous intensity physical activity (VPA) energy expenditure is more than 6.0 METs (30, 31). Finally, the type or mode of PA refers to the activity type e.g. running, jogging or walking (32).

1.2.1.2. Physical Activity in Healthy Children

Physical activity, particularly MVPA is associated with a wide range of health benefits in adults. MVPA plays an important role in maintaining their health as well as protecting against several diseases such cardiovascular disease, diabetes, hypertension and obesity and also of reduced risks of all-cause mortality, some cancers and depression (33-37).

In children too, several reviews have summarised the substantial evidence of the relationship between physical activity and health and have concluded that meeting a minimum of 60-minute per day in MVPA.

The largest and most consistent body of evidence has been accumulated for a few outcomes: children should spend at least 60 minutes in MVPA per day in order to promote healthy growth and development (20, 38-41), to obtain cognitive and educational effects (41, 42), and multiple associated benefits for physical, mental, and psychosocial health (43-45) leading to improved health and reduced morbidity and mortality in the general child population (42). Further, MVPA has a positive impact on aerobic capacity, insulin sensitivity, lipid profiles, and it also reduces stress, anxiety, and depression (36, 43, 44, 46, 47). Indeed, the benefits of adequate childhood PA could be summarised in three ways: an improvement in childhood health status and quality of life; an increased likelihood of maintaining adequate activity into adulthood and an improvement of future adult health status by delaying the onset of chronic disease in later life (48, 49), as summarised in Figure 1.2.

In some children levels of MVPA are low while levels of LPA are extremely high as resulted they spent many hours per day walking, but the pace of walking was slow (50). One of the most valuable sources of evidence on physical activity and health during childhood and adolescence is the large prospective Avon Longitudinal Study of Parents and Children (ALSPAC) study conducted in England. In adolescent ALSPAC participants, it was found that body fatness was influenced by MVPA (rather than LPA or VPA), LPA was the main influence on blood pressure, while VPA was the main influence on bone health (51).

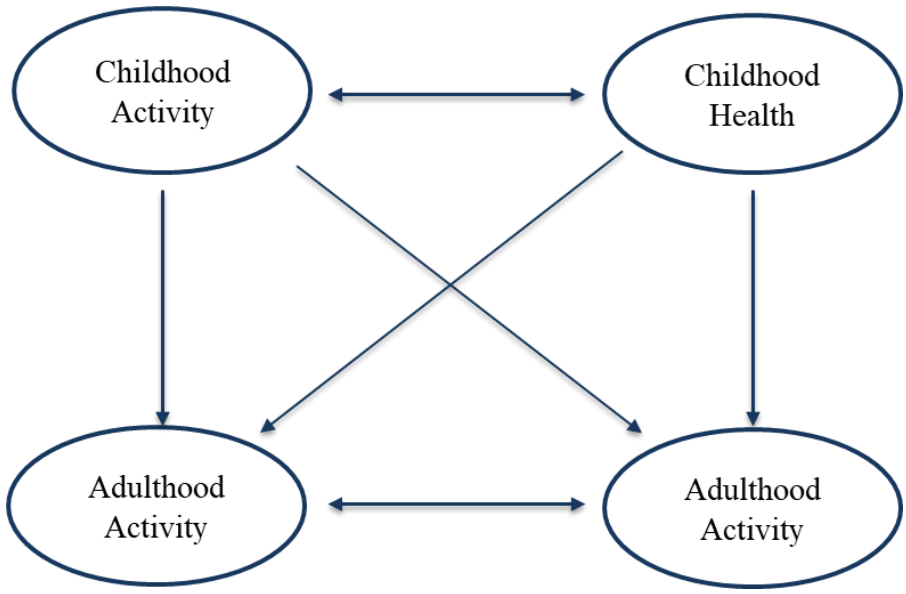


Figure 1.2: The relationships between physical activity and health in children and adults, adapted from Blair et al (49)

On the other hand, low PA in childhood compromises child health and development (43) and is associated with adverse effect on adult health. Because levels of PA have been shown to track from the childhood to adulthood (52), low childhood PA predisposes to low adolescent PA, and in turn predisposes to low adult PA (52-54). Moreover, a report in the Lancet 2012 (37) had reported that low PA level in childhood creates two adverse effects constituting a ‘double hit’ on PA and health in adulthood,

as shown in Figure 1.3. The first ‘hit’ is that low PA acts directly and has biological effects (e.g. on the cardiovascular system) from childhood that are cumulative over the time. The second ‘hit’ is an indirect behavioural effect stems from the fact that low childhood PA tracking to low PA in adulthood (52), and this then causes many and serious health effects such as increased risk for several diseases and poorer overall quality of life (37, 55).

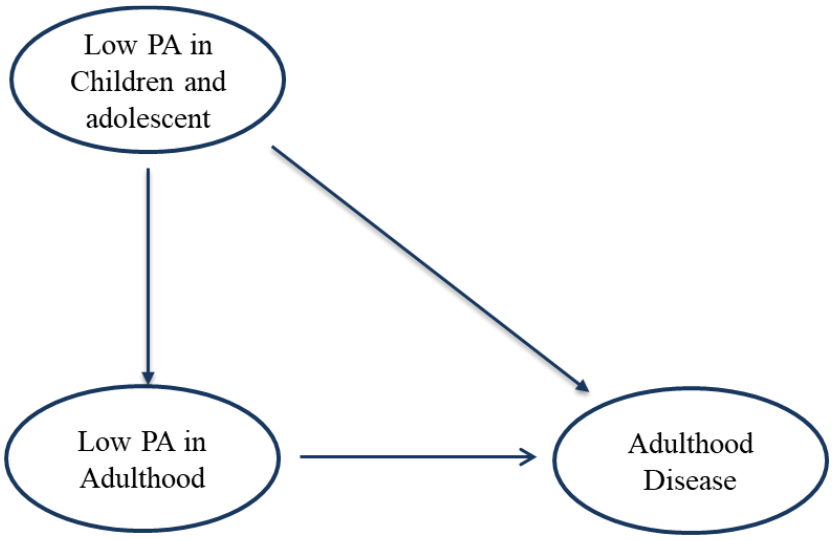


Figure 1.3: The effect of low physical activity (PA) in childhood on adult health, adapted from Lee et al (37)

1.2.1.3. Physical Activity in Children with Obesity

The prevalence and severity of obesity is increasing in children and adolescents (obesity defined as body mass index (BMI) above the 95th percentile for age and sex) (56-58). The short- and long-term association with poor health outcomes raises the level of importance for understanding childhood obesity as a major public health concern (59). Moreover, in children and adolescents with obesity obesity is more likely to persist into adulthood and has been shown to be associated with increased overall mortality rate and specifically with increased risk of cardiovascular disease and diabetes in adulthood

(60). Obese children also are more likely to experience significant short-term health problems such as hyperlipidemia, hypertension, glucose intolerance and orthopedic complications than their children and adolescents with healthy weight (59, 61). In addition, the adverse social consequences of obesity in children and adolescent may have long-lasting negative impact on self-esteem, body image and economic mobility (62).

Previous studies have linked levels of PA and obesity in children and adolescent and suggested that lack of PA is an important contributing factor in the development and or maintenance of childhood obesity (63, 64). However, such a relationship between and low PA could potentially be bidirectional with low PA increasing the risk of developing obesity in children and adolescents. In keeping with this possibility, obese children and adolescents have been shown to be less active than their normal-weight peers with a level of PA in those children lower than the recommended level (65, 66).

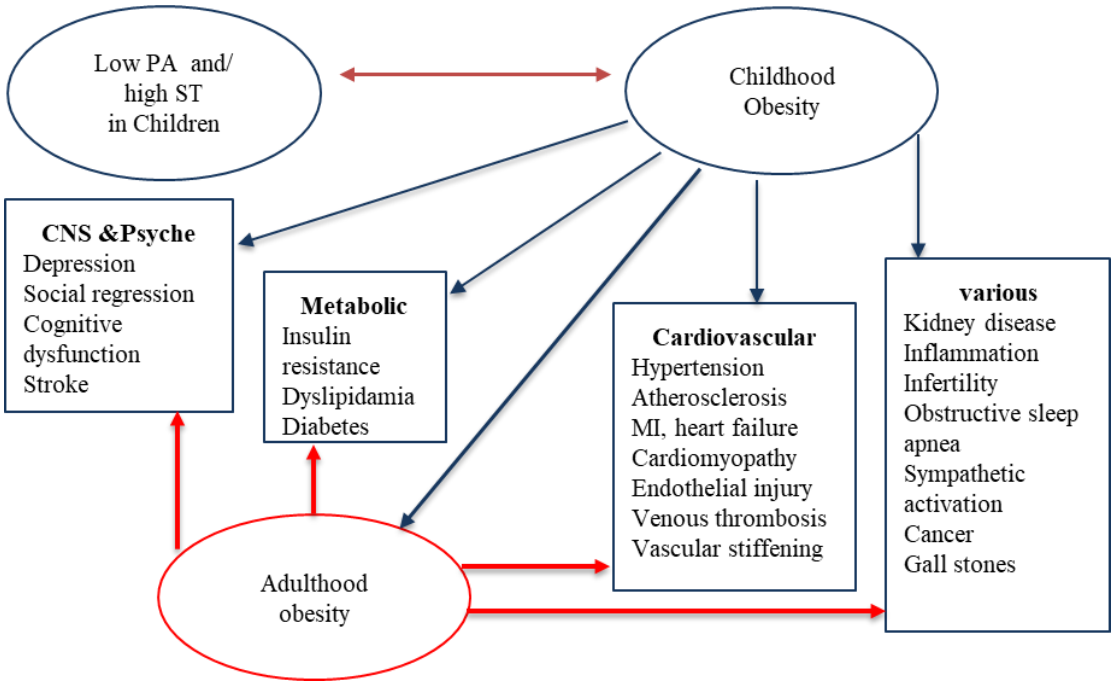


Figure 1.4: Aggravating effect of childhood obesity on the life-time risk for other disease conditions, including a greater risk for adult obesity, which itself continues to worsen disease development, adapted from Barton et al (69).

Thus, its attendant health risks justify widespread efforts toward prevention of obesity in children and adolescent. PA therefore has been emphasised as an appropriate intervention in childhood obesity that by increasing energy expenditure and resting metabolic rate help could protect from the development of obesity. Indeed, several public health bodies' interventions designed to increase levels of PA in children at schools, families and communities suggest these might be promising strategies for the prevention of childhood obesity (65, 67, 68).

1.2.1.4. Physical Activity in Children with Chronic Disease

In children with chronic disease increasing PA, specifically MVPA, has a significant positive impact on their disease by improving their quality of life, reducing or preventing co-morbidities and premature mortality (70, 71). Recently, for example, epidemiological studies have provided evidence that MVPA has a significant effect on lowering high blood pressure, preventing obesity, reducing body fat and controlling weight, improving cardio-metabolic profile, and increasing bone mineral density, as well as reducing rates of depression and improving self-esteem in children with chronic disease (34, 72, 73). Thus PA is considered a principal intervention for primary and secondary disease prevention (74). Indeed, it is important for patients with chronic diseases, especially for paediatric patients, because it influences their growth, promoting bone strength and improves body composition (75). Further, some studies have shown that in adult patients regular PA during treatments helps them to tolerate better treatment-induced side effects and improves their quality of life.

1.2.1.5. Physical Activity Guidelines in Children

The appropriate amounts of PA for general population, including children and youth have been developed by several government and non-government organisations. The first PA guidelines for children and youth were introduced by Canada in 2002 (76, 77). The basic recommendation within these guidelines was that children and youth should increase their time spent on PA by 30 minutes per day, independent of their current PA level and progress over approximately 5 months to more than 90 minutes per day Based on large amounts of strong and consistent evidence which have been summarised and synthesised in several systematic and narrative reviews (notably (20, 38, 78-82) it has been suggested in numerous more recent evidence-based guidelines that participating in a minimum 60 minutes per day of MVPA will have meaningful health benefits for children and youth. As an illustration of the available evidence, the systematic review of Strong et al (20) reviewed 850 articles. They found that evidence-based data are strong for beneficial effects of physical activity on musculoskeletal health, several components of cardiovascular health, adiposity in overweight youth, and blood pressure in mildly hypertensive adolescents. Evidence was adequate to make informed judgments about the beneficial effects of physical activity on lipid and lipoprotein levels and adiposity in normal weight children and adolescents, blood pressure in normotensive youth, other cardiovascular variables, self-concept, anxiety, and depression symptoms, and academic performance. Although the definition of the metabolic syndrome for youth is not yet firmly established, the association between the MS and adiposity, lipid and lipoprotein levels, and blood pressure suggests that regulation of overweight through physical activity may have a beneficial effect on components of the syndrome. The authors noted that most of intervention studies used supervised programs of moderate to vigorous physical activity of 30 to 45 minutes

duration 3 to 5 days per week. The reviewing panel believed that a greater amount of physical activity would be necessary to achieve similar beneficial effects on health and behavioural outcomes in ordinary daily circumstances where activity is typically intermittent and unsupervised. They concluded by recommending that school-age youth should participate daily in 60 minutes or more of moderate to vigorous physical activity that is developmentally appropriate, enjoyable, and involves a variety of activities. Several world public health organisations now recommend that, children and adolescents should accumulate a minimum of 60 minutes of MVPA daily. A dose greater than 60 minutes provides greater health benefits (9, 20).

While national and international guidelines recommend at least 60 minutes/day of MVPA for school-age children and adolescents, it is widely accepted ((81, 82)) that for those individuals with levels of MVPA below the recommendation there should be benefits of increasing MVPA levels, even if they do not meet the 60 minutes/day recommended. In addition, the recent evidence based guideline acknowledge that the 60 minutes per day is somewhat arbitrary, and based on the need to have a simple recommendation for public health messaging, and for public health surveillance (e.g. national and international surveys of MVPA in children and adolescents) (83). Recent evidence based guidelines also acknowledge that there are benefits to increasing MVPA beyond the 60 minutes/day (81-83), and that the recommendation should not be seen as a simple target or threshold. Therefore, children and youth who are very inactive and could not achieve the MVPA recommendation should be encouraged to accumulate a minimal target of 60 minutes of MVPA per day in shorter bouts (e.g., 10- 15 min) throughout the day (80, 84).

In respect of the number of steps needed per day to achieve the daily recommended levels of physical activity to promote and maintain the health, Tudor-Locke provided accumulated evidence from reviewing objectively monitored step-defined PA literature; the minimal recommendation of total volume of PA is associated with 10,000-14,000 free-living steps/day in children aged 4-6 years; for children aged 6-11 years 12000-16000 steps/day in boys and 10000 to 13000 steps/day in girls with this difference in the steps recommendation could be related to sex-and-age specific data of Beets et al (85). For children aged 12-19 years 8000-9000 steps/day is recommended and associated with good health (86). These recommendations have also been applied to children with chronic disease (30, 87).

1.2.2. Sedentary Behaviour

1.2.2.1. Definition

Sedentary behaviour (SB) – often called “Sitting“ is defined currently as any PA that has an energy requirement of less than 1.5 METs in sitting/lying position as noted above (88). Total sedentary time (ST) can be further sub-classified into a variety of specific categories of SB such as reading, playing quietly, or engaging in screen-based entertainment include watching television, using a computer, or playing video games (5, 89). Thus, SB is a complex construct which includes both being sedentary and a range of behaviours that take place while being sedentary, some of which may be more harmful than others (e.g. screen time); as explained in details later (36, 90).

1.2.2.2. Sedentary Behaviour in Healthy Children

The previous literature clearly indicates that SB might have an impact on health status. The first report provided by Bernadino Ramazzini that showed there is a relationship between SB and deleterious health consequences (91, 92). Indeed, the original Morris studies of London bus drivers vs bus conductors have even been re-interpreted by some as providing evidence of the harmful effects of sitting rather than just evidence of the benefits of PA (2). Many epidemiologic studies have now linked high levels of SB in childhood with many of unfavourable health consequences (36, 55), which lead to an increased risk of morbidity and premature mortality in adult life (88). A sedentary lifestyle has been consistently and positively associated with an increased risk of various chronic diseases in adult life including cardiovascular diseases, diabetes, cancer and psychological problems (36).

So far, multiple lines of evidence have suggested a link between screen-time sedentary and gain weight in children (65). Indeed, it has been clearly demonstrated that there is a time dependent dose response relationship; every additional hour of time spent on viewing television, using computer and playing video games was significant associated with being overweight and having higher central adiposity among in children and adolescents (6, 67, 90, 93-96). Screen time guidelines are now common around the world (5, 9, 89, 96).

Further, while children and adolescents typically do not have cardiovascular diseases there is a positive association between SB and risk factors for development of cardiovascular diseases in children and adolescents. Byun *et al* has shown that time spent on screen-based SB was significantly positively associated with cardiovascular diseases risk factors independent of levels of PA (97). A cross sectional study in

Portugal on the associations between cardiovascular risk markers and three types of screen-time SB (viewing television, using computer and playing video games) in school children, with screen time data collected by a questionnaire reported that, time spent on television viewing was strongly associated with increased risk of cardiovascular markers especially for those children watching television > 2 h/day, independent of levels of PA (98). In addition, some studies have reported that SB, such as excessive time spent in television viewing, video games and computer use, is associated with raised blood pressure in both childhood and adolescence (99, 100).

1.2.2.3. Sedentary Behaviour in Children with Obesity

In addition to insufficient PA and diet, sedentary life have been suggested as one of the causes in the development and or maintenance of obesity in children and adolescent (67). As noted above, the relation between both might be bidirectional: more time spent on SB might increase risk of development of obesity while obesity could be the cause of more time spent sedentary in children and adolescent (101). Indeed, a cross-sectional study that included 712 child aged from 9-16 years old in Mexico using questionnaires to evaluate the time spent watching television, reported that children spent an average of 4 hours/ day watching television and this time was related to increase obesity prevalence with each additional hour of watching associated with 12% greater risk of obesity (102). This observation was confirmed by large cohort study were included 5434 children used an accelerometer for seven days to examine the association between ST and obesity among 12-year-old children (68).

This is of importance and concern, since more time spent in SB has been shown to increase the risk of obesity-related health problems, including adverse metabolic

profiles as a consequence of the increased adiposity in children (67), and type II diabetes, CVD, certain cancers, and various metabolic risk factors in adult (103).

1.2.2.4. Sedentary Behaviour in Children with Chronic Disease

Children where health impairments are present (e.g. chronic cardiovascular or respiratory disease), grow up with a daily burden of disease, such as disease symptoms, or treatment effects that might encourage the adoption of a sedentary lifestyle (104). There are a growing number of studies exploring ST in children with chronic disease which have demonstrated that children with chronic disease spend most of their waking time sedentary, a behaviour that seems to be associated with increased risk of co-morbidities and reduced quality of life (105, 106).

1.2.2.5. Sedentary Behaviour Guidelines in Children

Currently there are no guidelines for total time spent in SB with those available only for SB based on screen time. Several bodies have recommended minimizing the screen time for 1-2 hours/day in children and adolescents and have recommended that those aged 0-2 years should not spend any time watching TV or electronic media to maintain healthy growth and wellbeing, as well as reducing the risk of development of chronic diseases (9, 96).

1.2.3. Sleep

1.2.3.1. Definition

Perhaps the most novel aspect of the integrated movement behaviours concept is the inclusion of sleep, usually regarded as a period of very reduced or no movement, as

part of the spectrum of movement behaviours. Sleep is a natural occurring state resulting from a complex amalgam of physiological and behavioural processes (107). It is a reversible, periodic and recurring state of perceptual disconnection from and unawareness of the environment (108). Sleep can be defined as a behavioural state controlled by the hypothalamus and brainstem where the response to outside stimulation is reduced, consciousness and muscular activity is temporarily suspended or diminished. Individuals vary greatly in their need for sleep, and the amount of sleep needed depends on many factors including age with duration of sleep shorter as age increases (109). Not surprisingly, infants require the greatest amount of sleep − about 16 hours per day − as hormones that promote growth are released during sleep. Children and adolescents need about 9 -11 hours on average per day (110). For most adults, 7 - 8 hours per day are required although some people such as pregnant women may need as many as 10 hours of sleep each day during the first 3 months of pregnancy (109, 111).

1.2.3.2. Sleep in Healthy Children

Sleep is critically important to children's health and wellbeing (112). Sleep (quantity as well as quality) are essential for physical growth, mental development and maintenance of emotional and mental wellbeing in children and adolescents (113). Thus, healthy sleep (meaning adequate sleep duration, at appropriate times, and of good quality - with no or limited disturbance/interruption by awake episodes) is particularly important during childhood, as inadequate sleep is associated with atypical physical and cognitive development (112, 114).

In recent years, the notion that children are sleeping less has become popular and there is evidence of a secular decline in sleep duration in children, the cause of which is not

fully understood (115). However, the literature has suggested a number of reasons including increased use of technology leading to later bed times “onset of sleep” with unchanged wake time “sleep offset” as they have to go to school in morning. As a consequence it is widely suggested that many children are getting less sleep than they should be (115-118).

Inadequate sleep during the childhood is associated with increased risk of a number of medical conditions that may contribute to the premature mortality rate in later adult life (119, 120). Unfavourable consequences include: obesity, diabetes, depression, suicidal ideation, and poor academic performance that may occur with either short or long sleep duration independent of other movement behaviours (115, 121-124).

1.2.3.3. Sleep in Children with Chronic Disease

Healthy sleep is an integral part of physical and mental health in children as noted above (112, 125) and influences risk of premature mortality in later adult life (119). Children with chronic disease are especially believed to be at increased risk for sleep problems in terms of sleep duration, quality and night time awakenings, and a number of epidemiological studies have found an increased rate of sleep problems in children with chronic diseases (126-129). In one Norway study, that included 496 children with different chronic diseases and used both parent and child reports to assess sleep problems, Hysing et al. found that the children and their parents reported more problems falling asleep and had more night-time awakenings compared to healthy children (130).

1.2.4. Integrated Movement Behaviours Guidelines

The 24-hour movement behaviours guidelines for children and young people have been developed from both Canadian and Australian 24-Hour movement guidelines in healthy preschool, children and adolescent (131-133). This new a paradigm that consider all movement behaviours occurring over 24 h period in combinations for optimal health (132). Twenty-four-hour movement behaviours guidelines are summarised in Table 1.1.

Table 1.1: Integrated movement behaviours guidelines for children and adolescents

Behaviours	<5 years	5 – 17 or 18 years
Sleep	Good-quality sleep including naps per night as14-17 h for age 0-3months, 12-16 h for age 4-11months, 11-14 h for age 1-2 years, 10-13 h for age 3-4 years.	Uninterrupted 9-11 h of sleep per night for age 5-13 years, 8-10 h of sleep per night for age 14-17 years, with consistent bed and wake-up times
Physical activity	For those< 1year: being physically active several times per day in variety ways. For those 1-4 years, accumulation of ≥ 180 minutes per day of a variety PA. For those 3-4 years, ≥ 60 minutes per day of an energetic play	An accumulation of ≥ 60 minutes per day of MVPA involving aerobic activity Vigorous PA and muscle and bone strengthening activities should be ≥ 3days per week
Light physical activity		Several hours of a variety of un/structured LPA
Sedentary behaviour	Not being restrained for more than 1 h at a time. No < 1 h per day of screen time For those 3-4 years; while no screen SB for 0-2 years	No < 2 h per day of recreational screen time. Limited sitting for extended periods
General recommendation	Replacing time restrained or screen time with additional energetic play, trading indoor time for outdoor time and preserving sufficient sleep	Preserving sufficient sleep, trading indoor time for outdoor time, and replacing SB and LPA with additional MVPA.

h - hour; LPA - light physical activity; MVPA - moderate to vigorous physical activity; SB - sedentary behaviour. Adapted from Canadian and Australian 24-hour movement behaviours guidelines for children and youth (131-133).

1.2.5. Measurements of Integrated Movement Behaviours

The 24-hour movement behaviours concept is new and guidelines based on it even newer. Few studies have addressed basic issues such as measurement of the 24-hour movement behaviours in healthy children. In the available studies the PA, SB and sleep were measured either subjectively, or objectively, or using a combination of subjectively and objectively. The previous literature reported pros and cons of the several methods that available to assess PA, SB and sleep in free-living conditions, summarised in Table 1.2. The accurate combined measurement of these behaviours is a key factor in improving our understanding how these behaviours interact together and impact on our health, for example. Low PA levels have been linked to poor sleep quality (134) while sleep deprivation is linked to decline in daily PA and to increases in obesity in children. Thus, accurate and reliable measurement of the 24-hour movement behaviours may be an important step in guiding activity recommendations throughout a day, but there is difficulty inherent in measuring PA, SB and sleep simultaneously. Although, the 24-hour movement behaviours is a new concept and the researches still going on and currently the most of the studies have used self-report data to investigate the levels of activity, SB and sleep which are not reliable in children (135) and do not allow for distinguishing between SB/sleep, LPA, and MVPA.

Accelerometry is now one of the most widely, accurately and valid tools for measuring PA levels, SB and sleep objectively. There are a variety of accelerometer types and models and with different measurement protocols.

Traditionally, accelerometers have been worn on the hip or low back as this location has been considered to provide the best estimates of PA intensity and energy expenditure (136). Accelerometers worn on the wrist or ankle have been shown to

promote good device compliance over longer wear times and have been used to assess sleep among children (137-139). Accelerometer worn on the thigh provided high accuracy for classification of PA intensity (LPA and MVPA) and sitting/lying behaviours and breaks in SB with other advantages such as improved comfort and better compliance over longer periods of measurement(140). However, until now, there is no single device could be captures all behaviours data across the entire 24- hour and the accurate assessment may require a subject to wear two accelerometers or more that would likely be an expensive and result in lower compliance, particularly when a minimum of four consecutive days of accelerometer data are recommended to obtain valid and reliable measurements.

For several reasons, the ActivPAL™ device was chosen as the assessment method in the present studies. These includes that while most accelerometers are usually worn around the waist, hip or lower back with an elastic belt and adjustable buckle, while The ActivPAL™ is a thigh-worn accelerometer, which, when compared with wrist and waist-worn monitors is more convenient to keep in place for longer periods. This is an important benefit in young children including those with chronic diseases when prolonged periods of wear are planned. Further, it has proved to be the best at measuring and identifying times spent in postures such as sitting/lying, standing and walking (141). Also, it is a very useful characteristic for determining time spent in SB, walking and total number of steps. The strong evidence shows that the ActivPAL™ offers acceptable validity, utility and reliability tool in measuring posture and activity during the daily activities of children, further details provided in Chapter II, section 2.2.6 pages 84-86.

Table 1.2: Measurements of integrated movement behaviours

Behaviours	Methods	Type	Advantage	Disadvantage
Physical activity and sedentary behaviours	Subjective methods	Self-report; interviews, proxy-report (informed by another person usually parent for children under 10 years old); diaries and questionnaires	Non-invasive; inexpensive; not require a well- trained researcher to apply; suitable for large studies	Recall bias; low reliability and validity; potential reactivity.
	Criterion methods	Direct and indirect calorimeter (27, 142)	Accurate method for measuring EE and assess PA	Relatively expensive; not suitable for children
		Doubly labelled water	Gold standard method for evaluating TEE in free living conditions; safe, easily applied and is not affected by patterns PA (27, 143).	Relatively expensive; not suitable for children and large studies; difficult to obtaining the isotope; cannot provided information about patterns PA (27, 143).
		Direct observation	Non-invasive; reliable and valid; eliminated self-report bias; gold standard for SB and posture changes.	Potential reactivity; high cost of time and energy; not suitable for large studies lack objective measures of energy expenditure (144)
	Objective methods	Heart rate monitor	Non-invasive; measures of full day over multiple days; relatively inexpensive (145).	Heart rate changes maybe unrelated to PA; not suitable for water activity; requires a known relationship between heart rate and PA workload; provided only total activity per time period; affected by environmental and emotional factors (145).
		Pedometers (146)	Non-invasive; relatively inexpensive; visibility of measurements to user varies between models; provided total activity and number of steps over period of time.	Measurements accuracy various with cost; not suitable for water activity; technical limitation to detection and measurement of certain types of activity depending on model used and it placements on body
		Accelerometer including Actigraph, actical	Non-invasive; activity intensity and duration; measures of full day over	Technical limitation to detection and measurement of certain types of activity

		and activPAL™	multiple days; shock and water resistant, with some models being suitable for water activity; suitable for adult and children; measurements are not visible to user; recording of activity cannot be altered by user (146).	depending on model used and it placements on body
Sleeping behaviour assessment	Subjective methods	Sleep habits questionnaires and structured sleep diaries (147, 148)	Non-invasive; inexpensive; ease to use, not require a well- trained researcher to apply; suitable for large studies	Low degree of accuracy to recall information and the variability inherent subjective reporting
	Criterion methods	Polysomnography (149)	Gold standard procedure to monitoring the sleep stages	Relatively expensive; complicated procedure that needs well-trained personnel
	Objective methods	Accelerometer (138, 139)	Gold standard measure of in community research to measure sleep time and pattern; gathering PA, SB and sleep data simultaneously with/out an accompanying sleep diary; suitable for large studies	Technical limitation depending on model used and its placements on body

EE- energy expenditure; SB- sedentary behaviours; PA- physical activity; TEE- total energy expenditure.

1.2.6. Factors Influencing Integrated Movement Behaviours

1.2.6.1. Age

Age is the one of the main factors believed to determine levels of integrated movement behaviours in children and adolescents. There is a decline in PA level with age, confirmed by cross-sectional studies and longitudinal studies (150-155). For example, a cross-sectional study in Canada that included (n=401) children aged from (8-13 years of age) and measured daily MVPA and VPA by actiGraph accelerometer over seven consecutive days found that levels of PA decreased with increasing chronological age (151). A recent longitudinal cohort study in United Kingdom (UK) (Gateshead Millennium Study) with 8 years of follow-up included 545 children and measured habitual MVPA objectively by ActiGraph GT1M accelerometer first at 7 years of age, and then at 9, 12 years of age. This study reported there was a decline in levels of PA across the eight years, with evidence that the total volume of PA had started declining by age 7 years (156).

Several studies have confirmed that time spent in sitting and screen based activity was higher in adolescents compared to young children (157). Increasing age was associated with more prolonged sitting bouts with fewer breaks in sitting. Strong recent evidence comes from a longitudinal analysis of the Gateshead Millennium Study cohort in the UK in 2016 with eight years follow up as noted above - in this study ST increased with chronological age from 7 to 15 years of age and this increase in ST displaced time spent in PA; median ST increased from 51% of waking hours at 7 years to 74% at 15 years of age, with sedentary fragmentation decreasing from 7 years to 15 years as median number of breaks in sitting time /hour decreased from 8.6 to 4.1 (158).

Duration of sleep is also age-dependent as noted above: preschool-age children had longer sleep durations than school-age children (earlier bed time and later wake-up time), while children at school age and older had less sleep duration as they had later sleep onset time with unchanged wake-up time. Waking time appears more stable perhaps because of the need to wake-up early to go to school (118).

1.2.6.2. **Sex**

Sex is a second important determinant of levels of integrated movement behaviours in children and adolescents. Boys are more active compared to girls of the same age, confirmed by both cross-sectional studies and longitudinal studies (151-156). For instance, evidence comes from the Lifestyle of our Kids (LOOK) longitudinal study, which included 276 boys and 279 girls from 29 schools aged 8-12 years of age. PA was measured using pedometers (Walk 4 Life, Plainfield, IL, USA) over seven consecutive days and the results revealed that, level of PA was lower in girls compared to boys and girls were 19% less active than boys (159).

Similarly, on average girls accumulate higher ST than boys (67, 101, 157, 160). Interestingly, an observational cross-sectional survey within the framework of the ENERGY-project (EuropeaN Energy balance Research to prevent excessive weight Gain among Youth) that included 686 children aged 10-12 year of age, 53% girls, across 5 European countries using accelerometers to determine the amount of ST again found that ST was higher in girls and girls spent significantly more time sedentary (500 minutes/day) than boys (474 minutes/day) (161).

There is only limited evidence that sleep duration and timing are influenced by gender, at present. In the French Mother–Child Cohort (EDEN Study) cross-sectional study factors associated with short sleep duration 1028 child (boys (n=546) and girls (n=482)) aged 3 years of age, were investigated by using parent report. This study found that, boys had significantly shorter sleep duration compared to girls as boys had later bedtimes and earlier wake-up times than girls. However, the mean total sleep duration, if the time naps were included, did not differ significantly by gender (162). Sleep duration guidelines are not gender-specific at present (131-133).

1.2.6.3. **Season**

Lastly, some studies confirm that there is seasonal effect on at least some of the 24 hour movement behaviours in at least some parts of the world. Seasons are defined as the natural periods in which the year is divided, which vary by weather conditions, daylight hours and temperature (163). A systematic review included 37 primary studies with a total of 291,883 children and adolescents (140,482 male and 152,085 female) from eight different countries to explore the effect of season, and consequently weather, on levels of PA, and they revealed that, level of PA varies with season (163). Further, boys had different PA patterns as they tended to be more sedentary and less active during the winter, while girls had more consistent levels of PA and ST across the seasons. A pilot study in 24 participants aged 10-13 years characterised seasonal variation in MVPA and ST. They found that, participants were more active in the summer and activity levels were higher after school than in school and ST was higher in winter than in the summer time (164).

At present, there is limited evidence that sleep duration and timing are influenced by seasons in children and youth. A recent cross-sectional analysis of 669 participants aged at age's 12–14years, used wrist accelerometers to assess the sleep timing, duration and quality with season and daily weather conditions. They found that season was associated with large changes in sleep timing but not with sleep duration. Sleep onset time was 41 minutes later in summer and 28 minutes earlier in spring and autumn compared to winter and that indicating seasonal variation in the timing of the sleep period (165).

In summary, these three factors – age, sex and season - are amongst the most important confounding influences in studies 24-hour movement behaviours in children. Thus, investigators need to consider these three factors (age, gender, time of year) when designing studies to consider variation in or differences in 24-hour movement behaviours between groups.

1.3. Integrated Movement Behaviours in Children with Chronic Disease

Although, there are many studies of levels of PA, ST and sleep in healthy children and adolescents, there are surprisingly few such studies in those with chronic disease. In fact, numerous previous studies and national PA surveillance programmes have actually excluded children and adolescents with chronic disease. Also, the 24-hour movement behaviours concept is so new that it has not yet been applied to studying children with chronic disease.

Chronic illness in children and adolescents can be defined as any physical, emotional, or mental health problem that lasts at least three months, and affects a child's physical appearance and/ or growth and daily normal activities and results in frequent hospitalisations with regular therapy and sometimes unpleasant procedures, with home and medical care (166). Chronic illness frequently results in impairment of a child's psychosocial development and impairment of their educational progress through possible loss of schooling (166). Indeed, the most important features that characterise chronic medical conditions are their prolonged duration, their lack of spontaneous resolution, and the fact that are rarely cured completely. Chronic illness in children is also disrupting to their families and that might lead to negative impact on daily functioning and quality of life for multiple family members (167).

The prevalence of chronic diseases in children and adolescent is often hard to ascertain due to the varying conceptual definitions and differing approaches to measurement. But epidemiologic studies suggest that the prevalence of chronic disease in children and adolescents has actually been increasing and is likely to continue to rise (166, 168), accompanied with rising obesity rates (169). Increasing childhood obesity could be driving the increase in a number of other chronic conditions (166). Further, based on evidence from the United States. National Survey of Children's Health, in children and adolescents aged from 0-17 years 13.6% were living with one chronic disease, around 8.7% had two or more chronic conditions excluding obesity. In 65.6% of them their health conditions affected their daily activities at least some of the time. In the UK about one in seven (15%) children aged 11-15 report having been diagnosed with a chronic disease (170).

Common chronic childhood diseases

Chronic condition is an "umbrella" term. The most common childhood chronic illness are asthma, cystic fibrosis (CF), diabetes either type 1 or type 2 (T1DM and T2DM), obesity, arthritis, malnutrition, congenital heart disease (CHD), developmental disabilities, including attention-deficit/ hyper-activity disorder and the autism spectrum disorders, cerebral palsy and mental illnesses (171).

The present thesis focuses on four common chronic childhood diseases: T1DM, juvenile idiopathic arthritis (JIA), CHD and CF. These conditions were chosen due to their prevalence and their potential to impact on 24-hour movement behaviours (PA, SB and sleep), as described below.

1.3.1. Type 1 Diabetes Mellitus

T1DM is a serious lifelong condition and is defined as an autoimmune disease characterised by inability of the beta cells in the pancreas to produce endogenous insulin needed to regulate blood glucose. The lack of insulin leads to high levels of blood glucose (hyperglycaemia) and the need for insulin therapy to control the level of blood glucose (172).

1.3.1.1. Incidence and Prevalence

The incidence of T1DM in children under the age of 15 years is increasing in many countries, and it is now usually counted as the third most common chronic disease in the paediatric population after asthma and cerebral palsy (173). In the UK, prevalence of T1DM in children aged < 19 years of age is 1 in 430-530 children, and the disease incidence about 24 in 100,000 in children aged <14 years of age each year (174).

1.3.1.2. Diagnostic Criteria and Glycemic Control

T1DM is characterised by a fasting plasma glucose concentration of ≥7.0 mmol/l (126 mg/dl) in repeated measurements, or a 2-h plasma glucose concentration of ≥11.1 mmol/l (200mg/dl). Additionally, a random plasma glucose value of ≥11.1 mmol/l (≥200mg/dl) in conjunction with symptoms of diabetes (thirst, polyuria, weight loss) also leads to a diagnosis of diabetes (172). In children with T1DM long-term glycaemic control is clinically determined by level of the HbA1c. According to the UK National Institute for Health and Care Excellence (NICE guideline) the optimal blood glucose control that children should be aiming to achieve will result in an HbA1c ≤ 48 mmol/mol (HbA1c referred to glycated haemoglobin (A1c)), with higher HbA1c levels indicating poorer diabetes control (175).

1.3.1.3. Treatment of Type 1 Diabetes Mellitus in Children

Treatment optimisation requires a lifelong commitment to achieving optimal blood glucose control. Insulin is delivered subcutaneously, either by injected boluses (multiple daily injection therapy) or a continuous subcutaneous infusion administered by an insulin pump attached to the skin by cannula (insulin pump therapy) (175).

1.3.1.4. Type 1 Diabetes Mellitus Complications

Children with T1DM are at high risk of diabetic complications. The complications are divided into micro-vascular complications (nephropathy, retinopathy, and neuropathy) and macro-vascular complications such as coronary artery disease, peripheral arterial disease, and stroke. (176) Recent studies show that signs of atherosclerotic disease, diabetic retinopathy, and diabetic nephropathy are already detectable in young children with T1DM (177-179). T1DM complications are related to blood glucose

levels, and are more pronounced in children with poor glycemic control HbA1c > 48 mmol/mol. In the UK 2013-2014 evidence from England and Wales reported that, less than 19% of children with T1DM had achieved the NICE guideline target for blood glucose control when it was set at 58 mmol/mol (175). Development of diabetes complications could be prevented only by good metabolic control of the disease through maintaining target blood glucose levels (175). Achieving control is based on treatment with insulin, compliance with the dietary restrictions and rules and proper level of PA (discussed below) combined with good education (172, 175).

1.3.1.5. Possible Disease Effects on Integrated Movement Behaviours in Children with Type 1 Diabetes Mellitus

Physical activity is routinely recommended in paediatric T1DM management (180, 181). PA recommendations for those with T1DM are to achieve a minimum of 60 minutes of MVPA per day (175, 180), the same as for healthy children. Achieving this could have significant positive effects on short- and long-term health outcomes (182), such as improving insulin sensitivity and glycaemic control, limiting excessive weight gain, increasing sense of wellbeing, improving known risk factors for atherosclerosis and helping in the prevention of later cardiovascular disease (181, 183).

Current research indicates that most children with T1DM lead sedentary lifestyles, and high amounts of SB have been linked with poor glycemic control (184). Sedentary lifestyles in those with T1DM have also been associated with a rapid reduction in insulin sensitivity and raised blood glucose level particularly postprandial glucose, leading to increased risk of obesity, hypertension and cardiovascular disease (106), and the consequent development of cardiovascular disease already has been observed

in diabetic children with abnormal lipid concentrations level (185). Cardiovascular diseases are the main cause of increased morbidity and mortality rates in adults with T1DM (186, 187). Indeed, recent evidence suggests that children with T1DM had remarkably high levels of SB and focusing just on MVPA may not be enough to reduce risk of diabetic complications. Hence focusing on simultaneously decreasing levels of SB is warranted to decrease cardiovascular risks (188, 189).

Sleep has physiological and behavioural impacts on health outcomes in children with T1DM (190). It is therefore increasingly identified as an important variable to consider as part of management in children with T1DM (190). Recent evidence shows that children with T1DM had short sleep duration with more disturbances that were due to disease management issues such as night-time blood glucose monitoring (127), as most of those with diabetes might wake up several times during the night to check or adjust level of blood glucose to avoid the nocturnal hypoglycaemic attack (190). Inadequate sleep whether in terms of sleep quality and or sleep duration had negative impact on children with T1DM (191, 192), either directly through poor control of blood glucose and reduced insulin sensitivity, or indirectly through reduced self-esteem and decreased academic performance. Short sleep duration in children with T1DM has been linked with increased risk of cardiovascular disease through lack of the normal decline in blood pressure during sleep (193, 194).

It is believed that many diabetic children do not follow the PA recommendation, as they or their parents may fear hypoglycaemia from PA in spontaneous or organised exercise, thus leading to spent greater amounts of their daily time in SB. Fear of hypoglycaemia may also impact their sleep quality and duration (106, 190, 195, 196). Hypoglycaemia could be due to administration of an excessive dose of insulin before

exercise, increased of glucose uptake, or may due to increased insulin sensitivity (197, 198). Despite risk of hypoglycaemia, children with T1DM should be encouraged to participate in PA and reduce the time spent in SB, by taking into account duration and intensity level of PA and adjusting the insulin dose, level of blood glucose and need for carbohydrate replacement (175).

1.3.2. Juvenile Idiopathic Arthritis

Juvenile idiopathic arthritis (JIA) previously also called juvenile chronic arthritis and juvenile rheumatoid arthritis has been regarded as an autoimmune disease and is the most common arthritic disease of childhood. The underlying cause and processes are poorly understood (199). JIA is not a single disease; rather it is a heterogeneous group of diseases and based on the current concepts, system-onset JIA is an auto-inflammatory than autoimmune disease (200). According to the International League of Associations for Rheumatology (ILAR) (200), JIA is defined as joint pain, swelling, tenderness and morning stiffness associated with a limitation in the range of joint movement that begins before the sixteenth birthday and persists for at least six weeks or more, after other reasons for arthritis are excluded (201). In addition to arthritis, children with JIA frequently have extra-articular manifestation such as uveitis (Uveitis is the inflammation of the uvea (comprising the iris, choroid and retina) and it is most frequent extra-articular manifestation.

1.3.2.1. Incidence and Prevalence

The incidence and prevalence of JIA are exactly unknown worldwide (202), and several epidemiological studies have reported a wide variance in different regions of the world. In the United States prevalence of JIA in children aged less than sixteen is

about 6 in 10,000 children (202), and the annual incidence is about 1 per 10,000 children (203, 204). In Europe annual incidence is about 16–150 per 100.000 children. In the UK an estimated 12, 000 children have JIA (205, 206).

1.3.2.2. Diagnostic Criteria and Classification

There are no specific diagnostic tests for JIA. Thus, children aged less than 16 years old with chronic arthritis lasting for more than six weeks in the absence of any known cause, may be diagnosed as having JIA. Further, JIA can be classified into eight different categories based on the ILAR (201), as follow: systemic onset JIA, oligoarthritis persistent, oligoarthritis extended, polyarthritis (RF-negative), polyarthritis (RF-positive), psoriatic arthritis, enthesitis-related arthritis and an undifferentiated arthritis, diagnostic, definition and excluded criteria are provided in Table 1.3.

Table 1.3: International League of Associations for Rheumatology classification of JIA

Category	Definition	Exclusions
Systemic arthritis	Arthritis in one or more joints with fever for two weeks (at least 3 days with a daily pattern) plus one or more systemic manifestations: 1. Erythematous rash. 2. Generalized lymphadenopathy. 3. Hepatomegaly and/or splenomegaly. 4. 4. Pericarditis and/or pleuritis and/or peritonitis.	A. Psoriasis or history of psoriasis in a first-degree relative B. Arthritis in a HLA-B27 positive male beginning at 6 years of age or older C. History of ankylosing spondylitis, enthesitis-related arthritis, sacroilitis with inflammatory bowel disease, Reiter's syndrome D. IgM RF on two or more occasions, 3 months apart
Oligoarthritis Persistent	Arthritis affecting 1–4 joints throughout the disease course	A–D above, plus E. The presence of systemic

		JIA
Oligoarthritis Extended	Arthritis affecting 1–4 joints during the first 6 months, than affecting more than four joints	A, B, C, D and E
Polyarthritis (RF-negative)	Arthritis affecting 5 or more joints during the first 6 months following the onset of the disease RF negative	A, B, C, D and E
Polyarthritis (RF-positive)	Arthritis affecting five or more joints during the first six months of the disease rheumatoid factor positive two or more times at least three months apart	A, B, C, D and E
Psoriatic arthritis	Arthritis and psoriasis, or arthritis and at least 2 of the following: 1. Dactylitis* 2. Nail pitting** and onycholysis 3. Psoriasis in a first-degree relative	B, C, D and E
Enthesitis-related arthritis	Arthritis and Enthesitis+, or arthritis or enthesitis with at least 2 of the following: 1. The presence of or a history of sacroiliac joint tenderness and/or inflammatory lumbosacral pain++ 2. The presence of HLA-B27 antigen 3. Onset of arthritis in a male over 6 years of age 4. Acute anterior uveitis 5. History of spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome	A, D and E
Undifferentiated arthritis	Arthritis that fulfils criteria in no category or in 2 or more of the above categories.	

RF- rheumatoid factor, the table Adapted from (Petty *et al* (201).
***Dactylitis is swelling of one or more digits, usually in an asymmetrical distribution, which extends beyond the joint margin.**
****A minimum of 2 pits on any one or more nails at any time.**
+Enthesitis is defined as tenderness at the insertion of a tendon, ligament, joint capsule, or fascia to bone.
++Inflammatory lumbosacral pain refers to lumbosacral pain at rest with morning stiffness that improves on movement.

1.3.2.3. Evaluation of Disease Activity

In children with JIA, persistent active disease could be the primary cause of joint damage and physical disability; thus evaluation of disease activity is a critical component of the clinical assessment of those children (207). In clinical assessment the JIA disease activity is evaluated by using a number of variables such as: the number of swollen joints, number of tender joints, number of painful joints, number of joints with restricted movement, inflammatory markers (erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) values), physicians global assessment of disease activity (range from 0= best to 10=worst), and the parents/patients global assessment of disease activity (range from 0= best to 10=worst) (208). Recently, a composite tool to assess the disease activity in JIA has been developed, named the Juvenile Arthritis Disease Activity Score (JADAS). JADAS has been developed and validated in children (207) and consists of 4 components: number of joints with active disease assessed in 10, 27 or 71 joints; an inflammatory marker ESR and/or CRP; physician global assessment of disease activity; parent/patient global assessment of well-being (207). Using the JADAS tool gives the capacity to assess the disease activity at a single visit as well as to compare the results between patients or groups, and to assess changes over time (209).

1.3.2.4. Inactive Disease and Remission

Recently, the American College of Rheumatology published provisional criteria for inactive disease and remission in children with JIA, in order to standardise the definition of inactive disease and remission states in those children (210). ACR criteria had summarised in Table 1.4.

Table 1.4: American College of Rheumatology provisional criteria for inactive disease and remission of juvenile idiopathic arthritis

Category	Criteria
Inactive disease*	• No joints with active arthritis. • No fever, rash, serositis, splenomegaly, or generalized lymphadenopathy attributable to JIA. • No active uveitis as defined by the SUN Working Group** • ESR or CRP level within normal limits or, if elevated, not attributable to JIA • Physician's global assessment of disease activity score = best
Clinical remission on treatment	The criteria for inactive disease must be met for a minimum of 6 continuous months while the patient is on medication in order for the patient to be considered to be in a state of clinical remission on treatment
Clinical remission off treatment	The criteria for inactive disease must be met for a minimum of 12 continuous months while off all anti-arthritis and anti-uveitis medications in order for the patient to be considered to be in a state of clinical remission off treatment

ESR - erythrocyte sedimentation rate; CRP - C-reactive protein. This table Adapted from Wallace et al (210, 211)
***All criteria must be met.**
****The Standardization of Uveitis Nomenclature (SUN) Working Group defines inactive anterior uveitis as "grade zero cells," indicating <1 cell in field sizes of 1 mm by a 1-mm slit beam.**

1.3.2.5. Treatment Options in Children with Juvenile Idiopathic Arthritis

There is no cure for JIA at the moment. However, there are a variety of treatments available that promote remission and make the disease inactive (212, 213). Around 10% to 20% of children with JIA are at risk of developing anterior uveitis, a condition that potentially can lead to blindness later, so early treatment with aggressive use of therapies in treatment children with JIA is recommended (212, 214).

1.3.2.6. Possible Disease Effects on Integrated Movement Behaviours in Children with Juvenile Idiopathic Arthritis

JIA may have considerable impact on growth and development, physical and psychosocial functioning with a wide range of potential consequences. It has been suggested that PA should be included in any JIA treatment protocol, for a number of

reasons. Activity may improve disease signs and symptoms; PA could lead to reduced pain and medication use (215, 216); PA might have a role in reducing inflammation (217). Indeed, some studies have shown an improvement of disease signs and symptoms or cardiorespiratory fitness (CRF) after exercise training and this has led to the inclusion of physical conditioning of various kinds in many JIA treatment protocols. In addition to the physical benefits of PA in children with JIA, PA may also positively impact on the psychological health of children with physical impairments by allowing them to feel that they can participate in the same activities as their peers (218, 219).

Therefore, those with JIA should be encouraged to achieve at least 60 minutes per day of MVPA (219-221). Despite such guidance, children with JIA had less active and more sedentary lifestyles (222), associated with inadequate sleep (short sleep duration and more disrupted sleep) compared to their healthy children in a few studies (200, 223, 224). Although results varied, most of the studies suggested that potential factors lead to low level of PA, high amount of SB, with short sleep duration and more disturbance in children with JIA, which might modulate the disease-related factors (such as disease duration, number of painful and swollen joints), severity and frequency of pain, medications, and poor physical fitness (223, 225-227). Those children with JIA were at high risk of decrease of bone density (Osteopenia) due to high disease severity and side effect of glucocorticoids treatment that lead to decreased bone strength and increase risk of fracture (228).

1.3.3. Congenital Heart Disease

Congenital heart disease (CHD) is one of the major global health problems and is one of the most common causes of morbidity and mortality in childhood (229, 230). CHD

is also named congenital heart anomaly, as the problem is present at birth and affects the heart structure and function. There are many types of CHD ranging from simple to complex and critical, depending on the affected part in the heart (231).

1.3.3.1. Incidence and Prevalence

CHD represents about 28% of major congenital malformations (229). CHD at birth had affected approximately 1- 4 in 1,000 worldwide, but this figure has been rising steadily to 12 - 14 in 1,000 live births worldwide. In UK, up to 8 in every 1,000 new-borns, and more than 35,000 child in the United States are born with CHD (232, 233). Indeed, according to very recent evidence from British Heart Foundation report from the UK, at least 1 in 180 births had diagnosed with CHD - that is an average of 12 babies had diagnosed each day with CHD with more diagnoses later in life; eventually, as many as 1-2 per cent of the population may be affected.

1.3.3.2. Pathophysiological Classification of Congenital Heart Disease

There are several classifications for CHD (234). However, the pathophysiological classification is more practical, because it is based on the clinical consequences of structural defects impairing the physiology of blood circulation and gives clearer meaning for clinical and laboratory findings in those patients (234-237). In this classification, patients with CHD have been grouped into:

- **CHD with increased pulmonary blood flow** arising from septal defects without pulmonary obstruction and left-to-right shunts. These include venous pole, atrial septum defect, atrio-ventriculay septum (connection), ventricular septum defect, and patent ductus arteriosus.

- **CHD with decreased pulmonary blood flow** arising from septal defects with pulmonary obstruction and left-to-right shunt. These include pulmonary valve stenosis with atrial septum defect, tetralogy of fallot, tricuspid atresia, Ebstein anomaly of the tricuspid valve and single (double inlet) ventricle with pulmonary stenosis.
- **CHD with obstruction to blood progression** and no septal defects and no shunt either right-to-left shunt or left-to-right shunt. These include pulmonary stenosis, aortic stenosis and coarctation of the aorta.
- **CHD incompatible with postnatal blood circulation;** these are the most severe forms of CHD and include ductus-dependent CHD (pulmonary atresia, aortic and mitral atresia, and interrupted or atretic aortic arch), parallel systemic and pulmonary circulations (transposition of the great arteries) and anomalous connection/obstruction of the pulmonary veins
- **CHD silent until adult age.** There are some CHD conditions that are asymptomatic before adult age or are discovered incidentally. These include bicuspid aortic valve, some congenital anomalies of coronary arteries, Wolff–Parkinson–White syndrome, and congenitally corrected transposition of the great arteries.

1.3.3.3. Categories of Congenital Heart Disease Severity

CHD is a significant cause of morbidity and mortality in children. It is therefore useful to grade CHD according to the severity of cardiac lesion. Based on a consensus guideline (238), CHD is classified into three categories depending on severity of cardiac lesions and impact of surgery: severe CHD, moderate CHD and mild CHD, as summarised in Table 1.5.

Table 1.5: Consensus guideline of classification of congenital heart disease severity*

Category	Definition	Congenital heart disease
Severe CHD group	These patients at high-risk, should be seen regularly at CHD centres.	Cyanotic congenital heart (all forms); double-outlet ventricle; Eisenmenger syndrome; mitral atresia; single ventricle; pulmonary atresia; pulmonary vascular obstructive disease; transposition of the great arteries; tricuspid atresia; truncus arteriosus; other abnormalities of atrioventricular or ventriculoarterial connection (i.e., criss-cross heart, isomerism, heterotaxy syndromes, ventricular inversion)
Moderate CHD group	These patients at Moderate –risk, should be seen periodically at regional congenital heart disease centres.	Aorto–left ventricular fistulas; APVD; AVD; coarctation of the aorta; Ebstein's anomaly; infundibular right ventricular outflow obstruction of significance; ostium primum ASD; PDA (not closed); pulmonary valve regurgitation (moderate to severe); pulmonary valve stenosis (moderate to severe); sinus of valsalva fistula/aneurysm; sinus venosus ASD; TOF; VSD; absent valve or valves; AR; COA; mitral disease; right ventricular outflow tract obstruction.
Mild CHD group	These patients at lowest-risk, usually be cared for in the general medical community.	Native disease; isolated congenital aortic valve disease; isolated congenital mitral valve disease (eg, except parachute valve, cleft leaflet); small ASD; isolated small VSD; mild pulmonary stenosis; small PDA; repaired conditions; previously ligated or occluded ductus arteriosus; repaired secundum or sinus venosus ASD without residua and repaired VSD without residua

APVD - anomalous pulmonary venous drainage; ASD- atrial septal defect; AR - aortic regurgitation; AVD- atrioventricular septal defects; CHD- congenital heart disease COA - coarctation of the aorta; PDA- patent ductus arteriosus; TOF- tetralogy of fallot; VSD- ventricular septal defect.
***Congenital heart disease severity was categorised in accordance with consensus guidelines and this table adapted from Warnes *et al* (238).**

1.3.3.4. Possible Disease Effects of Integrated Movement Behaviours in Children with Congenital Heart Disease

The life expectancy in children with CHD has improved dramatically in the last decade because of advances in preoperative care, surgical procedures and postoperative management. However, even after the cardiac repair those with CHD remain at high-risk of cardiovascular complications (176). Children with CHD may have other risk factors such as – possibly-inactive lifestyles, poor diet, stress, sleep disturbances and sedentary lifestyle that may contribute to progression of increase the risk of cardiovascular disease (239). Indeed, consistent evidence demonstrates the beneficial

impact of PA on the cardiovascular system in both healthy children as well as children living with CHD (240). Thus active lifestyles are believed to be important to achieve optimal long-term outcomes in CHD; to reduce or prevent co-morbidities; and to improve the physical (cardiovascular health) and psychosocial (self-esteem, anxiety, and depression) health in children with CHD (87). Children with CHD have been identified as spending more time in SB or inactivity than their healthy peers (241). Sedentary lifestyles in children with CHD have been recognised to increase risk of co-morbidities such as obesity, diabetes and atherosclerosis and coronary artery disease (242) with increased risk of premature mortality in later adult life. It also has been associated with poor motor skill development and decreased activity self-efficacy (243, 244). Sleep too has an important role to maintain the normal physical and mental growth in those with CHD similar as in healthy children, and inadequate sleep linked to co-morbidity as mentions earlier (121-123). However there is a suggestion those with CHD had shorter low quality sleep as they have difficulty in initiating and maintaining sleep with early waking, as well as frequent sleep disturbance due to or from the symptoms that associated with their cardiac problems such as abnormal heart rhythms and sleep apnoea (a series of breathing pauses during sleep that stress the cardiovascular system (245, 246)).

It is generally thought that children with CHD may be hesitant to participate in PA for a number of reasons that include reduced cardiac output, impaired myocardial contractility, and disrupted blood flow due to endothelial dysfunction as well as use of antithrombotic medication and history of arrhythmia (247); non-cardiac physical reasons including neurologic and or orthopaedic problems, which may prevent participation in PA; or psychosocial reasons including reduced self-efficacy, health-related quality of life, and increased parental overprotection (248, 249). In addition,

lack of understanding of their situation by their teachers at school was identified as limiting PA in children with CHD (244), and other environmental factors, such as seasonality that also has been observed affect PA level in children with CHD (247). Despite these problems, most children with CHD are recommended to participate in PA and accumulated at least 60 minutes of daily MVPA (248). It is believed that low PA among the CHD population is more harmful than adequate PA (87, 240).

1.3.4. Cystic Fibrosis

Cystic fibrosis (CF) is a hereditary autosomal recessive disorder affecting the exocrine glands (mucous and pancreatic glands) in the body. It is a progressive condition and the most common deadly genetic disease affecting Caucasians (250, 251), although it also occurs in other races. Cystic fibrosis is a disease that involves several organs in body by affecting the transport of sodium across cell membranes. This causes the production of abnormally thick mucus (252), leading to the blockage of the pancreatic ducts, intestines, and bronchi. In the chest this often results in frequent respiratory infection (251, 253).

1.3.4.1. Incidence and Prevalence

CF is the most common life-threating inherited conditions. It affects the white population more than the black population. CF incidence varies depending on the method of diagnosis (screening the new-born, from death certificates, or reports of new case diagnosis) and origin of sample population raging from 1 in 2000 to 1 in 3000 live births in white population (254). According to the CF Foundation Patient Registry in United State the incidence of CF was approximately 1 in 3,200 white and 1 in 15,000 black live birth (255). It is estimated that > 30,000 people are living with

cystic fibrosis (> 70,000 worldwide); around 1,000 new cases of CF are diagnosed each year with > 75% of these people with CF are diagnosed by second birthday. In the UK CF occurs in around one in 2,500 live births and around 10,000 people in the UK have CF (256).

1.3.4.2. Diagnostic Criteria

The diagnosis of CF is mainly made on the basis of clinical signs and symptoms and a sweat test (252) and can now often be confirmed with genetic analysis. Rosenstein et al, reported that diagnosis of CF requires one criterion from each of the following two groups (257, 258):

Group one:

- Two occasions of sweat chloride concentration of >60 mmol/L.
- Two genetic mutations causing CF.
- Disturbed chloride transport measured as an epithelial potential difference.

Group two:

- Family history of CF.
- Positive new-born screening.
- Clinical symptoms; recurrent chest infection, weight loss, diarrheal, constipation, steatorrhoea, coughing, short of breathing and pulmonary exacerbations and a bowel obstruction in newborn (meconium ileus).

In UK, children with CF are usually diagnosed shortly after birth during the newborn screen blood test with the diagnosis then confirmed by sweat and genetic tests (256).

1.3.4.3. Evaluation of Disease Activity

Cystic fibrosis is a complex disease and the severity of disease differs between patients. Contributing factors to disease variation include: age of diagnosis, an individual's health, nutritional status and the course of the disease and treatment have an important role in disease outcomes (259, 260). Thus, severity of disease provides a guide for the physician to adapt therapies. The Shwachman-Kulczycki score was the first score to assess the severity of CF (261). CF severity tools scores are mainly focused on 4 groups of variables: physiology, infection, inflammation, and radiology (262). Forced expiratory volume in 1 second (FEV1) is the typical measure of lung function and a key predictor of life expectancy in people with CF (263).

1.3.4.4. Treatments Options for Cystic Fibrosis

There is currently no cure for children with CF, and they may need to take a range of different medicine to help control the symptoms and prevent or reduce complications (259). Specific treatment plans for each child with CF should be determined by close work between family and medical professionals based on several factors such as: child age, health, medical history, extent of the disease and child's tolerance for specific medications, procedures, or therapies (260). Treatment options may include: **Chest physical therapies** to help loosen and clear lung secretions (264). Medical treatment such as **antibiotics** - the main treatment of the lung infections; **mucus thinning medicines** like dornase alfa that make the mucus easier to cough up (265, 266); **bronchodilators and anti-inflammatories treatment** help to widen the airways, decrease the inflammation, reduce the mucus section in lung and make breathing easier; **management of digestive problems** that include: appropriate diet, digestive enzymes, minerals and vitamins supplements (260). Also, **Exercise** can help loosen

mucus, stimulate coughing, and improve overall physical condition. Finally, those with CF may need **psychosocial support** to help them deal with issues such as surviving with CF, independence, fertility, and sexual issues.

1.3.4.5. Cystic Fibrosis Complications

Serious complications include: lung complications like chronic obstructive bronchitis, recurrent chest infection with pseudomonas aeruginosa (267), pneumonia and destruction of the lung tissue, bronchiectasis, fibrosis and emphysema (255) leading to respiratory insufficiency and cor-pulmonale. At this stage lung transplantation is the only possible treatment option (268). Children with CF are also at risk of the following common complications: malnutrition and vitamin deficiencies (269), liver disease, meconium ileus (affects 1 in 7 newborn live birth), deficits in bone mineral density, reduced female fertility and male fertility (270).

1.3.4.6. Possible Disease Effects of Integrated Movement Behaviours in Children with Cystic Fibrosis

Several studies show that exercise and daily habitual PA can improve health-related quality of life (271-274), pulmonary function and aerobic fitness, and help in improve bone mineral density in patients with CF (256), as well as reducing the rate of hospitalisation and (275, 276). PA may help in improving airway clearance by increasing trans-epithelial fluid transport and raising ventilation (277). Moreover, an active lifestyle in children with CF might reduce even prevent decline in lung function (272, 278, 279). Therefore, several bodies have recommended a minimum of 60 minutes of MVPA every day for children with CF (30, 87, 256, 280), These recommendations for the general population are usually also considered to be

applicable to children and adolescents with chronic disease (39, 281). Further, increased time spent in SB has been associated with increased risk of co-morbidities, reduced quality of life and increased mortality rate in adult life (282). Collectively, sleep in children with CF had been inadequate in term of duration and quality. Some studies had noted that children with CF had short sleep with more sleep disturbance compared to healthy (129, 283, 284); reasons of short sleep could related to delay of sleep time with early of wake-up time (284) or might related to frequent awakenings episodes and more wake after sleep onset (129) or combination of the two. Overall, the lifestyles of children with CF might be less active and more sedentary with inadequate sleep (poor quantity and quality), and the reason for these compared to healthy children and recommendations, possibly related to disease symptoms or characteristics such as coughing or pain, or due to treatment regimen which is usually complex with multiple medications and airway clearance and physiotherapies that require several hours every day.

1.4. Aims:

The aims of the present study were to:

1. Complete a systematic review and meta-analysis (Chapters III) examining whether children and adolescents with chronic disease meet the current MVPA recommendations (79, 80, 281). Secondary aims were to examine the amount of accelerometer-measured ST in children and adolescents with chronic diseases, and to determine whether accelerometer measured MVPA and ST in children and adolescents with chronic disease were different from those in healthy control or comparison groups. (Paper I).

2. To complete a systematic review (Chapters IV) to determine obese children's and adolescents' habitual amount of time spent in MVPA, and examine whether those living with obesity met the current MVPA recommendation for health of a minimum of 60 minutes per day (9, 30). Secondary aims were to examine time spent in accelerometer-measured SB by obese children and adolescents, and to determine whether MVPA and SB in obese children and adolescents were different from the non-obese peers (Paper II).

3. To complete a study (Chapters VI) investigating the 24 hour-movement behaviours (Sitting/lying, PA, standing, and sleep) for 5-7 days in children with common chronic childhood diseases and test whether there were differences between children with chronic disease and their healthy peers, and whether both meet the current sleep duration recommendations (Manuscript submitted to PLOS One Paper III).

4. To complete a study (Chapters VII) investigating sleep quantity – particularly sleep timing (sleep onset/offset), and sleep duration - and sleep quality in children with chronic diseases and test whether these aspects of sleep in children with chronic disease differed from healthy controls and whether both met the current sleep duration recommendations (131, 132).

CHAPTER II

GENERAL MATERIALS AND METHODS

This chapter provides detail on the generic materials and methods used in the studies within this thesis. Specific methodological details of individual studies are described in the relevant study chapters.

2.1. Materials and Methods of Literature Systematic Reviews

The two systematic reviews of the literature included in this thesis (Chapters III and IV) were performed in accordance with the PRISMA guidelines (285) and the review protocols were registered on PROSPERO (registration numbers RD42015016783 and CRD42015026882). Study eligibility, search strategy and selection, data extraction and synthesis, and quality assessment tools used for each study are described in detail in relevant chapters (Chapters III and IV). Full details of the literature searches in electronic databases are summarised in Appendix I.

In brief, the literature searching was focused on four key elements: children and/or adolescents, MVPA, ST and/or SB, measured objectively by accelerometer, and common chronic disease (obesity, chronic cardiovascular disease, chronic respiratory disease, diabetes mellitus and malignancies). For each review, an extensive search was conducted using the five most relevant electronic databases from the year 2000: MEDLINE OVID; Cochrane library; EMBASE; SPORTSDiscus and CINAHL. The year 2000 was chosen to increase generalisability because levels of MVPA, ST and/or SB might be different now than in the recent past, and because accelerometry became more widely used in research from the early 2000s. The literature search was adapted as required for the other four databases. The electronic search was complemented by reference tracking (forward and backward citation searching) of the included studies.

2.2. Materials and Methods of Primary Data Collection Studies

Primary data collection was required for two of the studies:

1. Study in Chapter VI was an investigation of 24-hour movement behaviours (PA, standing, sedentary and sleep behaviours) over period of 5-7 days in children with common chronic childhood diseases and aimed to test whether there were differences between children with chronic disease and their healthy peers.
2. Study in Chapter VII investigated sleep quantity – particularly sleep timing (sleep onset/offset), and sleep duration - and sleep quality in children with chronic diseases and aimed to test whether these aspects of sleep in children with chronic diseases differed from healthy controls and whether both met the current sleep duration recommendations (131, 132).

2.2.1. Study Design

We carried out an observational case-control study to make pair-wise comparisons of the behaviours; we know that the power of the study is considerably increased if the subjects are matched for the main determinants of PA and SB in UK children (age, sex, and time/season of measurement (156, 158).

2.2.2. Participants

2.2.2.1. Children with Chronic Diseases

We investigated children with four common chronic diseases (children with T1DM, children with JIA, children with CHD and children with CF). The children were recruited from Out Patient Clinics at Royal Hospital for Children, Glasgow, UK.

These conditions were chosen for a number of reasons: they are all examples of common, serious and chronic diseases that affect childhood. The frequency of their occurrence allowed us to recruit an appropriate number of children to study the inter-relations between PA, SB or sleep, as described in Chapter I (Section 1.3).

2.2.2.2. Healthy Control Groups

Healthy children were recruited from local primary schools in Glasgow, UK; from the Libyan weekend school for children of Libyan parents temporarily resident in Glasgow; from children of University of Glasgow staff members and friends. Libyan children were recruited from a Libyan school that runs only on Saturdays, for half days, to teach children an Arabic language and Libyan curriculum. The Libyan children attended their normal classes in local primary schools during weekdays; they therefore have almost similar daily activity like the other healthy children who recruited to enrolled in our study. Further, Libyan children were included as control groups in previous studies where their levels of SB and PA were similar to the other controls (286), as shown in Appendix III. It therefore was anticipated that most of these children would be suitable as controls for children with chronic disease in our studies.

Further, the study had a paired design, with each patient matched with a healthy control child (matched for age, gender, and time/season of measurement - the main influences on PA and SB in UK children (287-290).

2.2.2.3. Participants Age

We concentrated on preschool and primary school children (age range 3 -10 years old). The upper age was chosen because most children below 10 years are still expected to be pre-pubertal. Pre-pubertal children are more homogeneous between sexes in terms of their height and weight and in their patterns of activity, though with age-related changes within this range as noted in Chapter I (Section 1.2.6).

2.2.3. Inclusion and Exclusion Criteria

2.2.3.1. Inclusion Criteria of Children with Chronic Disease and Healthy Controls

Children and parents/ carers were asked to participate in the study if they meet the following eligibility criteria:

For children with Chronic Diseases:

Children with T1DM: (1) Attending the Outpatient Diabetic Clinic at Royal Hospital for Children (Glasgow, U.K.); (2) meeting WHO diagnostic criteria for T1DM; (3) between 3 years and 10 years of age; (4) with duration of diabetes longer than 3 months; (5) with no known kidney or cardiovascular complication; (6) with no limitations to walking or PA because of other mobility issues.

Children with JIA: (1) Attending the Outpatient Rheumatology Clinic at Royal Hospital for Children (Glasgow, U.K.); (2) meeting ILAR diagnostic criteria for JIA; (3) between 3 years and 10 years of age; (4) with duration of JIA longer than 3 months; (5) with no major limitations to walking or PA because of other mobility issues.

Children with CHD: (1) Attending the Outpatient Cardiac Clinic at Royal Hospital for Children (Glasgow, U.K.); (2) previously diagnosed with CHD with a history of

surgical intervention for the cardiac lesion; (3) between 3 years and 10 years of age; (4) with no history of cardiac surgery within the last 3 months; (5) with no major limitations to walking or PA because of other mobility issues.

Children with CF: (1) Attending the Outpatient Clinic at Royal Hospital for Children (Glasgow, U.K.); (2) previously diagnosed with CF; (3) between 3 years and 10 years of age; (4) with no limitations to walking or PA because of other mobility issues.

For Children who Acted as Healthy Controls: (1) In good health; (2) with no chronic illness that would limit their PA; (3) between 3 years and 10 years of age; (4) not taking any medications that might influence cardiorespiratory function; (5) with no limitations to walking or PA because of other mobility issues.

2.2.3.2. Exclusion Criteria of Children with Chronic Disease and Healthy Controls

Participants/ their families were excluded from the study if they:

Children with T1DM: (1) Had diabetes as a secondary condition; (2) were taking any medications other than insulin which might influence cardiorespiratory function; (3) were and younger than 3 years and older than 10 years of age; (4) had an orthopaedic condition limiting PA or who were using a wheelchair for mobility or with another condition that may have impacted their PA.

Children with JIA: (1) Were taking any medications (except glucocorticoids/disease modifying anti-rheumatic drugs for JIA), which might influence cardiorespiratory function; (2) were younger than 3 years and older than 10 years of age; (3) had other conditions that might have led to limitations in PA and mobility.

Children with CHD: (1) Had cardiac surgery within the last 3 months; (2) had any neurological dysfunction that might impair their ability to perform PA e.g. due to

chromosomal abnormalities such as Down's syndrome; (3) were younger than 3 years and older than 10 years of age; (4) had an orthopaedic condition limiting PA or who are using a wheelchair for mobility or with another condition that may have impacted their PA.

Children with CF: (1) Had an orthopaedic condition limiting PA or who are using a wheelchair for mobility or with another condition that may have impacted their PA; (2) were younger than 3 years and older than 10 years of age.

For Children who Acted as Healthy Controls: (1) Children with any physical or mental dysfunction likely to affect their PA or ST; (2) were younger than 3 years and older than 10 years of age; (3) had an orthopaedic condition limiting PA or who were using a wheelchair for mobility or with condition that may affect their PA.

2.2.4. Sample Size

The study was designed as an observational case-control study. We aimed to recruit 160 participants (80 pairs); 80 children with chronic disease and 80 healthy controls matched for age, sex and time/season of measurement. For the clinical groups we considered recruitment of 20 participants for each group should be feasible from the appropriate specialist clinics.

Sample Size Calculation: Based on previous experience with the activPAL^{TM}, we expected that recruiting 160 children would provide reliable activPAL^{TM} data ($\geq$ 4 days with at least 10 hours of waking wear time in 24h period) from at least 140-150 children. At the time our study started, there were no data to guide sample size calculations of 24-hour movement behaviours in children with chronic disease. Our recent systematic review (291) found that previous studies that examined differences in MVPA and ST between children with chronic disease and healthy controls using paired study designs

found significant differences with relatively small samples ranging between 7 pairs (7 patient and 7 healthy children (292), and 38 pairs (38 children with chronic disease and 38 healthy children) (75). Thus, we expected that a sample of around 73-75 paired comparisons might be sufficient to detect with a high degree of significance differences in 24-hour movement behaviours between children with chronic diseases and healthy controls.

From previous studies, we know that the power of the study is considerably increased if the subjects are matched for the main determinants of PA and SB in UK children (age, sex, time/season of measurement (287, 288) with number of pairs of around 15-20 often being sufficient to demonstrate significant differences in activity levels. In our study, we closely matched children with chronic illnesses and healthy controls on the basis of age, sex and time/season of measurement (287, 288). Age is particularly important because it is known that activity declines with age (156).

The primary analysis examined the differences between children with each particular illness vs their healthy controls for each of the 24-hour movement behaviours. As a secondary exploratory analysis, we also compared the results in all children with chronic disease as a group with all healthy controls as a group using paired statistical tests. Such an approach could be justified on the basis that all the children in the chronic illness groups met the definition given earlier - any physical, emotional, or mental health problem that lasts at least three months, and affects a child's physical appearance and/ or growth and daily normal activities and results in frequent hospitalisations with regular therapy and sometimes unpleasant procedures, with home and medical care. However, it is a difficult to know if the chronic disease group was sufficiently homogenous to allow a comparison as a group with the healthy children.

2.2.5. Study Plan and Procedure

2.2.5.1. Study Plan and Procedure for Children with Chronic Disease

Families of children were initially approached when attending outpatient clinics at the Royal Hospital for Children, Glasgow, UK. They were informed about the study and if they were interested in taking part were given a written information sheet explaining the study. If after reading this they were still interested in participating, a meeting was arranged at a mutually convenient time and place. At that meeting, any further questions were answered. If they were happy to proceed, informed written consent was obtained from the parent and written assent from the child, if appropriate, as summarised Figure 2.1.

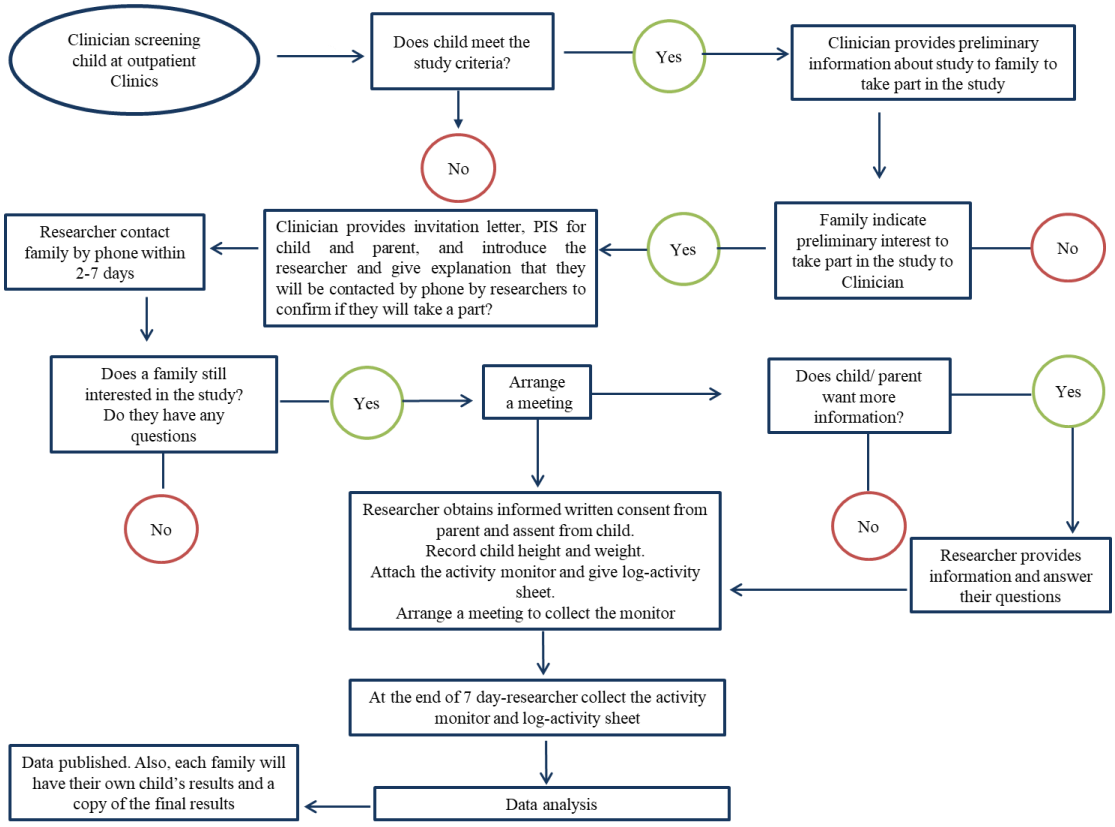


Figure 2.1: Flow chart for identification of child with chronic diseases at Out patients Clinics at Royal Hospital for Children, Glasgow, UK.

2.2.5.2. Study Plan and Procedure for Healthy Control Children

In schools, head teachers were asked to identify potentially suitable children of an appropriate age and sex. Selection was only on the basis of age and sex. Suitable children were given a letter, information sheet about the study and a participation form to take home to their parents. For parents who were willing to participate, they were asked to complete the form and return it in an enclosed stamped addressed envelope. They were contacted by phone and a meeting arranged to discuss the study in detail and obtain informed consent and the completion of a consent form by a parent/carer and an assent form for the child, as summarised in Figure 2.2.

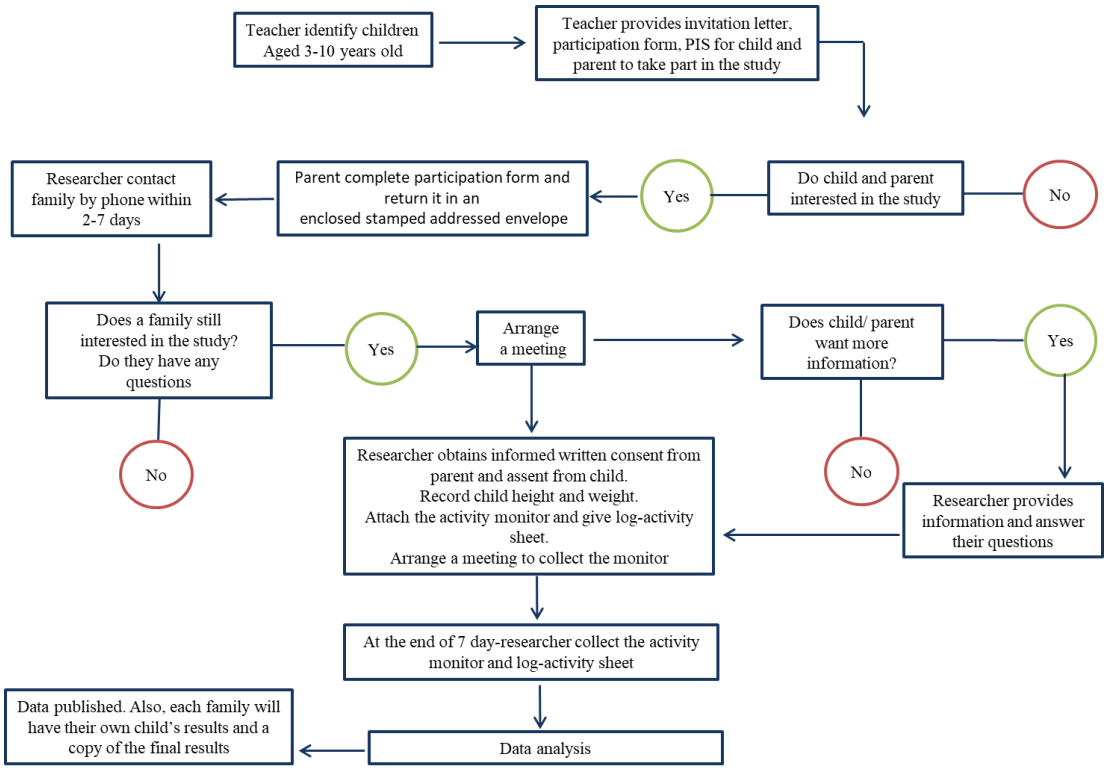


Figure 2.2: Flow chart for identification of healthy children controls at schools and nurseries, Glasgow, UK.

Children were enrolled in the study only after their parent or guardian had given informed consent to participate in the study and the child had given assent, if appropriate.

2.2.6. Movement Behaviours Monitoring

The 24-hour movement behaviours were measured objectively using an activPAL™ micro accelerometer (PAL Technologies Ltd., Glasgow, UK). The activPAL™ micro is a small (23.5mm x 43mm x 5mm), lightweight (10g) triaxial accelerometer with storage capacity to record more than 10 consecutive days successively (293), as shown in Figure 2.3. The accelerometer provided information about the thigh position and posture changes, and can thus distinguish very accurately time spent sedentary, standing or walking, and transitions between these postures (standing up and sitting down). It has been shown to be a valid and reliable tool for objective measurement of posture and motion during everyday activities in children (141, 294, 295) and adults (296, 297). This makes it a useful tool for studying a number of the 24-hour movement behaviours consecutively for seven days (295). The data output can be presented per second, 15-second, hour, day or week epochs.

Figure 2.3: The activPAL™ micro monitor (PAL Technologies Ltd., Glasgow, UK).

The activPAL™ micro is placed directly onto child's skin on their mid-anteriorly on the thigh and covered with a transparent sticky film (Tegaderm™) to secure it. Children

were asked to wear the monitor continuously including sleep; 24 h a day, for seven consecutive days. As the monitor was not waterproof, parents were asked to remove it for any showering, bathing or swimming during the monitoring period and they were supplied with extra sticky film (Tegaderm) to reapply the device with orientation to correct direction indicated by the figure on the front of the monitor, if it was removed.

2.2.7. Duration of Participation

The monitor was worn on the mid-thigh. The researcher first attached the monitor to participants (at Out Patient's Clinics at Royal Hospital for Children (Glasgow, U.K.), schools or at a convenient time and place). The aim was for the activPAL^{TM} micro monitor to be worn continuously for 7 days. During this time, the child would be free to continue their normal activity. However, as the monitor is not waterproof, it needs to be removed for showering, bathing or swimming during the monitoring period. All parents received verbal and written information and instructions about using the device before giving informed consent to the study.

Parents also were provided with a Daily Activity Log sheet (as shown in Appendix II) and asked to keep a note of any time the device (date and timing) was removed and reattached. Participants were supplied with extra sticky film (Tegaderm) to reapply the device if it was removed. Children at this age were sleeping in their own rooms and timing for sleep onset/offset usually would not be known accurately to the parents. Accordingly, we did not ask them to record this in the Daily Activity Log sheet. For each child, periods noted in the daily diaries when the child was not wearing the device e.g. because of swimming, bathing/showering or delayed reattachment because of

forgetting were identified and excluded from the raw activPAL™ files before any analysis.

At the end of 7 days, the researcher collected the activity monitors and recording sheets from the participants. The data were then transferred to a computer for analysis using the special software provided by the manufacturer.

2.2.8. Criteria for Discontinuation

Because the activPAL™ micro monitor is small (23.5mm x 43mm x 5mm) and lightweight (10g) it does not interfere with normal activity or play. However, if a child was uncomfortable or not happy wearing the monitor, the parents were instructed to remove the monitor and so data collection was stopped for that participant.

2.2.9. Confidentiality

Each participant was assigned a numeric code number. Data such as name, medical condition and family contact details were kept in a separate database only accessible by the researcher. Study participant data was identified only by the assigned code number.

2.3. Data Collection

2.3.1. Participant Characteristics

At the time participants were enrolled in our study, the anthropometric parameters detailed below as well as any relevant clinical variables for participants were obtained.

2.3.1.1. Anthropometric Parameters

2.3.1.1.1. Age and Sex

We recorded the age and sex for children with chronic disease and healthy controls. The age of our participants was recorded from data of birth up to the data of enrolment in the study.

2.3.1.1.2. Weight and Height

Weight was measured to the nearest 0.1 kg using a Seca^{TM} scale. The children were weighted with light indoor clothing and we asked them to take off the outer clothing and shoes at the time of measurement. The participant's height was measured to the nearest 0.1 cm by using stadiometer (Leicester Height Measure^{TM}). To ensure accurate height measurements were taken, we asked children to take off their shoes, standing up straight on platform with arms at their sides and heels and buttocks positioned in contact with the vertical backboard. Then, the headboard of the apparatus was carefully placed on the child and the height measurement was recorded from the instrument to the last complete millimetre.

2.3.1.1.3. Body Mass Index

Body mass index (BMI) was calculated from the children's weight and height parameters using the formula weight in kilograms divided by the height in meters squared (i.e. weight (kg)/height^2 (m)). BMI was classified into normal weight, overweight and obese according to international age- and sex-specific BMI cut-offs proposed by reference data (298-300).

For each child, weight, height and BMI measurements were converted to Standard Deviation Scores (SDS) to allow comparison between age- and sex (301). To do this

we used the 1990 British growth reference database (302), and WHO Anthro software available at: http://www.who.int/childgrowth/software/en/). Participants were classified based on their BMI Z-score into overweight if BMI Z score was >+1SD and obese if BMI Z score >+2SD (302).

2.3.1.2. Clinical Variables

In children with chronic disease, we obtained clinical variables at the time of recruitment in our study to provide an indication of disease severity, and these variables depending to each disease were defined as follows:

2.3.1.2.1. Children with T1DM

In children with T1DM (diagnosis of diabetes was made based on WHO criteria described in the Chapter I)(166), we recorded the level of HbA1c to classify children into either those with:

- Good glycaemic control if their HbA1c was ≤ 48 mmol/mol,
- Poor glycaemic control if their HbA1c was ≥ 48 mmol/mol based on the 2015 NICE recommendation (175)

We also collected information the mode of insulin delivery. The mean disease duration, defined as the mean time from diagnosis to the time of enrolment in our study, was also collected.

2.3.1.2.2. Children with JIA

In children with JIA (diagnosis of JIA was made based on classification criteria described in the Chapter I), we recorded the following parameters to evaluate the current disease activity. These included number of joints actively inflamed; number

with limited joint movement; number of tender joint; Parents/Patient global assessments score; Physician global assessments score; subtype of JIA; type of treatment; and stage of disease. Disease duration was defined from date of diagnosis to the date of enrolment in our study. Recent measurements of anti-inflammatory biomarkers ESR and CRP were also recorded.

2.3.1.2.3. Children with CHD

The children with CHD were at least 3 months past their last operation. We recorded the cardiac diagnosis, number of surgeries for each child, current medical treatment. The disease 'duration' in children with CHD determined as the time from last surgery to the enrolment in our study time.

2.3.1.2.4. Children with CF

In children with CF (diagnosis of CF was made based on classification criteria, described in the Chapter I), we recorded percentage of forced expiratory volume in 1 second (FEV1 % predicted), current medical treatment and the disease duration. In our study, the severity of the obstructive lung changes was evaluated by FEV1 % and BMI-Z score.

2.3.2. Objective Measurement of the 24-Hour Movement Behaviours

As noted above, the activPAL^{TM} micro accelerometer was used to evaluate components of 24-hour movement behaviours (time spent in PA, standing, sedentary and sleep behaviours), as well as sleep quantity - in term of sleep timing (sleep onset/offset time) and sleep duration - and sleep quality in our studies. The activPAL^{TM} micro is a triaxial accelerometer with an inclinometer, which measures the acceleration of the thigh. This enables it to give information about the static (body posture sitting/lying and upright) and dynamic acceleration (body movement) that is used in algorithms to classify the

measured signal into sitting/lying, standing and walking. In addition to rich information about body posture and transitions between postures it may also be used in future to estimate energy expenditure (141, 303).

The activPAL™ micro has a 32 MB memory capacity, which with a default sampling frequency in the software of 20 Hz (80 Hz could be selected in research mood) allows up to 14 days of monitoring, The software also gives an option to changing the minimum sitting/upright transition period to define a new posture from 1 - 100 second and the manufacturer had recommended the 10 second, which meaning ≥10 s of sitting/lying or upright data is needed to register as a new event (303). It is therefore considered an ideal tool to use in our study for 7 days monitoring. The output data of activPAL™ summarised the behaviours in terms of "events" (i.e., changes in posture), and categories the behaviours into three behaviours categories "sitting/lying", quiet standing and "walking/stepping". It also quantifies steps and accumulation in periods of time and shows start time, end time and time spent in each behaviour (303). Based on validation studies in different population (such as both children and adults, in both sex, in both healthy and diseased population) the device is considered a reliable and valid tool to distinguish postural changes (sitting/lying, standing, and stepping) and features of SB, including time spent sitting/lying and breaks- transitions between these postures (standing up and sitting down) and sleep (293, 304-309).

Indeed, that based on the default values from the manufacturer, activPAL™ Professional Research Edition software classifies the recorded data of each child into the three different categories: lying/sitting (1.25 MET); standing (1.4 MET); and 'walking' (stepping at 120 steps per minute estimated to be 4 MET). This has

previously been shown to provide a valid measure of total physical activity- (141)). In addition, the software gives the number of transitions between the postures and the number of steps. ActivPAL data on movement/transitions has previously been used to successfully measure time spent asleep in children by identifying the timing of sleep onset and waking (286, 310, 311). It is correct that the activPAL cannot measure all of the 24-hour movement behaviours e.g. it cannot measure screen time and the time spent MVPA. Currently, no single device can do this and so we did not set out to measure all these components in the work for the thesis. We considered using additional devices, and/or adding parent-reports or diary measures of time spent in some of the behaviours (e.g. screen time, sleep), but these would have added to the burden of the study for families and a recent systematic review (312) found that there was little evidence that parent-report measures were accurate.

In summary, we chose to measure of those behaviours for which there was some evidence of validity, i.e. time spent in total physical activity, time spent in sleep, which were objective and did not rely on parental report and for which the experimental burden on families was considered both reasonable and achievable. Since the main aims of the research in the present study was to investigate differences between patient and control groups having exactly the same methods with a similar accelerometry monitoring duration between the groups was the most important experimental consideration.

Future studies with greater time/human resources and with newer technologies will be needed to do the kind of comprehensive 24-hour movement behaviour monitoring

which would be ideal. At present, the technology is not available to do such studies either practically or accurately.

2.3.2.1. Charging and Programming of ActivPAL™ Monitor

The activPAL™ is recharged using a docking station connected to a computer by USB cable. The ActivPAL device is placed into one of eleven ports of docking station for recharging. An orange light indicates the device is charging. Three hours is needed for full recharge and then the light disappears, as shown in Figure 2.4.

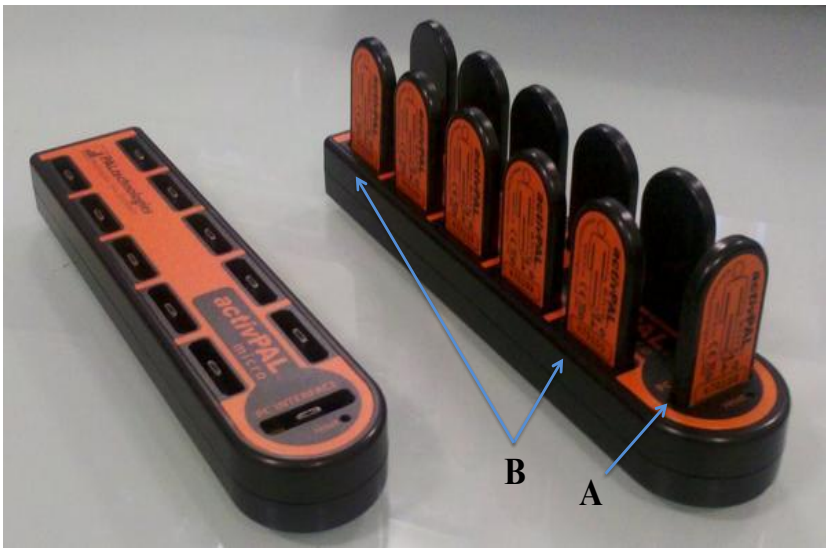


Figure 2.4: The docking station for activPAL™ A) A device in programming site. B) Devices being in charge sites.

There are some steps prior to the ActivPAL™ accelerometer programming. First of all, we downloaded the ActivPAL™ professional software from PAL Technologies Ltd web site, and installed it on a computer Windows 7. Then we connected the ActivPAL™ device to the computer by using a USB port in the docking station cable. Next, we placed the ActivPAL™ in programming port of docking station, as shown in Figure 2.4. After that we selected "Communicate with activPAL™" from the menu file in activPAL™ professional software (Version 7.2.32), then selected "reprogramming

and clear memory" option to clear the ActivPAL device memory and prepare it for measurements. A series of rapid green flashes indicates that the device is programmed and ready for use. In the professional software, we could choose the suitable starting data and time for monitoring based on convenient time of our participants. Once our participants were ready to start the monitoring then we entered the data and time. The green light flashes every six seconds throughout recording process indicate the ActivPAL device was recording (303).

2.3.2.2. Placement of ActivPAL™ and Monitoring Duration

Once an activPAL™ device was recharged and programmed, it was attached to the child at outpatient clinic, at school, or at suitable place for our participants. The researcher was attached the activPAL™ device to the child in front of their parents and they were given verbal information on how they could remove the device and reattach it again at home, if needed.

2.3.2.3. Monitor Collection and Data Download

At the ending of seven days monitoring period, the families removed the device from the child and returned it back to the researcher. Once the device had been returned, the data were downloaded via USB cable to a PC from the monitor using ActivPAL™ Professional software (Version 7.2.32). To do this we first connected ActivPAL™ by chose the option of "Communicate with activPAL" from the File menu in ActivPAL™ Professional software. Then download was initiated and the data saved to the PC by choosing the option of "download store data". The raw activPAL™ data for each child

were saved into a file labelled with an anonymous code for further analysis and long-term storage.

2.3.2.4. Definition of Valid Day

A day was defined from one wake time to the next day wake time (313). Valid day is defined by the minimum number of wearing during waking hours per day that is needed to provide a valid measurement of SB and low, moderate and high PA. In previous accelerometry studies, a valid day ranged from 6 to 10 hours per monitoring day (314, 315). In our studies, we requested the participants to wear the activPAL^{TM} for 24h per day and to provide at least ten hours wear time during the waking in a 24h period to be included in the analysis (316). The monitoring time provided by our participants was always much greater than the minimum previously established for reliable data.

2.3.2.5. Minimum Number of Valid Wear Days

Research has shown that the minimum number of days required to obtained a valid representation of usual SB, activity and sleep using accelerometers ranges from four to nine days (317, 318). In this study, the participants were asked to wear the activPAL^{TM} for 24h per day for seven consecutive days. This duration of wear allows for a reasonable estimate of usual levels of the behaviours, and for any differences between weekday and weekend days to emerge, as previous studies suggested that children were less active and more sedentary at the weekend compared with week days (319, 320). Although, seven days monitoring period were requested, children included in the study had to provide a minimum of four valid days of activity data (including one wakened day and night) to be included in the analysis as in previous studies (289, 316, 321).

The minimum number of days and hours required for adequate measurement of the usual (habitual) levels of the different 24-hour movement behaviours by accelerometry is currently unknown and has not been the subject of research attention, probably because the ’24-hour movement behaviours’ concept is so new (322). However, minimum numbers of days to obtain reliable estimates of usual levels of child PA and SB has been studied for a number of accelerometers (321, 323-325). These studies find consistently that across a wide age range in childhood and adolescence around 3- 4 days of accelerometry monitoring is an acceptable minimum, with as little as 4- 6 hours being an acceptable number of hours per day. A detailed investigation of the minimum number of hours and days required with activPAL in the present study was beyond the scope of this thesis, but the actual activPAL monitoring times were consistently far longer than minimum durations usually cited in the literature. In addition, one of the main aims of the research in the present study was to investigate differences between patient and control groups, and so having a similar accelerometry monitoring duration between the groups was important.

2.3.2.1. Definition of Valid Night and Minimum Number of Valid Night

Based on previous research that used the accelerometer to quantify sleep in healthy children (326-328), we defined a valid night as having at least 160 minutes of sleep (316), with measurements required over at least 3 valid nights, including 1 weekend night (Friday night and or Saturday night), before including it in this study (316).

2.3.2.2. Non-Wear Time within a Day

Non-wear time during a day refers to the number of consecutive zero counts that must be recognised before considering that the monitor is not being worn. Assuming there are no technical problems with the monitor, a period of consecutive zero counts (≥ 60 minutes within a day in "sitting/lying" posture (329)) is commonly taken to indicate that the monitor has been removed and is not attached. This might arise during removal for a period of water based activities or might reflect removal of the activPAL™ accelerometer because the participant is not complying with the monitoring protocol (330).

In our study, non-wear time was first identified from the parent note in the Daily Activity Log sheet for any time the device was taken off and reattached again. Then by manual inspection of the event file any unchanging sitting/lying period lasting for ≥ 60 minutes within a day (63, 329) that indicated the monitor was removed and placed in a horizontal position with no movement recording were noted and also considered as non-wear time (63, 329). Once the non-wear time was identified, the sum of the non-wear time data (identified by the parents and confirmed on the monitor output plus other periods not documented by the parents and defined as above) was calculated for each child and then excluded from the analysis.

2.3.2.3. Sleep Time and Wake Monitoring Time

The investigators needed a valid and reliable procedure to identify the sleeping time. Until recently, it has been difficult to differentiate between sedentary and sleeping time in accelerometer data (330). In previous studies with the activPAL™ and the present study (311, 331) the sleep time was identified by the researcher using manual inspection

of the event file created by HSC PAL analysis software v 2.14 to identify the sleeping time as described below. The wake monitoring times was calculated from the event file of HSC PAL analysis software v 2.14. For each participant, the wake monitoring time is calculated as total wake time after excluding sleeping time and non-wear time summed in hours per 24 h period, and then averaged as the total waking monitoring times over the number of monitoring days.

2.3.3. Data Processing

First of all, the activPAL™ data were processed and analysed by using the activPAL™ Professional Research Edition software (Version 7.2.32) which classifies the recorded data of each child into the three different postures: lying/sitting; standing; and walking, as well as giving the number of transitions between the postures and the number of steps. Although, the manufacturer had recommended the 10 second as a minimum of sitting/lying or upright transition period this might not be appropriate for all population. Indeed, Alghaeed et al found that the 2 second as minimum activPAL™ sitting/upright period is optimal for young children that they change their posture very rapidly (331), Thus, the 2 second as minimum activPAL™ sitting/upright period was used in our study, as shown in Figure 2.5.

The activPALTM files generated by Professional Research Edition software (Version 7.2.32), were imported into custom software known as HSC PAL analysis software (Version 2.14) developed by Dr. Dall and Professor Granat at Glasgow Caledonian University, Glasgow, UK. The HSC PAL analysis software generates an event file in seconds at which a change in postural (i.e., a transition) occurred. In this way the event file of HSC PAL software allows detailed analysis of the activPAL output.

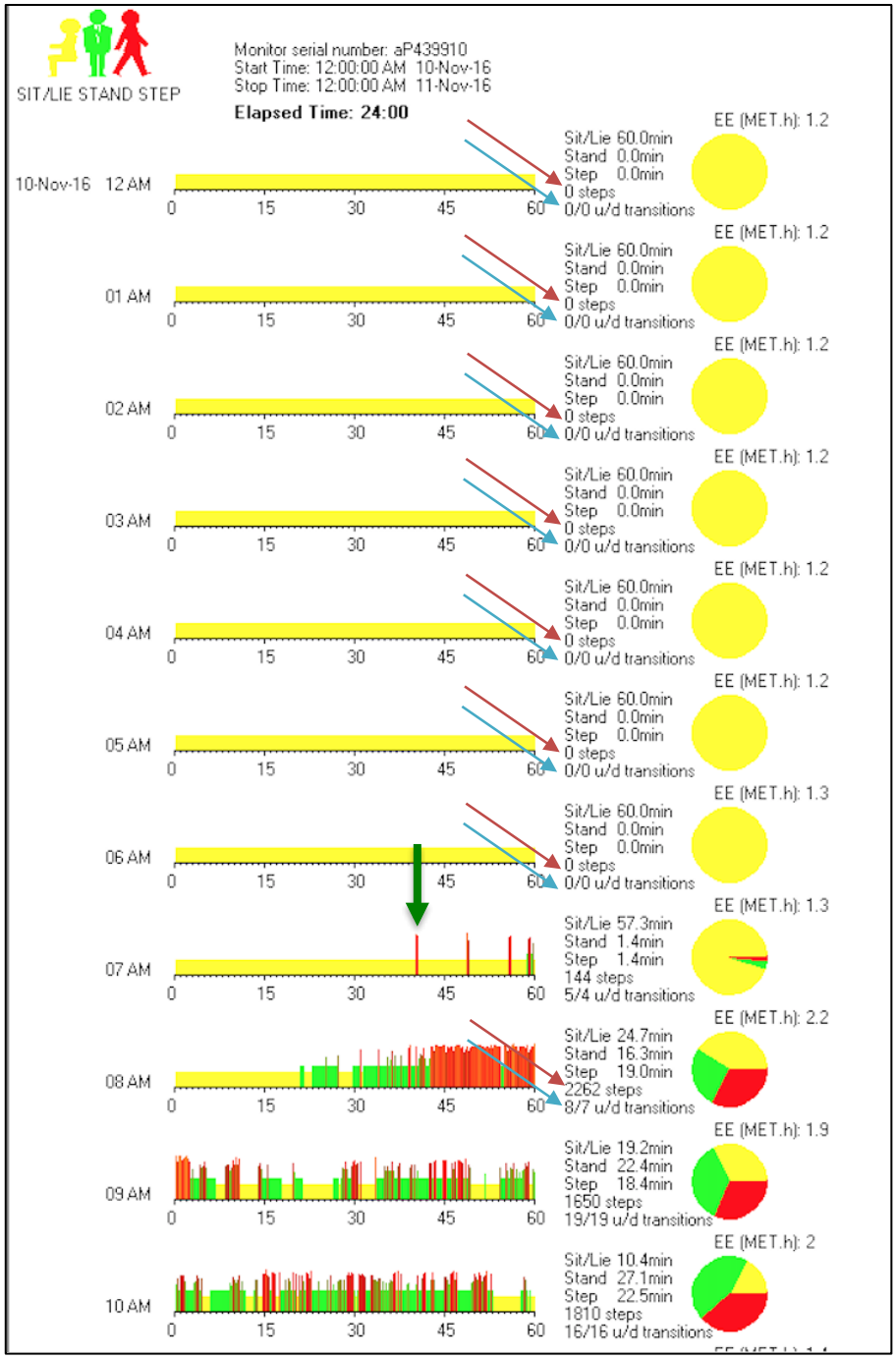


Figure 2.5: Example of output of the activPAL™ event file (summarised by hour).
Sit/lie period represented by yellow colour, stanfing period represented by green colour, and walk/steps represented by red colour. Red arrow for the number of steps per hour; Blue arrow for number of breaks in (Up transition [sit to stand (u)]); Green arrow represented the first transitions from sitting/lying-to-stand (i.e. sleep offset time where ended the day and starting the new monitoring day).

From the activPAL™ Professional software we obtained the number of steps per 24h period, and the number of sitting bouts (the number of breaks in sitting/lying periods) per 24h period. From the event file of the HSC PAL analysis software (version 2.14) we also obtained total time spent in 24h movement behaviours "sitting, standing, PA and sleep as well as the percentages of 24h movement behaviours, sleep onset/offset times, nocturnal sleep/wake episode and duration were calculated from the event file of the HSC PAL analysis software, as shown in Figure 2.6.

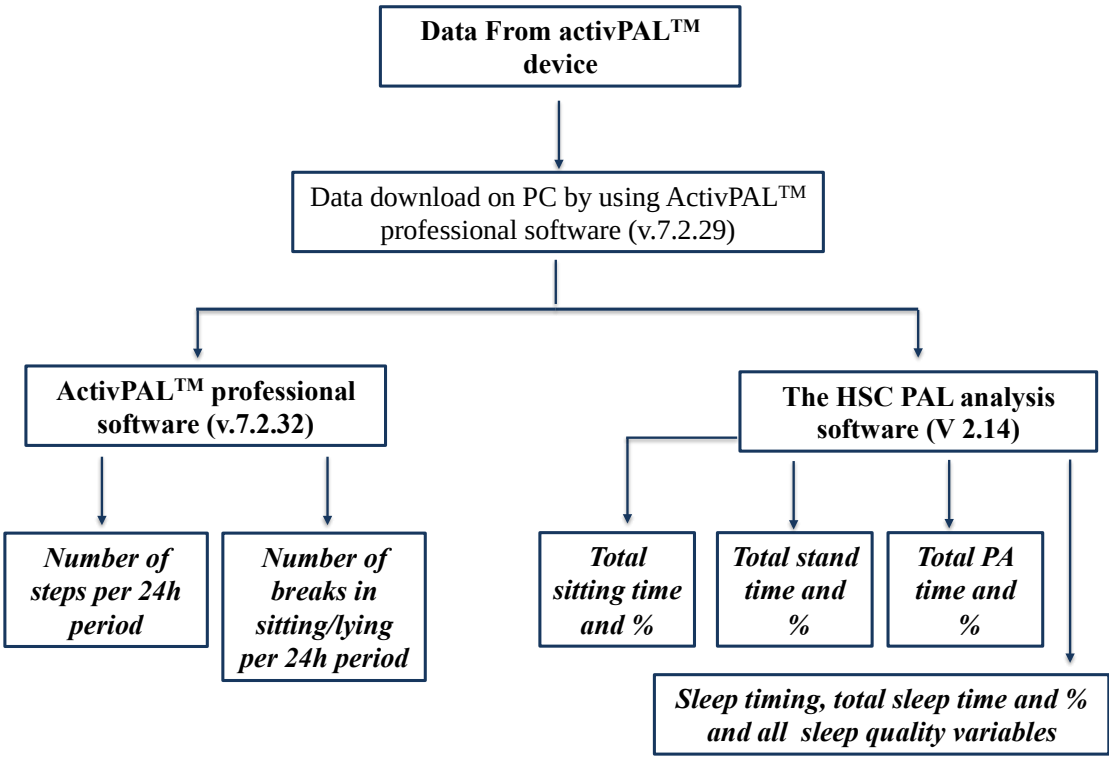


Figure 2.6: Flow chart the products of software programmes used in the analysis of ActivPAL data.

2.3.3.1. Characterising the 24-hour Movement Behaviours Study

As noted above, data included in this analysis came from only those children with ≥ 4 days with at least 10 hours of waking wear time in 24h period including one weekend day and night, in an effort to reflect habitual levels of the behaviours. During processing and treatment of the 24-hour data obtained from our participants we used HSC PAL

analysis software version 2.14 to first identify the nocturnal sleeping time (the time from sleep onset to the sleep offset, including all sleep/wakefulness period after sleep onset (332)).

Sleeping time for each participant was determined by manual inspection of the event file and was identified as the last transition from standing to sitting/lying in the day to the first transition from sitting/lying to standing of the next day as described by Alghaeed et al (141, 331). Non-wear time was identified from the parent activity Log sheet, and in activPAL file. Once the non-wear time was identified, the sum of the missing data was calculated for each child and then excluded from the recording before any data analysis was made. Finally, the remaining time that was not sleep or non-wear time was labelled as waking wear time. For these studies the monitoring day was defined as the first transition from sitting/lying to standing as the start of monitoring time of the day and the first transition from sitting/lying to standing of the next day was the end time of this day. While, awake time was defined by the first up transition in the morning to the last up transition in the evening, indicating the beginning of sleeping time. The total monitoring time during waking hours per 24 h period was calculated by taking the average of total monitoring times, after excluding non-wear and sleeping times, the data were sorted by colour for each day (yellow colour for sitting/lying, green colour for standing and orange colour for ‘walking/stepping’) for further analysis.

In this study, the 24h movement behaviours were characterised in the following ways:

2.3.3.1.1. Sedentary (Sitting) Time (ST)

ST for each participant in this study was quantified in 3 ways: 1. the total sedentary time per 24h period, 2. the percentage of sedentary time per 24h period, and 3. the number of sitting bouts (reflecting the number of breaks in sitting= posture transitions).

Total Sedentary Time (hours per 24h period):

Total ST during waking time per 24h period was calculated from the event file of HSC PAL analysis software version 2.14. The total time recorded as ‘‘sit/lie’’ during awake hours - from sleep offset till sleep onset- in HSC PAL analysis software event file was then calculated after excluding non-wear, all ST of participant were summed in hours normalised to per 24 h period and then averaged as time spent in ST over the number of monitoring days.

Percentage of Sedentary Time

Percentage of ST was calculated to quantify how much ST was in the daily life of child. For each participant in our study, the percentage of ST in waking hours per 24h period calculated as total ST in hours normalised to 24 h period and expressed as a percentage by multiplied by 100 (percentage of ST per 24h period = [total ST (h)/ 24 h period (h)] ×100).

Breaks in Sitting (Up transitions)

The number of breaks in periods of sitting was calculated as the number of up transitions recorded (postural change from “sit/lie” posture to “stand”) during each 24h period by using the activity profile file output file (data summarised in a 24 hour file) from the activPALTM Professional Research Edition software (Version 7.2.32), as shown in Figure 2.7. We avoided double counting by including the number of

transitions from sit/lie to stand posture (up transitions) only, but not from stand to sit/lie posture (down transitions) transitions. For each participant, the number of breaks (up transitions) was summed for each 24h period and then averaged over the total number of monitoring days. Breaks in sitting were quantified as a numerical value (i.e. the number of breaks).

2.3.3.1.2. Standing Time

The standing time was quantified for each participant in this study as 1. total standing time per 24h period and 2. the percentage of standing time per 24h period.

Total Standing Time (hours per 24h period)

Total time spent standing during waking hours per 24h period was calculated from the event file output of the HSC PAL analysis software version 2.14. The total time recorded as ‘‘stand’’ during awake hours in HSC PAL analysis software event file output was then calculated after excluding non-wear. For each participant, all standing times were summed in hours than normalised per 24 h period and finally averaged as standing times over the number of monitoring days.

Percentage of Standing Time

The percentage of standing in waking hours per 24h period was calculated as total standing time in hours divided by 24 h period and then expressed as a percentage by multiplied by 100 (percentage of standing time per 24h period = [total standing time (h)/ 24 h period (h)] × 100).

2.3.3.1.3. Physical Activity

The PA data were expressed in three ways: 1. the total time spent in PA (PA duration) in hours per 24h period, 2. the percentage of PA per 24h period and 3. the number of steps per 24h period.

Total Physical Activity Time (hours per 24h period)

Total time spent in PA during waking hours per 24h period was calculated from the event file output of the HSC PAL analysis software version 2.4. The total time recorded as ‘‘walk/stepping’’ during waking hours was then calculated after excluding non-wear and sleeping times. All ‘‘walk/stepping’’ times of participant were summed in hours, expressed per 24 h period and averaged as time spent in PA (‘‘walk/stepping’’ times) over the number of monitoring days.

Percentage of Physical Activity

Percentage of PA was calculated to quantify how much the PA contributed in 24-hour movement behaviours in daily lifestyle of child. The percentage of PA in waking hours per 24h period was calculated as total PA time in “hours” divided by 24 h period and then expressed as a percentage by multiplied by 100 (percentage of PA per 24h period = [total PA time (h)/ 24 h period (h)] ×100).

Number of steps per day

The total number of steps per 24 h period was obtained from the activPAL^{TM} professional research edition software (Version 7.2.32). For each participant, the number of steps was calculated by measuring the total number of steps per 24 h period,

as shown in Figure 2.7. The figure was then averaged to give the average number of steps per monitoring day.

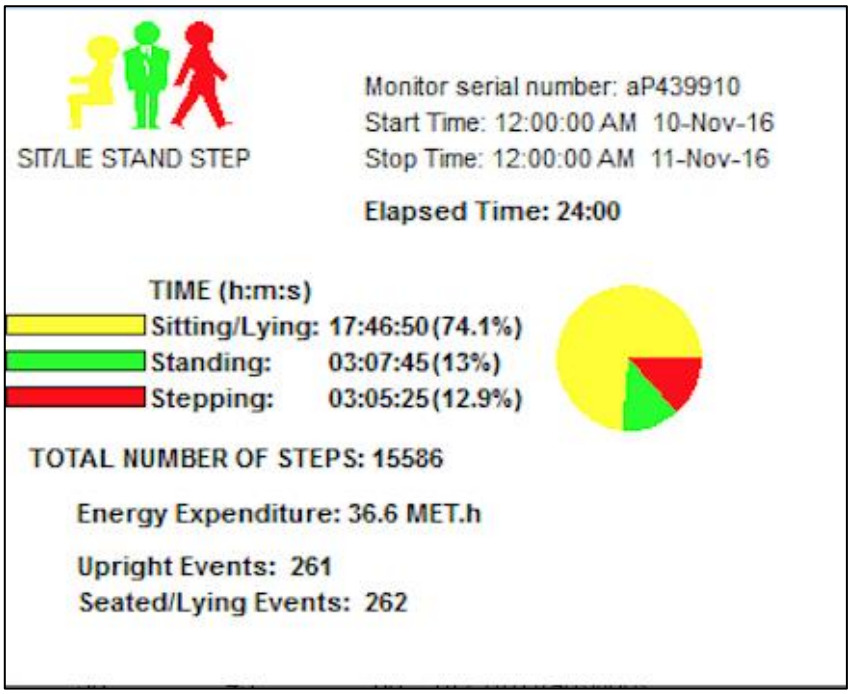


Figure 2.7: Example of output of the activPALT^{M} file (summarised by 24hour).

2.3.3.1.4. Sleep Behaviour

The nocturnal sleep behaviour in this study was expressed as 1. the nocturnal sleeping time (sleep duration) in hours per 24h period and 2. the percentage of sleeping time per 24h period.

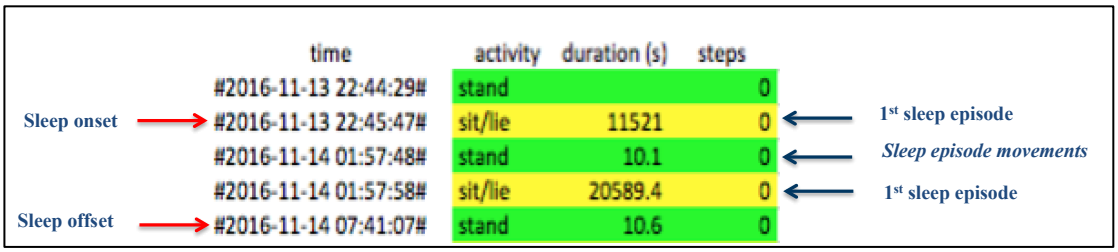
Nocturnal Sleeping Time (hours per 24h period)

As noted above, sleeping time was identified as the time from the last transition from standing to sitting/lying in the day to the first transition from sitting/lying to standing of the next day (331). In this study, nocturnal sleep-period time was defined as the duration accruing between sleep onset and offset time. Between these 2 time points, however, there were consecutive sequences of sleep and frequently minutes of

movement, suggesting repositioning, restlessness, wakefulness, or short breaks for visits to bathroom, to get drink etc. during the night. Thus our definition of "sleep-period time" reflects the time of sleep onset to the end of sleep "sleep offset", was including all sleep epochs and wakefulness after onset (332), as shown in Figures 2.8, 2.9 and 2.10.

Sleeping time for each participant was determined by manual inspection of the event file and was identified using the event file of HSC PAL analysis software version 2.14as the last transition from standing to sitting/lying in the day to the first transition from sitting/lying to standing of the next day as described by Alghaeed et al (286, 331). The nocturnal sleeping time for each participant was summed in hour per 24 h period and then averaged as time spent in sleep per monitoring nights.

A)



B)

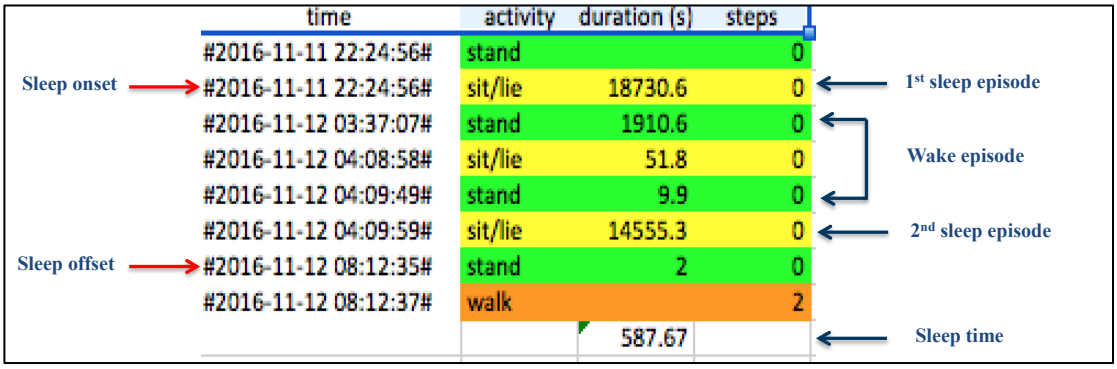


Figure 2.8: Example of event file produced by HSC PAL analysis software v 2.14 file for one of participants show sleep quantity and quality variables.
A) Sleep episode and sleep episode movements, and B) Sleep episodes and wake episode.

Percentage of Sleeping Time

Percentage of sleeping time was calculated to quantify how much the sleep was counted per 24-hours. The percentage of sleep per 24h period was calculated as a total sleeping time in hour divided by 24 h period and then expressed as a percentage by multiplied by 100 (percentage of asleep per 24h period = [total sleeping time (h)/ 24 h period (h)] ×100).

2.3.3.2. Comparisons Against Recommended Levels of the 24-hour Movement Behaviours

Currently the only 24-hour movement guidelines for school-age children and adolescents are from the Canadian Society for Exercise Physiology and these were published in 2016 (CSEP 2016) (131, 132) and are available at: http://www.csep.ca/home. These recommendations were evidence-based, i.e. they were based on a process of systematic reviewing and quality appraisal of the literature and followed standard GRADE methodology (Grading of Recommendations Assessment, Development, and Evaluation (333-335)). In summary, these Canadian Society for Exercise Physiology guidelines for school-age children and adolescents are expressed as what makes up a healthy 24-hour period and are as follows:

- Sleep = 10-13 h for age 3-4 years, 9-11 h of sleep per night for age 5-13 years, 8-10 h of sleep per night for age 14-17.
- SB = screen time=< 1 h per day of screen time for age 3-4 years and < 2 h per day for age 5-17of screen time.
- PA = ≥ 60 minutes per day of MVPA.
- LPA = several hours of a variety of un/structured LPA.

In the UK the guideline which applies to school-age children and adolescents (from Start Active Stay Active 2011(336)) refers only to MVPA, recommending that a minimum of 60 minutes per day every day is spent in MVPA; the only reference to SB is that time spent being sedentary should 'be minimised' (Start Active Stay Active 2011 (336)). One problem with the 24-hour movement guidelines at present is that measuring compliance with the guideline is not simple. There are no single methods which will measure sleep, screen time, and PA for example. Options include measuring as many behaviours as possible with a single device, using multiple devices to measure multiple behaviours (which would increase the burden on the researchers and the families), using devices for some of the behaviours and parent or self-report questionnaires for the other behaviours (but this latter option would involve subjective methods of unknown accuracy) or possibly measuring some parameters at different time and then combining them to produce a composite picture.

For the studies in this thesis it was felt that the activPAL would be a suitable method as it can measure time spent asleep, time spent in PA (both step counts and potentially also time spent in MVPA so long as methods are available to convert activPAL output to MVPA, which was true at least for pre-schoolers at the time the thesis work started-(337)), and time spent sedentary and breaks in sedentary time (though not screen time) (141, 294, 295). Obvious alternative accelerometers such as the Actigraph are probably less suitable for sleep measurement-or at least methods are not yet agreed for Actigraph sleep measurement - and are not designed to measure posture so only give proxy measures of sitting/lying and standing.

Given the difficulties with measuring the behaviours, and since the activPAL was chosen for the thesis studies, this left only a small number of comparisons with recommendations, which were possible at the present moment. First, sleep duration recommendations are available for school-age children and for pre-school children which are evidence based on CSEP 2016 and so activPAL measures of sleep were compared against these recommendations. These sleep recommendations were as follows: 10- 13 h per night in children aged 3-4 years, and 9- 11 h per night in children aged 5-13 years, with consistent bed and wake-up times (131, 132).

Second, while the activPAL cannot measure MVPA in school-age children at the moment, it can provide an accurate measure of step count (294) and step counting is being used as a convenient proxy for total volume of the physical activity in school-age children in many studies (86, 338). Recommended step count equivalents which are age-specific and which are equivalent to total volume of the physical activity have been suggested (86, 339), though these are not currently 'evidence based' i.e. not based on systematic review and evidence appraisal, but have effectively come from expert opinion. Number of steps per day and time were therefore compared against the appropriate age-specific recommendations: for steps per day 10,000- 14,000 steps/day in children aged 4-6 years, 13,000- 15,000 steps per day in boys and 11,000- 12,000 steps per day in girls aged 6-11 years old to achieve an average of 60 minutes per day of total physical activity volume (86).

2.3.3.3. Characterising of Sleep Quantity and Quality Study

Based on previous research that used the accelerometer to quantify the sleep in healthy children (326-328), we defined a valid night as having at least 160 minutes of sleep,

and participants had to have accumulated at least 3 valid nights, including 1 weekend night (Friday night and or Saturday night) (326, 328), to be included in this study. The nocturnal sleep-period time was defined as the duration accruing between sleep onset and offset time. In this study, sleep offset represent the time of transition in the morning to sustained upright activity, a point that was clearly evident in the data sets. Between these 2 time points, however, there were consecutive sequences of sleep and frequently minutes of movement, suggesting repositioning, restlessness, wakefulness, or short breaks for visits to bathroom, to get drink etc. during the night. Thus our definition of "sleep-period times" reflects the time of sleep onset to the end of sleep "sleep offset" including all sleep epochs and wakefulness after onset (332).

Sleeping time for each participant was determined by manual inspection of the event file and was identified as the last transition from standing to sitting/lying in the day to the first transition from sitting/lying to sustained standing in the next day as described by Alghaeed et al (286, 331). Thus, the sleeping time represented the longest sit/lie interval between two valid days and the mean number and duration of breaks (Up transition) during the sleeping time represented the quality of sleep, as shown in Figures 2.9 and 2.10 A-D to show our steps to determine all sleep quantity and quality variables.

Definitions of Sleep Behaviour Variables

As noted above, in our study the nocturnal sleep quantity and quality variables were identified by manual examination the event output file of HSC PAL analysis software version 2.14, these variables were defined as follows:

2.3.3.3.1. Nocturnal Sleep Quantity Variables

The nocturnal sleep quantity for each participant in this study was characterised as 1. sleep onset, 2. sleep offset, and 3. sleeping time (Duration h per 24h period).

Sleep Onset

Sleep onset is the clock time− identified manually by the researcher from the event output file of HSC PAL analysis software version 2.14 as the last transition from standing to sitting/lying (331) as shown in Figures 2.8, 2.9 and 2.10. For each participant, after we identified the time of sleep onset each night this was averaged as sleep onset time over the number of monitoring nights.

Sleep Offset

Sleep offset is the clock time - identified manually by the researcher from the event output file of HSC PAL analysis software version 2.14 as first transition from sitting/lying to standing in the morning of the next day, as shown in Figures 2.8, 2.9 and 2.10. For each participant, after we identified the time of sleep offset per night this was averaged as sleep offset time over the number of monitoring nights.

Sleeping Time (hours per 24h Period)

As noted above (in sleep behaviour section 2.3.3.1.4), sleeping time “sleep duration” defined as the sleep period time (i.e. the duration (h) from sleep onset to sleep offset). Sleeping time could be register as single or multiple sleep periods interrupted by posture changes, standing and stepping as explained in Figures 2.8, 2.9 and 2.10.

2.3.3.3.2. Nocturnal Sleep Quality Variables

The nocturnal sleep quality for each participant in this study was characterised as 1. Number of sleep episodes per night, 2. number of wake episodes per night, 3. duration of wake episode, 4. duration of sleep episode movements, and 5. total sleep disrupted.

Number of Sleep Episodes per Night

The number of sleep episodes per night was defined as a number of an occurrence of continuity of sleep episode including wake minutes that were less than 20 minutes and or < 20 steps during sleeping time (326, 328), as show in Figures 2.8, 2.9 and 2.10. While, when the wake minutes were ≥ 20 minutes and or ≥ 20 steps during sleeping time; the sleeping time in this case would be consist from 2 sleep episodes as show Figures 2.8, 2.9 and 2.10. For each participant, from the event output file of HSC PAL analysis software version 2.14 were identified the number of sleep episodes per night, then averaged as number of sleep episodes over the number of monitoring nights.

Number of Wake Episode per Night

The number of wake episodes per night in this study was defined as a number of occurrences of ≥20 consecutive wake minutes and or ≥20 steps preceded and followed by a sleep episode during sleeping time (326, 328), as show in Figures 2.8, 2.9 and 2.10. For each participant, the number of wake episodes were identified from the event file of HSC PAL analysis software version 2.14 for each night, and was then averaged as number of wake episodes over the number of monitoring nights.

Duration of Wake Episodes (Minutes per Night)

Duration of wake episodes defined as total minutes per night spent during an occurrence of ≥20 consecutive wake minutes and or ≥20 steps during nocturnal sleeping time (326,

328). Duration of wake episode (i.e. time spent in wake episode) during sleep time was calculated from the output event file of HSC PAL analysis software version 2.4. The total time recorded as ‘‘walk/stepping” with ≥ 20 steps’’ and /or total time recorded as “standing” with ≥ 20 consecutive standing minutes in output event file of HSC PAL analysis software during asleep hours per night was then calculated as shown in Figures 2.8, 2.9 and 2.10. All time spent in wake episodes were summed in minutes per night and was then averaged as duration of wake episode over the number of monitoring nights.

Duration of Sleep Episode Movements (Minutes per Night)

Duration of sleep episode movements (minutes per night) defined as duration of time that spent during an occurrence of < 20 consecutive wake minutes or < 20 steps during sleep episode (326, 328). Duration of sleep episode movements during sleep time was calculated from the event file of HSC PAL analysis software version 2.4. The total time recorded as ‘‘walk/stepping” with < 20 steps per minutes and /or as “standing” with < 20 consecutive standing minutes during asleep hours was then calculated. For each participant, all time spent in sleep episode movements of participant were summed in minutes per night and then averaged as the duration of sleep episode movements per monitoring night.

Total Sleep Disrupted (Minutes per Night)

Total sleep disrupted was defined as the summed duration of wake episodes during sleep time in minutes per night and then averaged as the duration of total sleep disrupted per monitoring night (326, 328).

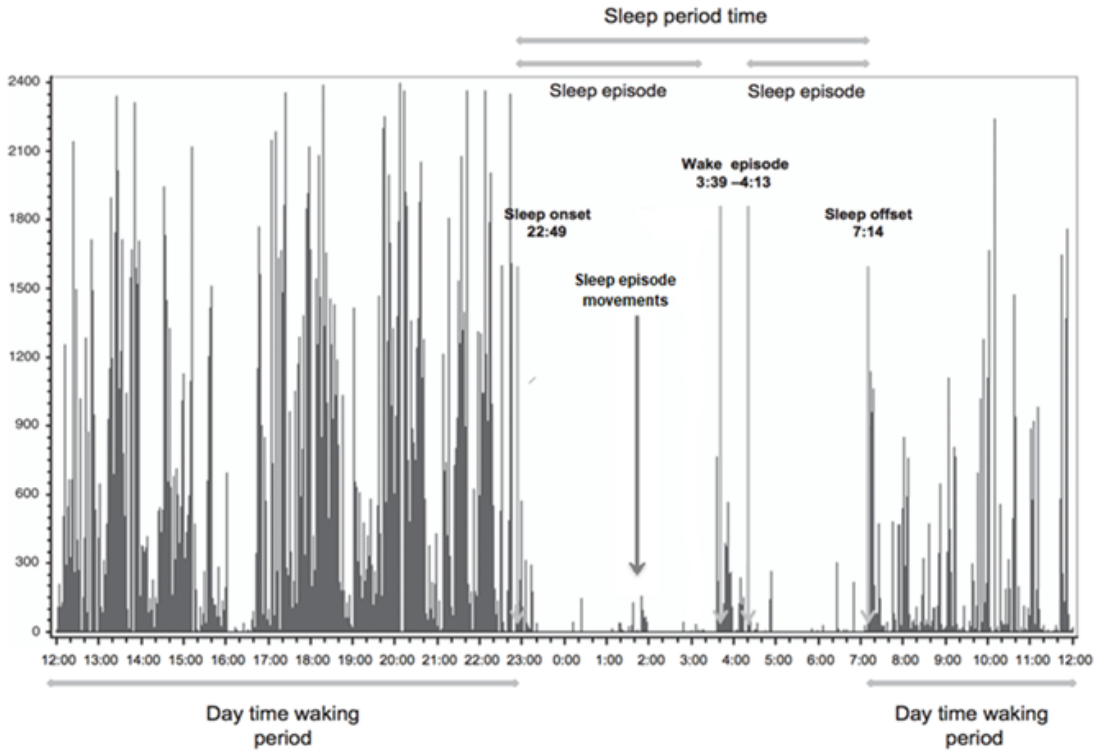


Figure 2.9: 24-h free-living worn accelerometer nocturnal sleep-related variables using one night's data drawn from a single US child participating in ISCOLE, adapted from Tudor-Locke et al. (326).

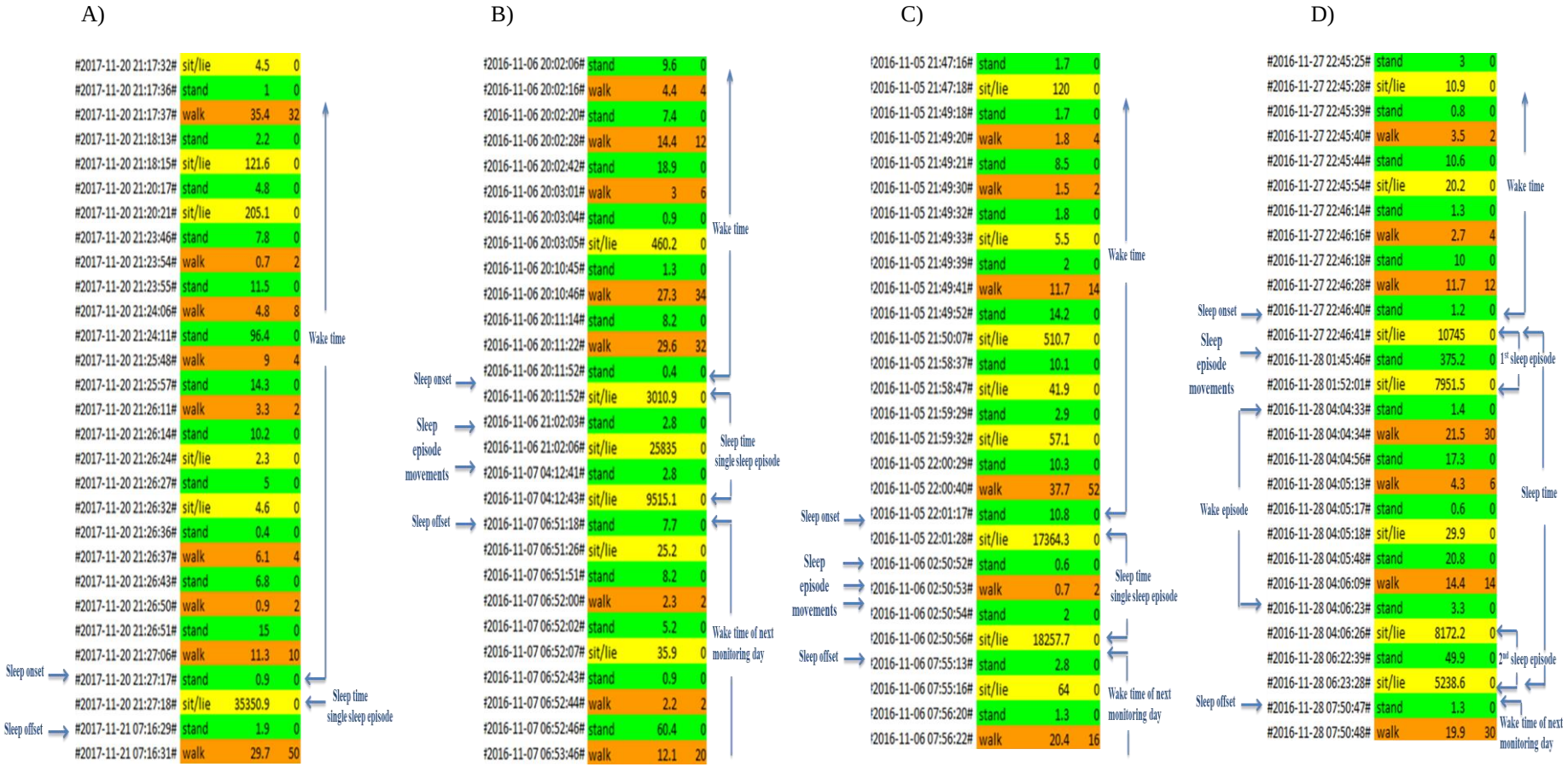


Figure 2.10: Example of event file produced by HSC PAL analysis software v 2.14 file for one of participants show sleep quantity and quality variables.

2.4. Ethics Statement

The study was approved by West of Scotland Research Ethics Committee 1 (Reference number 16/WS/0126) and NHS Greater Glasgow and Clyde Health Board. Parents of all participants provided informed written consent, and their children provided their informed assent -if applicable based on their age- to participate in the study prior to collection of any study data.

2.5. Statistical Analysis

In this study, the analysis was conducted using the IBM SPSS statistical software version 22 and Microsoft Office Excel 2010. Graphs were prepared using Graph Pad Prism version 6.00 software (San Diego, California, US). All study variables were screened for normality, and normally distributed data summarised as Mean (SD) while Median (interquartile range) were used for data not normally distributed. Since children with chronic disease were matched pairwise with healthy controls (for age, sex, and time of year) paired t-tests were used for the primary analysis which examined the significance of any differences between children with each particular illness vs their healthy controls for each of the 24-hour movement behaviours and in sleep quality variables. As a secondary, analysis we also compared the results in all children with chronic disease as a group with all healthy controls as a group using a paired t-test. Statistical significance was set at a cut-off value of ≤ 0.05.

2.6. General Results of Primary Data Collection Studies

This section illustrated details of descriptive results of primary data collection studies that included results of recrutment proceses, characteristics of the participants and accelerometer results for children with chronic disease and their healthy controls that were used in both studies of next two chpaters (Chapter V and VI)

2.6.1. Recruitment Process

Of 136 potentially eligible children identified from outpatient clinics with chronic disease a total of 99 (73%) agreed to take part. Of 111 potential healthy control children eligible based on a match for age and sex 89 (80%) agreed to take part. A total of 188 children (n=99 children with chronic disease and n=89 healthy controls) aged 3–10 years were recruited to participate in the study after their parent had given informed consent and the child had given assent, if appropriate.

28 children (n=19 children with chronic disease and n=9 healthy controls) were omitted from our study because of a number of reasons; six of the parents returned the monitor after 24 hours stating that the child was unhappy to continue wearing the monitor and asked their parents to remove it; three children were eliminated from the study because of loss of the monitor at their school. Another one of the monitors was accidently not removed when the child showered and suffered permanent water damaged. Additionally, twelve of the children were dropped from the study because they did not wear the monitor for the period of time that was considered adequate (≥ 4 days with ≥ 10 hours of waking wear time in a 24-hour period and with ≥ 3 valid nights (i.e. valid night having total sleep duration ≥ 160 minutes per night) including one weekend night – Friday or Saturday night). Lastly, six of the children were excluded from the study

due to loss of contact with their family to collect the monitor from them. Thus, a total of 160 children met all the inclusion criteria and successfully wore the monitors for the required time. Further details of recruitment process are illustrated in Figure 2.11.

2.6.2. Characteristics of the Participants

Descriptive data including age, sex, weight, weight Z-score, height, height Z-score, BMI, BMI Z-score, BMI category and disease duration are summarised in Table 2.1.

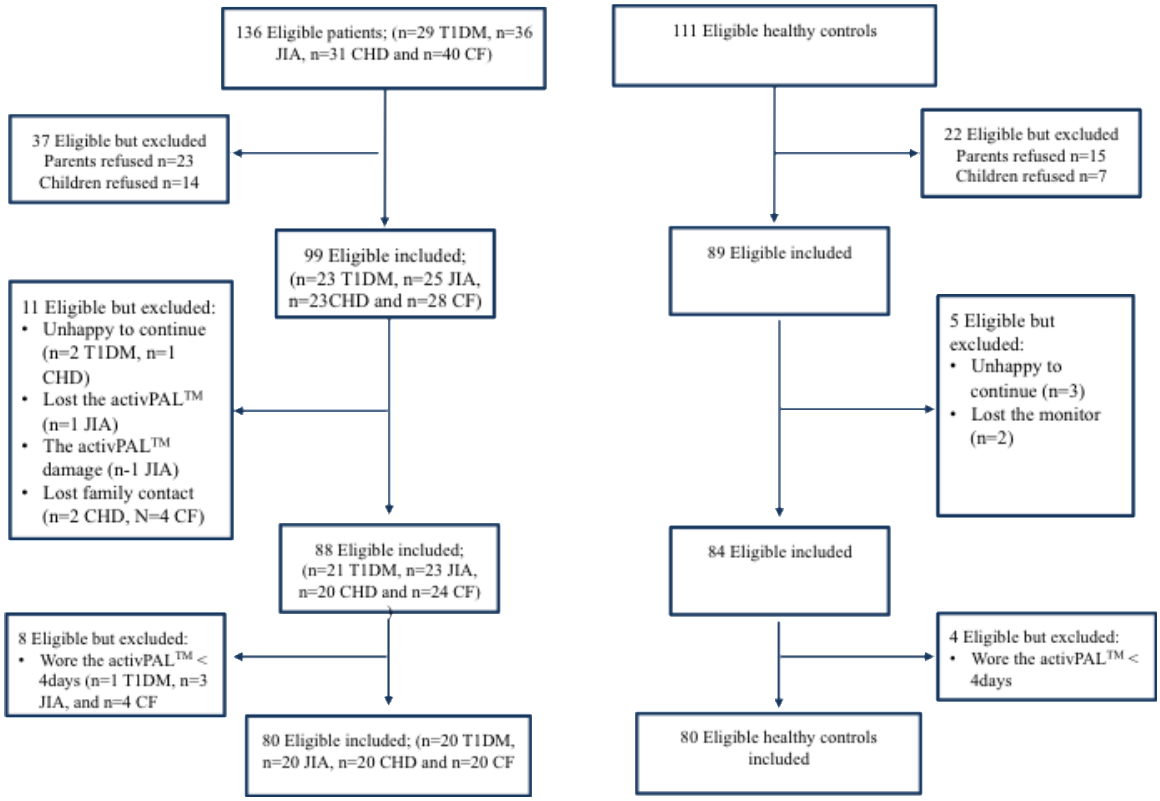


Figure 2.11Flow diagram of study recruitment.
CHD, congenital heart disease; CF, cystic fibrosis; T1DM, type1diabetes mellitus; JIA, juvenile idiopathic arthritis.

2.6.2.1. Children with T1DM and their Healthy controls

Twenty children with T1DM (diagnosis of T1DM was made based on WHO criteria described in the introduction) were recruited with a mean age 7.4 years (SD=1.9) while

in the matched healthy controls (n=20) the mean age was 7.3 (SD=1.8). There were 11 boys and 9 girls in each group. The mean BMI Z-score in children with T1DM was 0.3 (SD=1.2). Seventeen (85%) children with T1DM were classified as healthy weight according to BMI Z-score; two (10%) were classified as overweight and one (5%) as obese. In their healthy matched controls, the BMI Z-score in was 0.9 (SD= 1); sixteen (80%) children were classified as healthy weight according to BMI Z-score; two (10%) were classified as overweight and two children (10%) as obese.

The mean level of HbA1c in children with T1DM was 48.1 mmol/mol (SD=8.2 mmol/mol) (range of measurements 38-61mmol/mol). Based on the revised 2015 NICE recommendation of HbA1c ≤ 48 mmol/mol (340), twelve (60%) of children with T1DM were considered to have good glycaemic control and eight (40%) children had poor glycaemic control at the time of recruitment (175). Multiple daily injections using an insulin pen were the predominant method of insulin delivery (65%). The mean diabetes duration in those children was 2.1 years (SD =1.4 years), with a range (1-6 years). Further details of children with T1DM are in Table 2.2.

2.6.2.2. Children with JIA and their Healthy controls

There were twenty children with JIA (The diagnosis of JIA was made based on classification criteria described in the introduction) with a mean age 6.7 years (SD=2.1) compared with 6.7 years (SD= 2.1) in the matched healthy controls (n= 20). There were 8 boys and 12 girls in each group. The mean BMI Z-score in children with JIA was 0.1 (SD=1). Seventeen (85%) children with JIA were classified as healthy weight according to BMI Z-score; one (5%) was classified as overweight and two (10%) as obese. In their healthy controls, the mean BMI Z-score was 0.6 (SD=1.4); fourteen

(70%) children were classified as healthy weight according to BMI Z-score; five (25%) were classified as overweight and one child (5%) as obese as in Table 2.3.

The children diagnosed with JIA recruited to this project were RF positive with mean disease duration of 3.2 years (SD=2.0) from diagnosis to the time of enrolment. Nine had polyarticular arthritis, eight oligoarticular arthritis, two psoriatic arthritis, and one patient another other arthritis subtype. Nine (45%) of the children with JIA were considered in remission at the time of study. All JIA participants had received biologic therapies, although at the time of recruitment four out of the twenty of children with JIA were off such treatments. We also collected a number of clinical variables about their joint disease activity including number of tender joint, number of swollen joint and other clinical variable to identify the disease severity, as well as laboratory parameters such as ESR, CRP and treatment. All these data are presented in Table 2.4.

2.6.2.3. Children with CHD and their Healthy controls

Twenty children with CHD (all post-surgery) (mean age 6.0 years (SD=2.2)) and 20 matched healthy children (mean age 6.1years (SD = 2.1)) were studied. The mean BMI Z-score in children with CHD was 0.5 (SD = 1). Sixteen (80%) children with CHD were classified as healthy weight according to BMI Z-score; three (15%) were classified as overweight and one (5%) as obese. In their healthy controls, BMI Z-score in was 0.8 (SD = 1.1). Seventeen (85%) children were classified as healthy weight according to BMI Z-score; and three (15%) were classified as overweight.

In children with CHD, the mean time from the last surgical procedure at the time of enrolment was 3.5 years (SD=2.2). Although all children had had surgery for CHD, nine patients were classified as having mild CHD, eight with moderate CHD and three patients with severe CHD, 55% of children had to had moderate-severe CHD, and 40%

of children with CHD were on medical treatment at the time of enrolment. Further details are presented in Table 2.5 and 2.6.

2.6.2.4. Children with JIA and their Healthy controls

Twenty children with CF had mean age 6.7 years (SD = 2.0) compared with mean age of 6.9years (SD = 1.9) in the 20 matched controls. Girls were slightly over represented (12:8 F: M) in this group. The mean BMI Z-score in children with CF was 0.2 (SD= 2.7). Fourteen (70%) children with CF were classified as healthy weight according to BMI Z-score; three (15%) were classified as overweight and three (15%) as obese. In their healthy controls BMI Z-score was 0.2 (SD=7); nineteen (95%) children were classified as healthy weight and only one (5%) was classified as overweight. All children with CF on treatment at the time of enrolment, and had been identified by neonatal screening with a mean time from diagnosis at the time of study of 6.5 years (SD=2.0) years. Further details are presented in the Table 2.7.

2.6.2.5. All Children with Chronic Disease (n=80) Compared with Healthy controls (n=80)

Eighty children with chronic disease were recruited with a mean age 6.9 years (SD=2.0) while in the matched healthy controls (n=80) the mean age was 6.8 (SD=1.9). There were 37 boys and 43 girls in each group. The mean BMI Z-score in children with chronic disease was 0.3 (SD=1.5). Sixty-four (80%) children with chronic disease were classified as healthy weight according to BMI Z-score; nine (11%) were classified as overweight and seven (9%) as obese. In their healthy matched controls, the BMI Z-score in was 0.6 (SD= 0.8); sixty- six (82%) children were classified as healthy weight according to BMI Z-score; eleven (14%) were classified as overweight and three children (4%) as obese.

Table 2.1: Characteristics of children with chronic disease and healthy controls. Data are presented as means and (SD)

Characteristics	T1DM (n= 20)	HC (n= 20)	JIA (n= 20)	HC (n= 20)	CHD (n= 20)	HC (n= 20)	CF (n= 20)	HC (n= 20)	CD (n=80)	HC (n=80)
Age years	7.4 (1.9)	7.3 (1.8)	6.7 (2.1)	6.7 (2.1)	6.0 (2.2)	6.1 (2.1)	6.7 (2.0)	6.9 (1.9)	6.9 (2.0)	6.8 (1.9)
Sex F:M	9: 11	9: 11	12: 8	12: 8	10: 10	10: 10	12: 8	12: 8	43: 37	43: 37
Weight kg	25.6 (6.3)	28.7 (8.3)	23.4 (6.0)	25.7 (6.4)	24.0 (8.5)	25.1 (5.3)	24.8 (6.5)	22.6 (6.2)	24.4 (6.8)	25.5 (6.5)
Weight-Z-score	0.1 (1.0)	0.8 (1.4)	0.2 (1.2)	1.1 (1.2)	0.6 (1.0)	1.4 (0.9)	0.4 (2.1)	- 0.1 (0.7)	0.3 (1.3)	0.8 (0.7)
Height cm	122.6 (12.8)	125.4 (13.2)	119.6 (13.7)	123.2 (10.0)	117.1 (15.6)	118.7 (15.3)	119.7 (12.5)	117.0 (12.8)	119.7 (13.6)	121.1 (12.8)
Height-Z-score	-0.1 (1.1)	0.4 (1.8)	0.2 (1.9)	1.2 (1.0)	0.4 (1.1)	0.5 (1.0)	0.2 (2.0)	- 0.4 (0.8)	0.7 (1.0)	0.5 (0.8)
BMI kg/m2	16.6 (2.2)	17.8 (2.5)	16.2 (1.9)	17.3 (2.5)	17.0 (2.2)	17.2 (1.2)	17.3 (3.9)	16.2 (1.6)	16.8 (2.6)	17.1 (2.0)
BMI Z-score[1]	0.3 (1.2)	0.9 (1.0)	0.1 (1.1)	0.6 (1.4)	0.5 (1.0)	0.8 (1.1)	0.2 (2.7)	0.2 (0.8)	0.3 (1.5)	0.6 (0.8)
BMI category[2] **Normal weight n (%)** **Overweight n (%)** **Obese n (%)**	 17 (85%) 2 (10%) 1 (5%)	 16 (80%) 2 (10%) 2 (10%)	 17 (85%) 1 (5%) 2 (10%)	 14 (70%) 5 (25%) 1 (5%)	 16 (80%) 3 (15%) 1 (5%)	 17 (85%) 3 (15%) 0 (0%)	 14 (70%) 3 (15%) 3 (15%)	 19 (95%) 1(5%) 0 (0%)	 64 (80%) 9 (11%) 7 (9%)	 66 (82%) 11 (14%) 3 (4%)
Disease duration Years	2.12 (1.4)	-	3.2 (2.0)	-	3.5 (2.20)	-	6.5 (2.0)	-	3.8 (1.9)	-

BMI – body mass index; CHD – congenital heart disease; CF – cystic fibrosis – JIA, juvenile idiopathic arthritis, T1DM – type1 diabetes mellitus.
Data are presented as means and standard deviation SD unless otherwise specified.
[1]Based on World Health Organization Growth Reference data from 2007 (302).
[2]Based on age- and gender-specific cut-offs defined body mass index at 18.5, 25 and 30 kg/m^2 at age 18 years (298, 299).

Table 2.2: Characteristics of children with T1DM

Participants	Age (yr)	Gender	Height (cm)	Weight (kg)	BMI	BMI Z-score	HbA_{1c}	Duration	Treatment
T1DM01	7.2	F	122	28.1	15.52	-0.12	38	1.00	Insulin pen
T1DM02	8.6	M	124	24.2	15.74	-0.11	61	2.2	Insulin pen
T1DM03	6.3	F	117	23.6	17.24	0.95	60	1.2	Insulin pen
T1DM04	9.4	M	139	36.1	18.68	1.19	53	1.2	Insulin pen
T1DM05	5.8	M	121	23	15.71	0.16	56	1.7	Insulin pen
T1DM06	8.6	F	118	20.3	14.58	-0.96	59	3.2	Insulin pen
T1DM07	6.8	M	121	21.8	14.89	-0.50	48	4.3	Insulin pump therapy
T1DM08	4.3	F	103.8	17.8	15.99	0.28	37	1.0	Insulin pen
T1DM09	9.3	F	141	31.3	15.74	-0.41	53	1.4	Insulin pen
T1DM10	6.3	F	115	24.1	18.22	1.40	48	4.2	Insulin pump therapy
T1DM11	7.2	F	124	18.5	12.03	-2.93	50	1.5	Insulin pump therapy
T1DM12	9.9	M	133	28.2	15.94	-0.26	51	6.0	Insulin pump therapy
T1DM13	4.2	M	110.1	20.5	16.91	0.92	47	1.0	Insulin pen
T1DM14	7.3	M	116.8	20.6	15.10	-0.37	43	1.0	Insulin pen
T1DM15	7.7	M	113.2	28.1	21.93	2.64	31	1.0	Insulin pen
T1DM16	9	M	130	35	20.71	1.96	41	1.1	Insulin pump therapy
T1DM17	8.1	F	127	23.4	14.51	-0.92	43	2.8	Insulin pen
T1DM18	8.4	M	135.4	31.1	16.96	0.64	38	1.0	Insulin pen
T1DM19	3.3	F	93.8	15.6	17.73	1.28	47	1.0	Insulin pump therapy
T1DM20	9.9	F	146.8	38.0	17.63	0.351.28	48	3.8	Insulin pump therapy
Summary	7.4 (1.9)	F: M 9:11	122.6 (12.8)	25.6 (6.3)	16.6 (2.2)	0.3 (8.2)	48	2.12 (1.4)	

BMI – body mass index; HbA1c – Haemoglobin A1c ≤ 48 mmol/mol; Duration – Disease duration.
Summary data presented as mean and (SD)

Table 2.3: Characteristics of children with JIA

Participants	Age (yr)	Gender	Height (cm)	Weight (kg)	BMI	BMI Z score	Duration	Treatment
JIA01	5.5	M	116.7	21.4	15.68	0.13	4	Inflix+MTX+Rani
JIA02	9.2	F	131.4	29.4	17.00	0.25	5	Inflix
JIA03	8.5	F	127.1	24.5	15.17	-0.57	6	MTX
JIA04	3.8	M	96.8	19.5	20.81	3.02	2	Etan
JIA05	3.4	F	123.0	22.5	14.87	-0.72	7	Toci
JIA06	5.9	F	116.2	19.3	14.29	-0.84	4.1	Etan
JIA07	4.4	F	101.4	20.0	19.40	2.16	1.9	MTX
JIA08	8.5	M	138.0	31.0	16.28	0.24	3.8	Off treatment
JIA09	6.0	M	119.5	20.5	14.32	-1.01	2	Off treatment,
JIA10	3.8	F	97.5	15.8	16.62	0.64	1.4	MTX
JIA11	6.5	F	114.5	20.1	15.33	-0.14	4.2	Off treatment
JIA12	8.1	F	111.3	18.6	15.01	-0.59	8 MON	MTX
JIA13	8.2	F	128.9	28.5	17.18	0.56	7	MTX
JIA14	9.6	M	129.6	28.4	16.88	0.34	1	Off treatment
JIA15	3	F	97.0	15.2	16.10	0.17	1.4	MTX
JIA16	6.8	F	114.1	20.1	15.44	-0.12	4.9	Humira
JIA17	7.9	M	128.7	24.8	14.97	-0.52	2.9	Off treatment
JIA18	9.5	M	143.6	41.25	20.00	1.64	2.4	Etan
JIA19	7.7	M	129.7	23.5	14.00	-1.32	1	MTX
JIA20	7.8	F	127	24.0	14.88	-0.64	8	MTX
Summary	6.7 (2.1)	F: M 12:8	119.6 (13.7)	23.4 (6.0)	16.2 (1.9)	0.1 (1.1)	3.2 (2.0)	

BMI – body mass index; JIA - juvenile idiopathic arthritis; Etan – Etanerecept; Inflix – Infliximab; MTX- Methotrexate; Rani – Ranitidine.
Summary data presented as mean and (SD)

Table 2.4: Clinical variables of children with JIA

Participants	ESR	CRP	TJ	AJ	LJ	PAGA	PHGA	Subtype JIA	Stage
JIA 01	2	<1	2	0	0	0	0.5	Poly-articular	
JIA 02	2	<1	1	1	0	0.4	1.1	Poly-articular	
JIA 03	2	<1	3	0	0	0.1	1	Poly-articular	Remission
JIA 04	5	<1		0	0	0	0	Oligo-articular	Remission
JIA 05	2	<1	2	0	0	0.5	0.4	Poly-articular	
JIA 06	5	<1	0	0	0	1	0	Oligo-articular	Remission
JIA 07	8	4	1	0	0	0	0	Oligo-articular	
JIA 08	-	<1	0	0	0	0	0	Poly-articular	Remission
JIA 09	-	<1	0	0	0	0	0	Oligoarticular	Remission
JIA 10	70	52	0	0	0	0	2	Psoriatic	
JIA 11		<1	0	0	0	0	0	Oligo-articular	Remission
JIA 12	5	1	5	0	0	2	1	Poly-articular	Quiescent
JIA 13	2	<1	1	0	0	0	0	Oligo-articular	
JIA 14	-	<1	2	0	0	1	0	Oligo-articular	Remission
JIA 15	15	2	2	0	0	0	0	Psoriatic	Remission
JIA 16	5	6		0	0	0	0	Poly-articular	
JIA 17	0	<1	0	0	0	0	0	-	Remission
JIA 18	1	<1	0	0	0	0	0	Poly-articular	
JIA 19	5	<1		0	0	0.2	0	Oligo-articular	
JIA 20	11	<1	5	4	2	3	1	Poly-articular	

AJ – Active joint; CRP – C-reactive protein and the normal CRP is < 0.8mg/dl; Duration – duration of disease (years); ESR – erythrocytes sedimentation rate and the normal ESR is ≥20mm/hr; JIA – juvenile Idiopathic Arthritis; LJ – number of limited joint movement; PAGA – Patient global assessments (PAGA; where 0=best and 10=worst); PHGA – Physician global assessments (PHGA; where 0=best and 10=worst); TJ – number of tender joint. Summary data presented as mean and (SD).

Table 2.5: Characteristics of children with CHD

Participants	Age (yr)	Gender	Height (cm)	Weight (kg)	BMI	BMI Z-score	Diagnosis	No. of surgeries	Time from last surgery	Treatment
CHD 01	8.7	M	137.6	31.0	16.4	0.26	TGA	2	8	Sildenafil
CHD 02	3.1	F	104.0	16.3	15.1	-0.62	TAPVR	1	3	-
CHD 03	9.4	M	136.4	30.0	16.1	-0.03	ASD	1	9	Warfarin,
CHD 04	4.9	F	104.2	18	16.6	0.70	ASD	1	3	-
CHD 05	5.4	F	108	17.6	15.1	-0.25	ASD	1	2.7	-
CHD 06	3.2	M	92.1	13.6	16.0	-0.02	TOF	1	5.6	Aspirin
CHD 07	5.7	F	124.0	26.0	16.9	0.86	VSD	1	5.7	-
CHD 08	7.1	F	129.4	30.0	17.9	1.11	VSD	1	2	-
CHD 09	8.0	M	132.0	31.0	17.8	1.12	TOF	1	3.7	-
CHD 10	3.4	M	101.0	16.5	16.2	0.16	PDA	1	2.7	-
CHD 11	6.7	F	127.0	31.4	19.5	1.81	AVSD	2	2.2	Warfarin
CHD 12	4.8	M	106.0	20.0	17.8	1.56	ASD	1	2	-
CHD 13	3.9	M	104.0	19.6	18.1	1.64	Sinus AVSD	1	7.9	Salbutamol
CHD 14	9.3	F	139	46.0	23.8	2.35	Mitral atresia	2	2.8	-
CHD 15	8.7	F	135.5	35.0	19.1	1.19	HLHS	3	3.6	Warfarin
CHD 16	8.4	F	125	23.8	15.2	-0.52	HLHS	3	2	Warfarin
CHD 17	4.4	M	102.0	18.9	18.2	1.75	TOF	3	3.9	Aspirin
CHD 18	6.7	M	130.0	26	15.4	-0.11	ASD	1	1	-
CHD 19	4.3	F	102.9	15.0	14.2	-1.14	ASD	1	1.1	-
CHD 20	4	M	101.4	15.1	14.7	-0.95	TOF	3	2.0	-
Summary	6.0 (2.2)	F: M 10:10	117.1 (15.6)	24.0 (8.5)	17.0 (2.2)	0.5 (1.0)	-	-	3.5 (2.2)	-

ASD – atrial septal defect; AVSD – atrioventricular septal defect; HLHS – hypo-plastic left heart syndrome; TAPVR– total anomalous pulmonary venous return; TGA – transposition of the great arteries; TOF – tetralogy of fallot; VSD – ventricular septal defect.
Summary data presented as mean and (SD).

Table 2.6: Distribution and classification of cardiac diagnosis in children with CHD (n=20)

Cardiac Diagnosis	Type of CHD	Number of patients	Total umber (%)
Mild CHD			9 (45%)
	Ventricular septal defect	2	
	Atrial septal defect	6	
	Small patent ductus arteriosus	1	
Moderate			8 (40%)
	Tetralogy of fallot	4	
	Mitral atresia	1	
	Total anomalous pulmonary venous return	1	
	Atrioventricular septal defect	2	
Severe			3 (15%)
	Transposition of the great arteries	1	
	Hypoplastic left heart syndrome	2	

Congenital heart disease severity was categorised in accordance with consensus guidelines (238).

Table 2.7: Characteristics of children with CF

Participants	Age (yr)	Gender	Height (cm)	Weight (kg)	BMI	BMI Z-score	FEV_1 % Predicted	Treatment
CF 01	8.5	F	132.20	28.50	16.31	0.06	96	Fluc, Creon
CF 02	4.4	M	103.00	18.00	16.97	0.99	99	Fluc, Creon Mucoclear, Flixonase
CF 03	9.2	F	138.40	36.00	18.79	0.98	111	Fluc, Creon Cetirizine, Azith
CF 04	5.6	M	115.20	22.10	16.65	0.83	96	Benz Fluc
CF 05	5.0	M	111.90	18.20	14.53	-0.90	60	Fluc, Creon
CF 06	5.4	M	113.00	21.20	16.60	0.80	79	-
CF 07	5.2	F	111.60	19.20	15.42	-0.03	103	Fluc, Creon
CF 08	9.7	M	112.00	18.60	14.83	-0.96	98	Fluc, Creon
CF 09	9.0	F	134.00	28.25	15.73	-0.35	95	Fluc
CF 10	8.4	F	129.7	28.4	16.88	0.37	83	Fluc, Creon Azith
CF 11	3.8	F	101.0	18.4	18.04	1.49	99	Fluc, Movicol Cetirizine
CF 12	9.1	M	93.8	15.60	16.74	-0.41	98	Benz, Creon
CF 13	5.9	F	112.50	25.90	20.46	2.35	96	
CF 14	7.9	F	131.70	30.05	17.32	0.68	99	Dornase nebulised
CF 15	8.0	F	132.20	29.30	16.77	0.39	99	Creon, Fluc Sytron, Fultium
CF 16	7.8	F	127.00	30.00	18.60	1.23	103	Creon, Fluc Ivacaftor, Fultium
CF 17	6.7	M	118.40	33.80	24.11	3.51	104	Creon, Fluc
CF 18	4.3	M	106.00	18.75	16.69	0.78	97	Fluc, Creon
CF 19	3.0	F	97.0	15.2	16.10	0.16	99	Fluc, Creon
CF 20	6.7	F	114.1	20.1	15.44	-0.10	96	Creon
Summary	6.7 (2.0)	F: M 12: 8	119.7 (12.5)	24.8 (6.5)	17.3 (3.9)	0.2 (2.7)	95 (11)	

Azith – Azithromycin; Benz- Benzylpenicillin; BMI - body mass index; CF – cystic fibrosis; Fluc – Flucloxacillin; Summary data presented as mean and (SD).

2.6.3. Accelerometer Results

To be included in our analysis, participants had to have ≥ 4 days with ≥ 10 hours of waking accelerometer wear time in a 24-hour period including one weekend day. They also were required to have ≥ 3 valid nights (i.e. valid night having total sleep accelerometer monitoring duration ≥ 160 minutes per night) including one weekend night – Friday or Saturday night, as clarified in above in Section 2.3.3.

A total of 160 participants (n = 80 in children with chronic disease (20 per group) and n = 80 in healthy controls groups) met the accelerometer inclusion criteria and provided data that were deemed suitable to include in our study. Indeed, across all groups the number of monitoring days and nights was ≥ 6.6 days and ≥ 6 nights of data. For each group the monitored waking hours per 24 h period was as follows:

- In children with T1DM a mean of 13.2 h (SD 0.7) h per 24 h compared with 13.6 h (SD 0.6) h per 24 h in their healthy peers.
- In children with JIA 13 h (SD 0.7) h per 24 h period and 13.9 h (SD 0.9) h per 24 h in their healthy peers.
- In children with CHD a mean of 13.2 h (SD 1) h per 24 h and 13.5 h (SD 0.6) h per 24 h in their healthy peers.
- In children with CF mean of 13.5 h (SD 0.7) h per 24 h and 13.4 h (SD 0.4) h per 24 h in their healthy peers, as summarised in Table 2.8.

Overall, for both patients and controls the percentage of non-wear time per 24h period was very low (see above in section 2.3.4 for details of how non-wear time was calculated). For each group the mean (SD) non-wear time per 24h period was as follows

- children with T1DM and their healthy peers respectively 1.3% (SD 1.0) and 0.3 % (SD 0.6); in children with JIA and their healthy peers 1.1% (SD 1) and 0.9 % (SD 0.7); in children with CHD and their healthy peers 1.2 % (SD 1.4) and 0.5 % (SD 0.4); and in children with CF and their healthy peers 0.7 % (SD 0.6) and 0.6 % (SD 0.6). As we found that the non-wear time was only around 1% of total wear time per 24-hours period across all groups, we ignored it and analysed the recorded accelerometer data per 24h period.

Sleep period time for each participant was determined by manual inspection of the event file and was timed from the last transition from standing to sitting/lying in the day until the first transition from sitting/lying to standing in the next day. The monitoring day was defined as the first transition from sitting/lying to standing as the start of monitoring time of the day until the first transition from sitting/lying to standing of the next day (described in detail in Chapter II above) that made some ‘days’ very slightly more or less than 24h which depended on the exact sleep offset time for each participant. Thus, we noted that the average missed/unaccounted time for each group was as follows – children with T1DM and their healthy controls an average of 16 and 31 minutes per 24h; children with JIA and their healthy peers 21 and 12 minutes per 24h; children with CHD and healthy peers 14 and 37 minutes per 24h; and children with CF and their healthy controls 45 and 34 minutes per 24h.

Table 2.8:Accelerometer results based on 24-hour accelerometer data in children with chronic disease and healthy controls

Variables	T1DM (n =20)	HC (n =20)	JIA (n =20)	HC (n =20)	CHD (n =20)	HC (n =20)	CF (n =20)	HC (n =20)
No. of monitoring days	7.4 (0.9)	6.8 (0.9)	6.8 (1.0)	7.1 (0.7)	7.4 (0.8)	7.0 (0.9)	6.6 (1.4)	6.9 (0.6)
No. of monitoring nights	6.9 (0.4)	6.6 (0.7)	6.7 (0.7)	7.0 (0.6)	7.1 (0.9)	6.0 (0.9)	6.5 (1.5)	7.1 (0.5)
Monitoring time during waking hours/day	13.2 (0.7)	13.6 (0.6)	13.0 (0.7)	13.9 (0.7)	13.2 (1.0)	13.5 (0.6)	13.5 (0.7)	13.4 (0.4)
Non-wear time during waking time minutes/day	20.4 (13.9)	18.1 (10.2)	15.8 (14.8)	12.3 (10.8)	17.7 (20.4)	7.4 (5.9)	9.8 (8.7)	9.9 (8.1)
Non-wear time during sleep time minutes/day	0	0	0	0	0	0	0	0
% of total non-wear time per 24 hours period	1.3 (1.0)	0.3 (0.6)	1.1 (1.0)	0.9 (0.7)	1.2 (1.4)	0.5 (0.4)	0.7 (0.6)	0.6 (0.6)

BMI – body mass index; CHD – congenital heart disease; CF – cystic fibrosis; JIA – juvenile idiopathic arthritis; T1DM – type1 diabetes mellitus.
Data are presented as means and standard deviation SD unless otherwise specified.

CHAPTER III

Accelerometer Measured Levels of Moderate-to-Vigorous Intensity Physical Activity and Sedentary Time in Children and Adolescents with Chronic Disease: a Systematic Review and Meta-Analysis

This chapter has been printed exactly in its published format (291). Available at: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0179429

3.1. Introduction and Aim

Children and adolescents with low levels of PA are at increased risk of becoming inactive adults, and of diseases that result from inadequate activity (79, 341). In addition to low PA, there is increasing concern that high levels of ST may also be common, and both low PA and high ST are important risk factors for chronic disease (97, 342).

The MVPA recommendations was based on large bodies of generally strong and consistent evidence, and that this evidence has been summarised in several systematic and narrative reviews that a minimum of 60 minutes of MVPA every day for school-age children and adolescents (20, 39, 281). The main argument that a level of MVPA below recommendations is a concern is not supported by the evidence available and hence the recommendations do appear to be robust. These recommendations for the general population are usually also considered to be applicable to children and adolescents with chronic disease (30, 87, 280), with an understanding that usual levels of MVPA might be lower in such sub-groups, and achievement of the MVPA recommendation would be a slower and more gradual process than in the healthy population (30, 343-345).

Objective techniques such as accelerometry currently represent the most accurate methods for measuring the amount and intensity of PA and amount of ST (154, 346). While there have been many studies on the levels and adequacy of MVPA and ST in healthy children and adolescents (347-350), there are surprisingly few such studies in children and adolescents with chronic disease. In fact, numerous previous studies and national PA surveillance programs have actually excluded children and adolescents with chronic disease.

The primary aim of the present study was therefore to examine whether children and adolescents with chronic disease meet the current MVPA recommendation (79, 80, 281). Secondary aims were to examine the amount of accelerometer-measured ST in children and adolescents with chronic diseases, and to determine whether accelerometer measured MVPA and ST in children and adolescents with chronic disease were different from those in healthy control or comparison groups. This systematic review provides evidence on whether levels of MVPA are adequate and ST excessive in children and adolescents with chronic disease.

3.2. Materials and Methods

3.2.1. Review Governance and Registration

A systematic review of the literature was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (285). The review protocol was registered on PROSPERO (registration number CRD42015016783), the international prospective register for systematic reviews (http://www.crd.york.ac.uk/ NIHR_PROSPERO) and available in Appendix I.

3.2.2. Study Eligibility

3.2.2.1. Inclusion Criteria

To be eligible for inclusion in the review, papers had to meet all of the following criteria as per PICOS principles: **P**opulation (children and adolescents aged from 0–19 years); **I**ntervention or exposure: chronic childhood disease (chronic disease defined as any

physical health problem that lasts three months or more). The chronic diseases included were decided on following a scoping review and were cardiovascular disease, respiratory disease, diabetes type 1 or type 2, and malignancies); **C**omparison (where applicable): healthy children matched for relevant criteria (in particular age, gender); **O**utcome (accelerometer measured MVPA and/or ST of at least 3 days and 6 hours/day). All **s**tudy designs were considered eligible (cross-sectional, longitudinal, case-control studies and intervention studies if pre- intervention data could be extracted). We looked for original research studies, published in English, in peer-reviewed journals; a detailed description of the study eligibility criteria is available in Appendix I.

3.2.2.2. Exclusion Criteria

Studies that included participants with co-morbid acute or chronic medical diseases or conditions that may have impacted their PA were excluded. The present study aimed to examine the subtle impact of chronic disease on MVPA and ST, not the more obvious impacts from co-morbidities that preclude PA (e.g. arising from injury or acute illness requiring bed rest, and chronic physical limitations from e.g. cerebral palsy). Because of the ongoing debate about whether obesity is a disease, studies in children with obesity were also excluded and are the subject of a separate report.

Since the aim of the review was to examine habitual levels of MVPA and ST, studies that measured these variables for less than 6 hours per day or over two days or less were excluded. Recommendations currently exist for habitual (overall) MVPA rather than MVPA during specific domains (e.g. the after-school period) and so studies that

focused only on specific periods of the day (e.g. school activity only, or outdoor activity only, or weekend or weekday activity only, or after-school only) were also excluded.

3.2.3. Search Strategy

The literature search was conducted using the five most relevant electronic databases: MEDLINE OVID; Cochrane library; EMBASE; SPORTSDiscus and CINAHL. We searched from the year 2000 (to increase generalisability, since levels of MVPA and/or ST might be different now than in the past, and because accelerometery became more widely used in research from the early 2000's) up to March 2017. The literature search strategy used in MEDLINE is given in Table 3.1 and was adapted as required for the other four data- bases. Full literature search details are available in Appendix I. The electronic search was complemented by reference tracking (forward and backward) of the eligible studies.

3.2.4. Study Selection

Titles, abstracts, and full-text articles were screened in duplicate for eligibility and disagreements were resolved through discussions with other reviewers when required. Reference lists of eligible studies were examined for potentially eligible studies. Reasons for exclusion are summarised in the study flow diagram.

3.2.5. Data Extraction and Data Synthesis

This review used a standard form for extracting relevant information from the eligible studies. The systematic review identified that the eligible studies fell logically into four

categories: cardiovascular disease; respiratory disease; diabetes; malignancy. A fifth category (obesity) was identified but this is reported separately as noted above.

Obesity was not included here because of the on-going debate about whether obesity is a disease or not.

International recommendations for school-age children and adolescents specify at least 60 minutes of MVPA every day (39, 281), but in the eligible studies the achievement of MVPA recommendations was never operationalised in this way. In most studies, only the mean or median daily MVPA was provided (rather than achievement of MVPA recommendations on 7/7 days), and so this was used as a proxy for achievement of guideline recommendations in the present study.

Where suitable data for patients and healthy controls were reported, mean and standard deviation of MVPA and ST in minutes per day, and sample sizes for similar chronic disease conditions were combined in a random effects model accounting for heterogeneity between studies. Given the differing methods of determining MVPA levels obtained from accelerometers, differences in MVPA between patients and controls were generated as weighted standardised mean difference (SMD). While methodology (e.g. accelerometer model, accelerometry cut point and/or epoch) varied substantially between studies, within study comparisons are all based on the same methods. Separate meta-analyses were performed for MVPA and ST. Review Manager 5.2 was used for the quantitative analysis (351) .Some eligible studies recruited healthy control participants and measured MVPA and/or ST in the same way as in their patient group and at the same time (referred to here as studies with controls), while other studies compared patient data with other studies (e.g. published data) and are referred

to here as studies with comparison groups; some studies simply reported patient data in relation to PA recommendations.

Table 3.1: Search strategy used for MEDLINE database

1. exp Child/
2. exp Adolescent/
3. (child* or adolesc* or teen* or youth or girl* or boy*).tw.
4. (young adj1 (person or people)).tw.
5. 1 or 2 or 3 or 4
6. exp Exercise/
7. exp Motor Activity/
8. exp Sports/
9. exercis*.tw.
10. physical* activ*.tw.
11. (active adj2 (living or lifestyle)).tw.
12. sedentary behavi?r.tw.
13. exp Sedentary Lifestyle/
14. ((sedentary or sitting or screen or TV or television or computer or PC or video games) adj2 time).tw.
15. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp Obesity/ or exp Overweight/
17. (overweight or obes*).tw.
18. exp Accelerometry/
19. exp Actigraphy/
20. acceleromet*.tw.
21. actigraph.tw.
22. activity monitor*.tw.
23. (objective adj1 (measure* or monitor* or assess*)).tw.
24. 18 or 19 or 20 or 21 or 22 or 23
25. exp cardiovascular abnormalities/ or exp heart diseases/
26. exp Cardiovascular Abnormalities/
27. exp Heart Diseases/
28. "congenital heart disease".tw.
29. "Atrial Septal Defect".tw.
30. "Complete Atrioventricular Canal Defect ".tw.
31. "Ventricular Septal Defect".tw.
32. (Tetralogy adj2 Fallot).tw.
33. exp Asthma/
34. asthma.tw.
35. exp Respiratory Tract Diseases/
36. exp Respiratory Hypersensitivity/
37. exp Cystic Fibrosis/
38. (respiratory adj2 allerg*).tw.
39. "cystic fibrosis".tw.
40. wheez*.tw.
41. exp Bronchopulmonary Dysplasia/
42. lung diseases/ or exp alpha 1-antitrypsin deficiency/ or exp "cystic adenomatoid malformation of lung, congenital"/ or exp hepatopulmonary syndrome/ or exp hypertension, pulmonary/ or exp lung diseases, fungal/ or exp lung diseases, interstitial/ or exp lung diseases, obstructive/ or exp lung diseases, parasitic/ or exp lung injury/ or exp lung neoplasms/ or exp lung, hyperlucent/
43. "chronic lung disease".tw.
44. "chronic respiratory disease".tw.
45. exp diabetes mellitus, type 1/ or exp diabetes mellitus, type 2/
46. (diabetes adj1 mellitus).tw.

47. exp Leukemia/
48. Leukemia.tw.
49. exp Lymphoma/
50. Lymphoma.tw.
51. exp Neuroblastoma/
52. Neuroblastoma.tw.
53. "Wilms' tumor".tw.
54. exp Central Nervous System Neoplasms/
55. exp Sleep Apnea Syndromes/
56. "sleep apnea".tw.
57. 16 or 17 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58. 5 and 15 and 24 and 57
59. exp Adult/
60. 58 not 59
61. limit 60 to (english language and yr="2000 -Current")

https://doi.org/10.1371/journal.pone.0179429.t001

3.2.6. Quality Assessment

Eligible articles were assessed for methodological quality using a 15-item quality assessment scale as shown in Appendix I, collapsed to 6 items for scoring, with higher scores suggesting higher study quality. Each eligible study assessed independently by two authors (RE, JJR), and disagreements were resolved by discussion. The quality assessment scale was modified from the methodological quality assessment scale of Tooth *et al*. (352). This is a reliable and valid 30-item tool for assessing the quality of observational studies and was considered for use without modification initially. After careful reflection, modifications to the original scale were made to focus quality assessment on issues of particular importance to accelerometry measurement of PA. A modified Tooth tool has been used previously with several recent systemic reviews of PA studies with 8–17 items that were usually collapsed to a smaller number of items for scoring (54, 353-355).

3.3. Results

3.3.1. Identification of Eligible Studies

The PRISMA flow diagram with numbers of included and excluded articles at each step of the review process is provided in Figure 3.1. Table 3.2-3.5 provides a brief summary of all studies included in this systematic review. Of the 1592 identified records from the five databases, 504 were selected for full text screening and of these, 24 met the inclusion criteria. Additionally, 1 study was identified and deemed eligible through searching references of eligible studies, bringing the final total to 25 eligible studies (7 in children with cardiovascular disease; 7 in children with respiratory disease; 8 in children with diabetes; 3 in children with malignancies) and 11 of these 25 studies were suitable for inclusion in meta-analysis (4 in those with respiratory disease; 5 in those with diabetes; 2 in those with malignancies). All eligible studies measured MVPA, and 16 out the 25 eligible studies compared levels of MVPA between patients with chronic disease and a healthy control group (referred to here as studies with controls), while the other 7 eligible studies compared data from patients with data from previously published studies of healthy children and adolescents (referred to here as studies with comparison groups); and two studies simply reported patient data in relation to recommendations; 14 of the 25 studies also provided data on ST, and 10 of these 14 studies compared ST in those with chronic disease with a healthy control group, while another 4 eligible studies compared data from patients with data from previously published studies of healthy children and adolescents comparison groups.

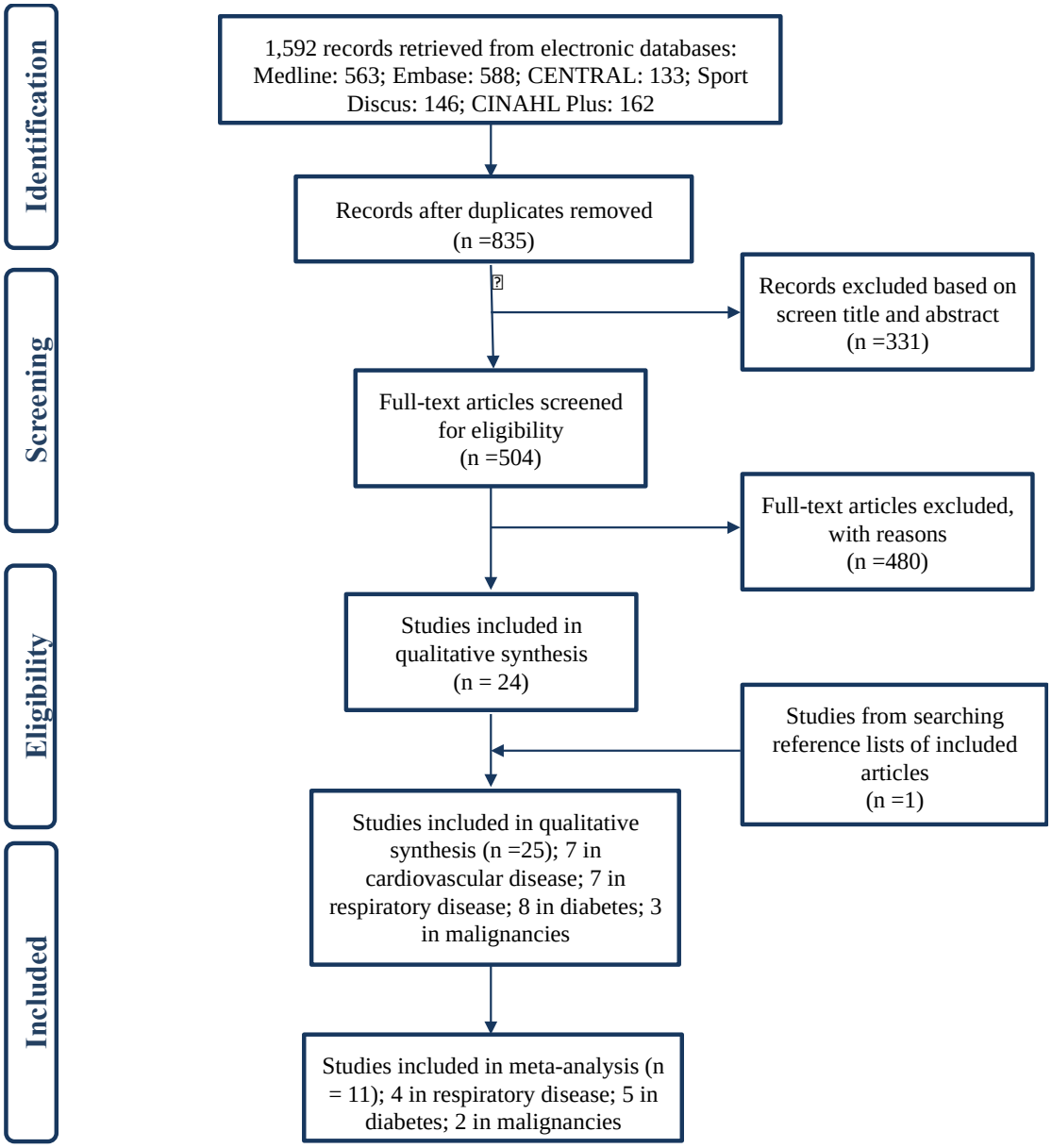


Figure 3.1: The PRISMA flow diagram with numbers of included and excluded articles at each step of the review process.

Table 3.2: Descriptive characteristics and levels of moderate-to-vigorous intensity physical activity and sedentary time in children with cardiovascular disease

Reference *	Place and publication year	Sample group n, male% and age (yrs)	Control group n, male% and age (yrs)	Measurement	Accelerometry methods	MVPA	Sedentary time
Banks et al **(356)**	Canada, 2012	n: 20, (60 % male) Age: mean 11.8 (SD 3)	N/A	Actigraph MTI, worn above the iliac crest for 4 days including 1 weekend day	Epoch = 60s MVPA cut-points not clearly reported.	Median 8 (Q1 4 - Q3 11) min/day MVPA lower in patients than healthy comparison groups All patients failed to meet an average of 60 min/day MVPA	N/A
Banks et al **(357)**	Canada, 2013	n: 50, (59 % male) Age: range 6-12	N/A	Actical, worn above the iliac crest for 7 days.	Epoch = 15s MVPA $\geq$ 1600 cpm	Mean 52 (SD 20) min/day MVPA lower in patients than healthy comparison groups All patients failed to meet an average 60 min/day MVPA	N/A
Duncombe et al **(358)**	Canada, 2016	n: 90, (54 % male) Age: mean 13.6 (SD 2.7)	N/A	Actigraph GT3X, worn on right hip for 7 days during waking hours.	Epoch =15s Evenson cut-point (359) MVPA $\geq$ 2296 cpm Sedentary time < 100 cpm	Median 43 (IQ range 29 - 60) min/day MVPA similar in patients and healthy comparison groups 8 % of patients achieved an average 60 min /day MVPA	Median 70 (IQ range 61 - 76) % of waking time sedentary Sedentary time similar in patients and healthy comparison groups
Ewalt et al (360)	USA, 2012	n: 21, (24 % male) Age: mean 10.7 (SD 3.2)	n: 21, matched for age and gender	Actigraph 7164, worn on right hip for 7 days during waking hours.	Epoch = 30s MVPA cut-points not clearly reported Sedentary time $\leq$ 50 counts /30s	Patients mean 71 (SD 50) min/day Control group mean 61 (SD 30) min/day MVPA difference not significant (p = 0.2)	Patients mean 399 (SD 107) min/day Control group mean 406 (SD 90) min/day Sedentary time difference not significant (p = 0.7)

						33 % of patients and 5 % of control group achieved an average 60 min /day of MVPA	
Gardner et al (361)	Canada, 2016	n: 30, (46 % male) Age: mean 10.7 (SD 3.2)	N/A	Actigraph GT3X, worn on right hip for 7 days during waking hours	Epoch = 15s Evenson cut-point (359) MVPA ≥ 2296 cpm Sedentary time < 100 cpm	Median 40 (IQ range 27 - 57) min/day 25 % of patients achieved an average 60 min /day of MVPA	Median 68 (IQ range 61 - 76) % of waking time sedentary
Longmuir et al (247)	Canada, 2011	n: 63, (60 % male) Age: range 5 - 11	N/A	Actical, worn above the iliac crest for 7 days during waking hours	Epoch =15s. MVPA ≥ 1,600 cpm.	Mean 51 (19) min/day MVPA 4 to 5 times lower in patients than healthy comparison groups 3 % of patients achieved an average of 60 min per day of MVPA	N/A
McCrindle et al (241)	USA and Canada. 2007	n: 147, (62 % male) Age: range 6 - 18	N/A	Actigraph MTI, worn for 4 days include 1 weekend day during waking hours	Epoch = 60s Freedson cut-point (362)	Absolute MVPA not given. MVPA lower in patients than healthy comparison groups 38 % of patients achieved an average of 60 min per day of MVPA	N/A

cpm – counts per minutes, MVPA – moderate-to-vigorous physical activity, n – number, N/A – no data included, S – second
Data are expressed as mean (SD) unless otherwise
Freedson MVPA cutpoint (362) calculated using the following equation: METS = 2.757 + (0.0015 x counts/min) – (0.08957 x age (yr)) – (0.000038 x counts/min x age (yr))
***One study (360) recruited healthy control and patient participants at the same time and measured MVPA and ST in the same way as (referred to here as studies with control group); five studies (241, 247, 356-358) compared patient data with other studies-previous published studies (referred to here as studies with comparison groups); and one study (361) reported patient data in relation to recommendations.**
*** Studies are listed in alphabetic order.**

Table 3.3: Descriptive characteristics and levels of moderate-to-vigorous intensity physical activity and sedentary time in children with chronic respiratory diseases

Reference *	Place and publication year	Sample group n, male% and age (yrs)	Control group n, male% and age (yrs)	Measurement	Accelerometry methods	MVPA	Sedentary time
Aznar et al **(363)**	Spain, 2014	n: 47, (51 % male) Age: mean 12.0 (SD 3.0)	N: 39; (59 % male) Age: mean 12.0 (SD 2.0)	Actigraph GT3X, worn on right hip for 7 days during waking hours	Epoch = 15s Evenson cut-point (359) MVPA ≥ 2296 cpm Sedentary time < 100 cpm	Patients mean 44 (SD 28) min/day Control group mean 54 (SD 15) min/day MVPA significantly lower in patient ($p < 0.02$) 2 % of patients and 34 % of control group achieved an average 60 min/ day of MVPA	Patients mean 362 (SD 67) min/day Control group mean 484 (SD 85) min/day Sedentary time was lower in patients ($p < 0.001$)
Kilbride et al **(364)**	Ireland, 2012	n: 16, (56 % male) Age: range 10 - 12	n: 99, (48 % male) Age: range 10 - 12	RT3 worn for 3 days	Epoch and MVPA cut-points not clearly reported Sedentary time = 0 – 99cpm	Patients mean boys 15 (SD 3); girls 16 (SD 3) min/day Control group mean boys 23 (SD 6); girls 15 (SD 3) min/day MVPA similar in patients and control group All patients failed to meet an average of 60 minutes/day MVPA	N/A
Smith et al **(365)**	Germany, 2016	n: 94, (56 % male) Age: mean 15.6 (SD 0.5)	n: 590, (40 % male) Age: mean 15.7 (SD 0.5)	Actigraph GT3X, worn on right hip for 7 days during waking hours	Epoch = 60s. Freedson cut-point (362)	Patients mean boys 41 (35) 11, 89; girls 43 (36) 14, 71 min/day Control group mean boys 46 (42) 19, 89; girls 38 (34) 13, 70 min/day	N/A

Tsai et al **(366)**	USA, 2012	n: 27, (70 % male) Age: range 9 - 11	n: 27, (59 % male) Age: range 9 - 11	actigraph (Actiwatch 64 MM), worn non-dominant wrist for 7 days during waking hours	Epoch = 60s MVPA ≥ 700 cpm Sedentary time = 0 - 49 cpm	Patients mean 265 (SD 83) min/day Control group mean 308 (SD 97) min/day MVPA similar in patients and control group (p = 0.09) Patients and control group achieved an average of 60 min per day of MVPA	Patients mean 87 (SD 48) min/day Control group mean 77 (SD 27) min/day Sedentary time difference not significant (p = 0.3)
Vahlkvist et al **(367)**	Denmark, 2010	n: 55 Age: range 6 - 14	n: 154 Age: range 6 - 14	RT3 worn for 4 weeks during 24 h a day	Epoch and cut-points not clearly reported	Patients mean of 32 (95 % CI 5) min/day Control group mean 34 (95 % CI 3) min/day MVPA similar in patients and control group Patients and control group failed to achieve an average of 60 min per day of MVPA	Patients mean 1270 (95 % CI 15) min/day Control group mean 1261 (95 % CI 9) min/day Sedentary time was similar in patient and control group
Van- Gent et al **(368)**	Netherlands, 2007	n: 81, (58 % male) Age: mean 9.4 (SD 0.8)	n: 202, (50 % male) Age: mean 9.4 (SD 0.7)	Pam AM 100, worn on hip for 5 days during waking hours	Epoch = 60s MVPA cut-points not clearly reported	Patients mean 99 (95 %, CI 80, 118) min/day Control group mean 98 (95 %, CI 85, 106) min/day MVPA similar in patients and control group Patients and control group achieved an average of 60 min per day of MVPA	N/A

Yiallouros et al **(369)**	Cyprus, 2015	n: 36, (64 % male) Age: range 8-9	n: 99, (60 % male) Age: range 8 - 9	Actigraph worn on wrist for 7 days during waking hours	Epoch not clearly reported. MVPA > 3200 cpm Sedentary time < 100 cpm	Patients mean 15 (95% CI 10-21) min/day. Control group mean 16 (95% CI 14-19) min/day. Similar in patients and control group	Patients mean 939 (95 % CI 915 - 963) min/day Control group mean 927 (95% CI 915 - 938) min/day Similar in patients and control group

cpm – counts per minutes, MVPA – moderate-to-vigorous physical activity, n – number, N/A – no data included, S – second
Data are expressed as mean (SD) unless otherwise

Smith et al (365): MVPA calculated as mean (Geometric mean) 5^{th}, 95^{th} percentile, and Yiallouros et al (369): MVPA Calculated as geometric means (95% CI) in min/day
Freedson MVPA cutpoint *(362)* calculated using the following equation: METS = 2.757 + (0.0015 x counts/min) – (0.08957 x age (yr)) – (0.000038 x counts/min x age (yr))
Studies recruited healthy control participants and measured MVPA and ST in the same way as in their patient participants and at the same time (referred to here as studies with control group)
*** Studies are listed in alphabetic order**

Table 3.4: Descriptive characteristics and levels of moderate-to-vigorous intensity physical activity and sedentary time in children with diabetes mellitus

Reference*	Place and publication year	Sample group n, male% and age (yrs)	Control group n, male% and age (yrs)	Measurement	Accelerometry methods	MVPA	Sedentary time
Cuenca-Garcia et al (370)	UK, 2012	n: 60, (67 % male) Age: mean 12.5 (SD 2.3)	n: 37, (54 % male) Age: mean 12 (SD 2.5)	Actigraph GT1M, worn for 7 days during waking hours	Epoch = 60s MVPA ≥ 3200 cpm	Patients mean 28 (SD 21) min/day Control group mean 20 (SD 11) min/day MVPA difference not significant (p = 0.06)	N/A
Kriska et al (105)	USA, 2013	n: 669, (51.5% male) Age: range 10-17	N/A	Actigraph AM7164, worn on waist for 7 days during waking hours	Epoch = 60s. MVPA Freedson cut-point (362) Sedentary time < 100 cpm	10-14 year old mean boys 35 (SD 26); girls 27 (SD 18) min/ day. 15-18 year old mean (boys 26 (SD 24); girls 8 (SD 9) min/day MVPA low in patients than healthy comparison groups All patients failed to reach an average of 60 min/day MVPA	10 - 14 year old mean boys 495 (SD 144); girls 479 (SD 141) min/day 15 - 18 year old mean boys 526 (SD 143); girls 546 (SD 143) min/day
MacMillan et al (371)	UK, 2014	n: 40, (50 % male) Age: mean 11.1 (SD 2.7)	N/A	Actigraph GT3X, worn on waist for 7 days during waking hours	Epoch =15s. MVPA ≥ 3200 cpm. Sedentary time < 100 cpm	Patients mean of 43 (SD 24) min/day MVPA similar in patients and healthy comparison groups 5 % of patients achieved an average of 60 min per day of MVPA	Patients mean 612 (SD 102) min/day

Maggio et **al (222)**	**Switzerland , 2010**	n: 45 Age: mean 10.7 (SD 0.4)	n: 85 Age: mean 10.1 (SD 0.3)	Actigraph 6471, worn for 7 days during waking hours	Epoch not clearly reported MVPA > 2000 cpm. Sedentary time < 500 cpm	Patients mean 54 (SD 7) min/day. Control group mean 71 (SD 5) min/day 39 % of patient and 60 % of control group achieved an average of 60 min/day of MVPA The difference not significant (p = 0.07)	Patients mean 77 % waking time sedentary Control group mean 70 % waking time sedentary. Significantly higher in patient (p < 0.01)
Nguyen et al **(372)**	Canada, 2015	n: 16; (n = 8) good glycemic control, (n = 8) poor glycemic control Age: range 8 - 16	n: 8 Age: range 8 - 16	Actigraph GT1, worn on the right hip for 7 days during waking hours	Epoch = 3s Evenson cut-point (359) MVPA $\geq$ 2296 cpm Sedentary time < 100 cpm	Patients with good glycemic control mean 46 (SD 16) min/day Patients with poor glycemic control mean 47 (SD 8) min/day Control group mean 54 (SD 28) min/day The difference not significant (p = 0.07)	N/A
Sarnblad et al **(373)**	Sweden, 2005	n: 26, (100 % female) Age: range 12 - 19	n: 49 Age: range 12 - 19	Actigraph 6471 worn on the hip for 7 days during waking hours	Epoch = 60s MVPA > 1952 cpm Sedentary time < 100 cpm	Patients mean of 56 (SD 20) min/day Control group mean 60 (SD 23) min/day The difference not significant (p = 0.07)	Patients mean 443 (SD 60) min/day Control group mean 390 (SD 27) min/day Significantly higher in patient than control group (P = 0.002)
Sundberg et al **(374)**	Sweden, 2012	n:24, (50 % male) Age: mean boys 4.3 (SD 1.6); girls 4.7 (SD 1.9)	n: 26, (46.2 % male) Age: mean boys 4.9 (SD 1.4); girls 4.4 (SD 1.8)	Actiheart, for 7 days	Epoch = 60s MVPA cut-point not clearly reported. Sedentary time < 100 cpm,	Absolute MVPA not given MVPA significantly lower in patients than the control group (p = 0.02)	Absolute sedentary time not given Significantly higher in patient than control group (p = 0.03)

Trigona et al **(375)**.	Switzerland, 2010.	n: 32, (53 % male) Age: range 6 - 17	n: 42, (40 % male). Age: range 6 - 17	Actigraph 6471, worn on hip for at least 4 days during waking hours	Epoch = 60s MVPA > 2000 cpm	Patients mean 53 (95 % CI 33 - 74) min/day Control group mean 77 (95 % CI 58 - 97) min/day Significantly lower in patients than the control group ($p < 0.008$) 35 % of patients and 57% control group achieved an average of 60 min/day of MVPA	N/A

cpm – counts per minutes, MVPA – moderate-to-vigorous physical activity, n – number, N/A – no data included, S – second
Data are expressed as mean (SD) unless otherwise
Freedson MVPA cutpoint (362) calculated using the following equation: METS = 2.757 + (0.0015 x counts/min) – (0.08957 x age (yr)) – (0.000038 x counts/min x age (yr))
Six studies (222, 370, 372-375) recruited healthy control participants and measured MVPA and ST in the same way as in their patient participants and at the same time (referred to here as studies with control group), and two studies (105, 371) compared patient data with other studies (referred to here as studies with comparison groups.
*** Studies are listed in alphabetic order.**

Table 3.5: Descriptive characteristics and levels of moderate-to-vigorous intensity physical activity and sedentary time in children with malignancies

Reference *	Place and publication year	Sample group n, male% and age (yrs)	Control group n, male% and age (yrs)	Measurement	Accelerometry methods	MVPA	Sedentary time
Aznar et al **(292)**	Spain, 2006	n: 7, (57.1 % male) Age: range 4 – 7	n: 7, (57.1 % male) Age: range 4 –7	Actigraph MTI, worn on waist for 7 days during waking hours	Epoch = 60s MVPA Freedson cut-point (362) Sedentary time ≤ 100 cpm	Patients mean 47 (SD 15) min/day Control group mean 72 (SD 25) min/day Significantly lower in patient group than control group (p =0.04) 0 % of patient, 57 % control group achieved an average of 60 min/day of MVPA.	Patients mean 41 (SD 18) % of time sedentary Control group mean 42 (SD 11) % of time sedentary Sedentary time was similar in patient and control group (p = 0.07)
Gotte et al **(376)**	Germany, 2017	n: 28, (57 % male) Age: range 11 – 15	N/A	Step Watch 3™ Monitor, worn for 7 days during waking hours	Epoch = 60s MVPA cut-point not clearly reported	Patients mean 4 (SD 5) min/day 3 % (n=1) of patient achieved an average of 60 min/day of MVPA	N/A
Tan et al **(75)**	Malaysia, 2012	n: 38 Age: range 3 – 12	n: 38 Age: range 3 – 12	Actical, worn on hip for 7 days during all the day	Epoch = 15s MVPA cut off points not reported Sedentary time < 100 cpm	Patients mean 20 (SD 28) min/day Control group mean 168 (SD 56) min/day Significantly lower in patient group than control group (p < 0.01)	Patients mean 1295 (SD 119) min/day Control group mean 925 (SD 111) min/day Significantly higher in patients than control group (p < 0.01)

cpm – counts per minutes, MVPA – moderate-to-vigorous physical activity, n – number, N/A – no data included, S – second
Data are expressed as mean (SD) unless otherwise
Freedson MVPA cutpoint (362)calculated using the following equation: METS = 2.757 + (0.0015 x counts/min) – (0.08957 x age (yr)) – (0.000038 x counts/min x age (yr))
Two studies (75, 292) recruited healthy control participants and measured MVPA and ST in the same way as in their patient participants and at the same time (referred to here as studies with control group) and one study (376) reported patient data in relation to recommendations.
*** Studies are listed in alphabetic order.**

3.3.2. Study Characteristics

Study samples: Eligible study sample sizes ranged from 14 – 699 with a total of 2062 participants with chronic disease and 1523 participants from healthy control groups. All studies were from high-income, developed nations. **Measurement methods**: A total of 17 out of the 25 eligible studies used the ActiGraph accelerometer to measure habitual MVPA and/or ST, though with a variety of different ActiGraph models and approaches to data collection and reduction. Of the remaining studies: three used the Actical (75, 247, 357); two the RT3 "Triaxial Research Tracker" (364, 367); one the PAM "Physical Activity Monitor" B.V. type AM 100 (368); one the Actiheart (which combines accelerometry and heart rate monitoring) (374); and one the Step Watch 3^{TM} (376).

3.3.2.1. MVPA in Children and Adolescents with chronic Disease

The mean reported daily MVPA accumulated by children and adolescents with chronic disease across the 25 eligible studies ranged between 4 (SD 4) minutes/day (376) to 265 (SD 83) minutes/day (366).

Children and adolescents with cardiovascular disease: Seven of the 25 eligible studies (n = 442) examined MVPA in children and adolescents previously diagnosed with a congenital heart defect. This included children who had received different types of cardiac surgery (358, 360, 361), including complex surgery such as a fontan repair (241, 247, 357), or cardiac transplantation (356). In all cases the patients were studied at least 6 months after surgery while well, clinically stable, free of acute illness, and living in the community. As summarised in Table 3.2, average daily MVPA in these studies ranged from a low of 8 (range, 4-11) min/day (356) to a high of 49 (range 39-

60) min/day (247). In 6/7 of eligible studies reported mean daily time spent in MVPA in minutes and in six studies mean daily MVPA failed to reach the recommended 60 minutes. Only 1 out of 7 eligible studies included data from a healthy control group, showing a higher MVPA level in the patient group compared to the healthy control group although the differences were not significant (360).

Children and adolescents with chronic respiratory diseases: Seven of the 25 eligible studies (n = 1013) investigated children and adolescents with chronic respiratory diseases; five studies in patients with asthma (365-369) and two in patients with cystic fibrosis (363, 364). In all cases, the children were studied while clinically stable, free of acute illness, and while living in the community. The mean daily MVPA reported ranged from 15 (SD 3) min/day (364) to 265 (SD 8) min/day (366) as summarised in Table 3.3. In 2/7 eligible studies (366, 368) mean daily reported MVPA reached or exceeded the 60 minutes recommended, though this included one study with exceptionally high reported levels of MVPA (30). Meta-analysis of all 4 studies indicated lower MVPA levels in the patient group compared to the healthy control group, approaching statistical significance. The standardised mean difference (SMD) was 0.39 (95% CI -0.80 to 0.02, p=0.06). The heterogeneity was substantial with an I^2 statistic of 68%, as shown in Figure 3.2

Children and adolescents with diabetes: Eight of the 25 eligible studies (n = 1323) involved children and adolescents with diabetes mellitus; 7 studies in children with type 1 diabetes (222, 370-375) and 1 in children with T2DM (105). Again, in all cases the patients were studied while clinically stable and free of acute illness or diabetes complications, and while living in the community. As summarised in Table 3.4, the average daily MVPA reported for diabetic patients ranged from a low of 8 (SD 9)

min/day (105) to a high of 56 (SD 20) min/day (373). Of the 8 eligible studies, 7 reported mean daily MVPA in minutes and in all 7 of these studies MVPA was < 60 minutes. Patient MVPA was compared to healthy peers in 5 studies (222, 370, 372, 373, 375), all of which included patients with T1DM as shown in Figure 3.3. There was no evidence of a statistically significant difference in MVPA in patients compared to healthy controls (SMD -0.70, 95% CI -1.89 to 0.48, p=0.25, n= 400). Case-control evidence on MVPA levels appears to be lacking for children with T2DM.

Children and adolescents with malignancies: Three studies, (n = 118) examined MVPA in those with malignancies including one study in acute lymphoblastic leukaemia on maintenance treatment (292), one in acute leukemia undergoing induction or consolidation chemotherapy (75) and a third in children and adolescents with different types of childhood malignancies (376). In all of these studies, the participants had no other co-morbid conditions that would have been a contraindication for PA such as anemia, fever, or other difficulties with mobility. The mean daily MVPA achieved during these studies ranged from a low of 4 (SD 4) min/day (376) to a high of 47 (SD 15) min/day (292), as summarised in Table 3.5. In all three studies mean daily MVPA failed to reach the recommended 60 minutes. Two out the three studies included data from healthy participants and in both of these studies; the level of MVPA was significantly lower in children and adolescents with malignancies (75, 292). Figure 3.4 shows the combined result, which suggests a standardised mean difference of 2.2 (95% CI -4.08 to -0.26, p=0.03). Despite the apparent similarity between the studies the statistical heterogeneity was considerable with an I^2 statistic of 88%. The heterogeneity noted could be due to differences in sample sizes, age and place of the studies, differences in the stage of treatment, or differences in accelerometer methodology.

3.3.2.2. Sedentary Time in Children and Adolescents with Chronic Disease

In this systematic review, 14 out of the 25 eligible studies reported on accelerometer measured ST, with a total of 1870 participants (with chronic disease n = 1325; healthy control group n = 545). Of the 14 studies that measured ST, the chronic diseases studied were as follows: cardiovascular disease - 3 studies (358, 360, 361); chronic respiratory diseases - 4 studies (363, 366, 367, 369); diabetes - 5 studies (105, 222, 371, 373, 374); malignancy - 2 studies (75, 292).

As summarised in Table 3.2- 3.5, the mean daily time spent sedentary in these eligible studies ranged from a low of 87 (SD 48) min/day (366) to a high of 1295 (SD 119) min/day (75). In 10 out of the 14 eligible studies, there was a healthy control group, and in 4/10 studies ST was significantly higher in those with chronic disease than in the healthy control groups (75, 222, 373, 374); in one study ST was significantly lower in the patient group compared to the healthy control group (363), while in 5 studies there was no significant group difference (292, 360, 366, 367, 369). Suitable summary data for combining individual study data were only available for three studies (n=355) in patients with chronic respiratory disease with findings indicating no statistically significant group difference in time spent sedentary (SMD -0.40, 95% CI -1.53 to 0.74, p=0.49, I^2=95%) as in Figure 3.5.

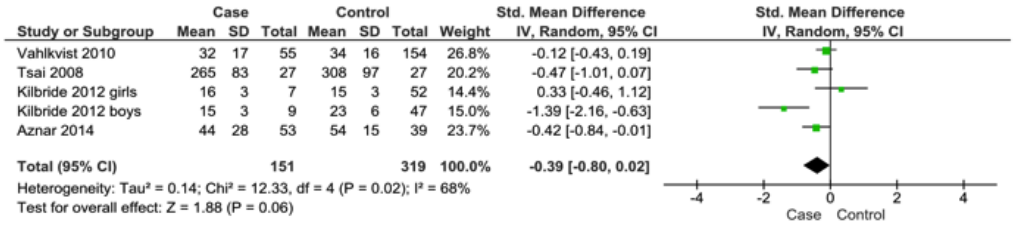


Figure 3.2: Forest plot of the comparison of moderate-to-vigorous intensity physical activity between children and adolescents with chronic respiratory diseases and healthy participants. SD: standard deviation; Std mean difference: Standardised mean difference; IV: Inverse variance; Random: random effect model; CI: 95% Confidence interval. (Forest plot is kindly supplied by Dr Anne Martin).

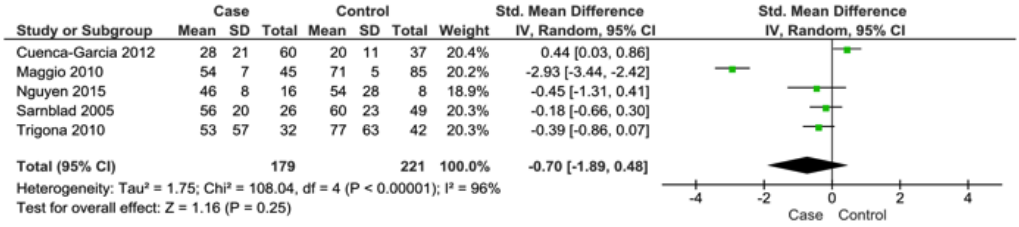


Figure 3.3: Forest plot of the comparison of daily moderate-to-vigorous intensity physical activity between children and adolescents with type 1 diabetes mellitus and healthy participants. SD: standard deviation; Std mean difference: Standardised mean difference; IV: Inverse variance; Random: random effect model; CI: 95% Confidence interval. (Forest plot is kindly supplied by Dr Anne Martin).

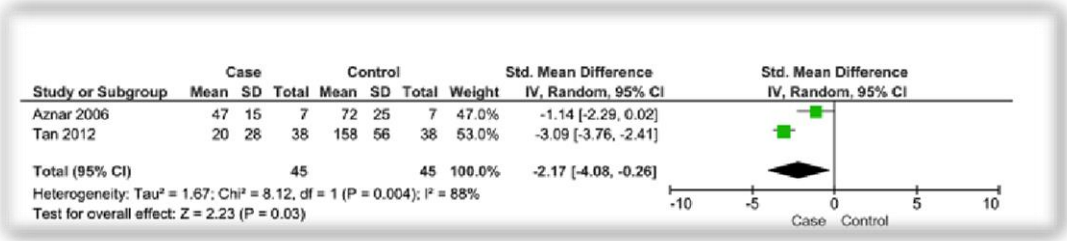


Figure 3.4: Forest plot of the comparison of daily moderate-to-vigorous intensity physical activity between children and adolescents with malignancies and healthy participants. SD: standard deviation; Std mean difference: Standardised mean difference; IV: Inverse variance; Random: random effect model; CI: 95% Confidence interval. (Forest plot is kindly supplied by Dr Anne Martin).

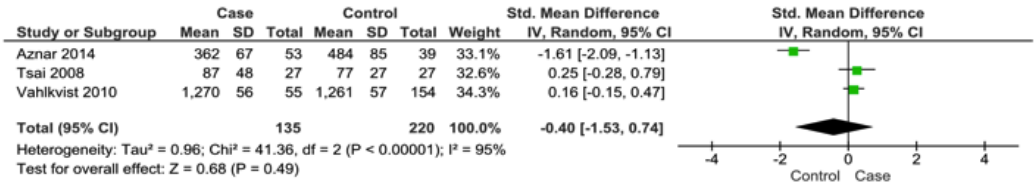


Figure 3.5: Forest plot of the comparison of sedentary time between children and adolescents with chronic respiratory diseases and healthy participants. SD: standard deviation; Std mean difference: Standardised mean difference; IV: Inverse variance; Random: random effect model; CI: 95% Confidence interval. (Forest plot is kindly supplied by Dr Anne Martin).

3.3.3. Study Quality Assessment

Study quality assessment summaries are given in Table 3.6: 3 studies scored 4/6; 13 scored 5/6; 9 scored 6/6 on study quality. Thus in general, studies were high methodological quality.

Table 3.6: Methodological quality assessment of the included studies

	Quality Assessment Criteria, Items 1-6						
***Reference**	**1**	**2**	**3**	**4**	**5**	**6**	**Total score**
Banks, 2012	-	+	+	+	+	+	5/6
Banks, 2013	-	+	+	+	+	+	5/6
Duncombe, 2016	+	+	+	+	+	+	6/6
Ewalt, 2012	+	+	+	+	+	+	6/6
Gardner, 2016	-	+	+	+	+	+	5/6
Longmuir, 2011	-	+	+	+	+	+	5/6
McCrindle, 2007	-	+	+	+	+	+	5/6
Aznar, 2014	-	+	+	+	+	+	5/6
Kilbride, 2012	-	+	+	+	+	+	5/6
Smith, 2016	+	+	+	+	+	+	6/6
Tsai, 2012	+	+	+	+	+	+	6/6
Vahlkvist, 2012	-	-	+	+	+	+	4/6
Van Gent, 2007	+	+	+	+	+	+	6/6
Yiallouros, 2015	+	-	+	+	+	+	5/6
Cuenca-Garcia	-	+	+	+	+	+	5/6
Kriska, 2013	+	+	+	+	+	+	6/6
MacMillan, 2014	+	+	+	+	+	+	6/6
Maggio, 2010	-	-	+	+	+	+	4/6
Nguyen, 2015	-	+	+	+	+	+	5/6
Sa¨rnblad, 2005	+	+	+	+	+	+	6/6
Sundberg, 2012	+	+	+	+	+	+	6/6
Trigona, 2010	-	+	+	+	+	+	5/6
Aznar, 2006	+	+	+	+	+	+	6/6
Gotte 2015	-	+	+	+	+	+	5/6
Tan, 2012	+	-	+	+	+	+	5/6

+ Indicates that a criterion was satisfied; − indicates that a criterion was not satisfied. 1, described of Sample recruitment?; 2, description of the sample.?; 3, Attrition of sample?; 4, Data collection and reduction?; 5, MVPA definition given?; 6, MVPA Results given?; * Studies are listed based on diseases groups.

3.4. Discussion

3.4.1. Main Findings and Study Implications

This systematic review provides evidence that children and adolescents with some of the common chronic childhood diseases have lower than recommended levels of MVPA. In most of the eligible studies, daily MVPA averaged less than the 60 minutes/day recommended. When comparing MVPA level between patients and healthy control or comparison groups, the findings indicated, within the limits of the available data, there were no marked differences for patients with T1DM, CVD and chronic respiratory diseases. However, in patients with leukemia compared to healthy control or comparison groups daily MVPA was significantly lower. With the respect to sedentary time the present review found that studies fairly consistently reported that children and adolescents with chronic disease accumulated a high amount of ST during their waking hours.

It should be noted that recommendations based on systematic reviews of the scientific evidence for MVPA state that 60 minutes per day is a minimum every day (e.g. usually operationalized as all 7 days in a week) (80), but adherence to recommendations was not operationalized in this way in any of the 25 eligible studies. We therefore used a mean or median daily MVPA of 60 minutes as a proxy for compliance, though this is conservative because in many cases where 60 minutes/day was reached as an average, levels of MVPA would have fallen below 60 minutes/day on at least one of the monitored days.

Reasons for lower than recommended levels of MVPA are unclear in both children with chronic disease and their healthy peers. Children and adolescents with chronic

disease may experience an over-protective care environment, a lack of supervised facilities/ opportunities for PA, and/or insufficient knowledge and self-efficacy about the types of PA suitable for the specific disease condition (377, 378). Such socio-environmental influences could contribute to low daily MVPA and high ST. Healthcare professionals, parents/caregivers and schools may need to be provided with adequate information and training to be able to encourage and support children with chronic disease to engage in regular and appropriate MVPA. However, it should also be noted that reported levels of MVPA among healthy peers were also generally low in the eligible studies, so it may be that any constraints on PA that apply to healthy children and adolescents also apply equally to those with chronic disease.

3.4.2. Comparisons with Other Studies

We believe that the present study is the first systematic review to ask whether or not levels of MVPA are adequate in children and adolescents with chronic childhood disease. There are therefore no directly comparable studies, but we note that in healthy children, and particularly in healthy adolescents, there is concern that levels of MVPA are generally much lower than recommended. A global analysis by Hallal et al suggested that less than 20% of 13-15 year olds meet the recommendation of 60 minutes/ day of MVPA (379). A recent pooling of international accelerometry data from nearly 21,000 healthy children and adolescents showed typically very low levels of adherence to the 60 minutes/day recommendation for MVPA (289), so it is perhaps not surprising that levels of MVPA among those with chronic disease were also found to be generally low in the present study. Furthermore, because of accelerometers was using to measures of PA in children have only been around since the early 2000s; so

the direct comparisons with objective levels of PA from the past are not possible and evidence of PA levels declining are too limited to make that conclusion.

We are also unaware of any previous systematic reviews of accelerometry measured ST among children and adolescents with chronic disease. Interpreting sedentary time data is even more problematic than interpreting the MVPA data in the present study because there are currently no evidence-based recommendations for accelerometer-measured ST.

3.4.3. Study Strengths and Limitations

Our review had a number of strengths. It was the first review to investigate objective levels of MVPA and ST in children and adolescents living with childhood chronic disease. Secondly, there are several methodological strengths to this study: in particular, studies were identified from an extensive search of the published literature conducted in a range of databases. The broad definition of search terms applied across multiple databases enabled the searching and identification across many potential studies. Restricting eligibility to accelerometry studies was important in increasing confidence in the objective measurement of MVPA (348, 380-382). Finally, all included studies were in general rated as being of high or very high quality.

However, there are several weaknesses worth highlighting. Firstly, as studies had to be published in peer-reviewed journals in English, this may have excluded some relevant evidence. Studies included in our review investigated MVPA and ST in children and adolescents with chronic childhood disease. However, we excluded some other common medical conditions where significant alterations in activity might have been expected because of the nature of the condition e.g. musculo-skeletal and neurological disease, and we also excluded studies of patients with acute illness or

injury requiring or associated with confinement or bed-rest. Future reviews should consider these other groups, and also consider the PA and ST of children and adolescents with the many chronic diseases not included in the present review. Our initial scoping review found that objectively measured PA data were available for only a few chronic disease groups and so the present review focused on those.

All eligible studies were from high-income developed nations. We therefore lack data from low-middle income countries where the prevalence of many childhood chronic disease will be common and lack of resources may limit medical care (383). Most of the included studies were based on relatively small samples of children with chronic disease (n 14 - 699) and their power to estimate habitual MVPA, or to distinguish between MVPA of patients and comparison group participants, might have been limited, and their representativeness was rarely clear.

Our method for assessing the quality of eligible studies has been used in variously adapted forms in a number of other recent accelerometry systematic reviews (54, 353-355), and used 15 items, but the process of collapsing these 15 items to a six-item scale might have reduced the possibility of identifying differences in quality between studies. Eligible studies made comparisons with healthy peers in a wide variety of ways (control groups; comparison groups; reference to recommendations). Use of control groups was considered ideal, but restricting our synthesis to only those studies would have reduced a small evidence base to an even smaller evidence base, so this was not done.

Further, the eligible studies varied substantially in terms of the accelerometers used, and even where the same accelerometer was used the methods varied in a number of potentially important accelerometer data reduction decisions e.g. the definition of a

monitoring epoch (370, 381); the number of hours and days of data constituting a valid data set (105, 222); MVPA and ST accelerometer cut-points; and criteria for the inclusion or exclusion of non-wear time (363, 371). These differences between studies are likely to have produced meaningful differences in MVPA and ST estimates (346) and they make it difficult to compare across studies. For the present review, the level of heterogeneity between eligible studies was high when combining data in meta-analysis across studies. However, in the case of all eligible studies the methods used for patient and control/comparison groups were identical, so comparison *within-studies* remain meaningful.

An example of how the choice of accelerometer cut-point could affect conclusions reached by individual studies is that studies using lower accelerometer cut-points to define MVPA tended to report higher levels of habitual MVPA than those which used higher accelerometer cut-points to define MVPA. Tsai et al (366), for example used an Actigraph accelerometer cut-off of ≥ 700 counts per minute to define MVPA in children with asthma. This cut-off point is well below the cut-points used more commonly and which are more evidence based (based on calibration studies such as the Evenson et al cut-point of 2296 counts per minute (359); or the Puyau et al cut-point of 3200 counts per minute (384)). The very low accelerometer cut-point used by Tsai et al almost certainly led to the very high estimate of 265 (SD 83) minutes of daily MVPA (366), and could lead to the erroneous conclusion that levels of MVPA among children with asthma are extremely high.

3.5. Conclusions

In summary, this systematic review found that overall (habitual) MVPA levels are well below international recommendations in at least some groups of children and adolescents with chronic childhood diseases. The present review suggests that management of pediatric chronic conditions should place greater emphasis on MVPA, and patients with at least some chronic diseases are probably not currently benefiting from the health and non-health benefits that MVPA can bring. Time spent sedentary is often higher than in the comparison groups, and probably too high in many patients, but this is difficult to interpret in the absence of health-related recommendations for accelerometer measured ST in children and adolescents. This valuable information about the MVPA and ST levels in children with chronic disease may help to stimulate improving PA guidelines, and improving PA for these children. The need for more extensive research in this area, including intervention studies of the impact of increased MVPA levels on health related outcomes, is clear.

CHAPTER IV

Comparison of Accelerometer Measured Levels of Physical Activity and Sedentary Behavior between Obese and Non-Obese Children and Adolescents: a Systematic Review

This chapter has been printed exactly in its published format (385) Available at: https://bmcpediatr.biomedcentral.com/articles/10.1186/s12887-018-1031-0#Bib1

4.1. Introduction and Aim

The prevalence of obesity among children and adolescents is now very high in both developing and developed countries (386, 387). The rising prevalence is recognised as a significant public health and clinical concern (73) and is attracting much research attention (388). Obesity is known to have a significant impact on both physical and psychological health and obese children and adolescents face a number of health, social, and psychological problems (387, 389, 390). Prevention of childhood obesity is now a public health priority while treatment is becoming an increasingly important clinical issue.

A number of health behaviors have been associated with risks of obesity (391). Poor diet, lack of PA and increased ST have been linked to the development and maintenance of childhood and adolescent obesity (67, 392-394). Many evidence-based guidelines focusing on the amount of PA, particularly moderate–to-vigorous intensity physical activity (MVPA), required producing health benefits, have been developed. These guidelines commonly recommend 60 minutes of MVPA as a daily minimum (7 days in a week) for school-age children and adolescents (9, 80, 343, 395).

Accelerometry currently represents the most accurate, inexpensive, and reliable method for objectively measuring both the amount and intensity of PA and amount of sedentary behavior (SB) (154, 346). There have been many surveys and studies on the levels and adequacy of MVPA in healthy-weight children and adolescents (347, 348). Since MVPA and SB are also important to health in those with obesity, and since obesity has been hypothesized to be associated with reduced MVPA (396), it is important to assess the extent of objectively measured time spent in MVPA and SB in obese children and adolescents. The primary aim of the present systematic review was therefore to review

the evidence on the habitual amount of time spent in MVPA by obese children and adolescents, and examine whether those living with obesity met the current MVPA recommendation for health of a minimum of 60 minutes per day (9, 30). Secondary aims were to examine time spent in accelerometer-measured SB by obese children and adolescents, and to determine whether MVPA and SB in obese children and adolescents were different from the non-obese peers.

4.2. Materials and Methods

4.2.1. Review Governance and Registration

A systematic literature review was performed in accordance with the Preferred Reporting Items for Systematic Reviews guidelines (285). The review protocol was registered on PROSPERO (registration number CRD42015026882), the international prospective register for systematic reviews (http://www.crd.york.ac.uk/NIHR_PROSPERO) and available in Appendix I.

4.2.2. Literature Search

The literature search was conducted by searching for English language peer-reviewed studies in the five most relevant electronic databases from 2000 up to March 2015 (accelerometry became more widely used in research from the early 2000's): MEDLINE OVID; Cochrane library; EMBASE; SPORTSDiscus and CINAHL by AM. The literature search in the Cochrane Central Register of Controlled Trials is shown in Table 4.1 and was adapted as required for the other databases. Full literature search details are available in Appendix I. The electronic search was complemented by

reference citation tracking (forward and backward) of the included studies and of previous reviews.

Table 4.1: Search strategy used for Cochrane central register of controlled trials

#1	MeSH descriptor: (Child] explode all trees
#2	MeSH descriptor: [Adolescent] explode all trees
#3	child* or adolesc* or teen* or boy* or girl* or youth:ti,ab,
#4	young near/1 (person or people):ti,ab,kw (Word variations have been searched)
#5	#1 or #2 or #3 or #4
#6	MeSH descriptor: [Motor Activity] this term only
#7	MeSH descriptor: [Exercise] explode all trees
#8	MeSH descriptor: [Sports] explode all trees
#9	MeSH descriptor: [Sedentary Lifestyle] explode all trees
#10	physical* activ*:ti,ab,kw (Word variations have been searched)
#11	exercis* or sport*:ti,ab,kw (Word variations have been searched)
#12	active near/2 (living or lifestyle):ti,ab,kw (Word variations have been searched)
#13	sedentary behavi?r:ti,ab,kw (Word variations have been searched)
#14	(screen or sedentary or sitting or TV or television or computer or PC or video games) near/2 time:ti,ab,kw (Word variations have been searched)
#15	#6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16	MeSH descriptor: [Accelerometry] explode all trees
#17	acceleromet*:ti,ab,kw (Word variations have been searched)
#18	actigraph*:ti,ab,kw (Word variations have been searched)
#19	activity near/1 monitor*.:ti,ab,kw (Word variations have been searched)
#20	#16 or #17 or #18 or #19
#21	MeSH descriptor: [Overweight] explode all trees
#22	overweight or obes*:ti,ab,kw (Word variations have been searched)
#23	#21 or #22
#24	#5 and #15 and #20 and #23

4.2.3. Inclusion Criteria

To be eligible for inclusion in the review, papers had to meet all of the following criteria as per the PICOS principles: Population: children and adolescents aged from 0 to 19 years as defined by World Health Organization (WHO); Intervention or exposure: children or adolescent classified as obese. Obesity had to be defined using an acceptable objective method, e.g. defined as having a body mass index (BMI) ≥ 95th percentile for children of the same sex and age, or defined as the equivalent of 30 kg/m^{2}International Obesity Task Force (IOTF definition), or defined as obese relative to WHO BMI for age and sex charts; Comparison: habitual amount of time spent in MVPA and/or ST of

non-obese children and adolescents; Outcomes: habitual amount of time spent in MVPA and/or ST measured by accelerometer and reported in the form of minutes/day of MVPA or ST; MVPA and its relationship to the 60 minutes /day recommended. All study designs were considered eligible: cross-sectional, longitudinal, case-control studies and intervention studies were eligible if pre-intervention data could be extracted.

4.2.4. Exclusion Criteria

We excluded studies that included only overweight participants, combined overweight and obese groups, or included participants with any known barrier or limitation to physical activity (e.g. physical disability). Studies that used subjective methods, objective (e.g. doubly labelled water) or direct observation methods apart from accelerometer measurements were also excluded.

Since the aim of the review was to examine habitual levels of MVPA and ST, studies that measured these variables for less than 6 h per day or over 2 days or less were excluded. Recommendations currently exist for habitual (overall) MVPA rather than MVPA during specific domains (e.g. in the after-school period) and so studies that focused only on specific periods of the day (e.g. school activity only, or outdoor activity only, or weekend activity only, or weekday activity only, or after-school only) were also excluded. A detailed description of the eligibility criteria is available in Appendix I.

4.2.5. Study Selection

Titles, abstracts, and full-text articles were screened in duplicate for eligibility by RE and JYP and disagreements were resolved through discussions with other reviewers when required. Reference lists of eligible studies were examined for potentially eligible studies, and studies that cited eligible studies were identified and tested for eligibility. The reviewers were not blinded to authors or journal of publication. Reasons for exclusion are summarised in the study flow diagram Figure 4.1.

4.2.6. Data Extraction

A standardised data extraction form was used to populate the evidence tables by RE and checked by JJR and JYP. The extracted items were: first author, publication year, country, study design, sample group, comparison group-if applicable, accelerometer type, cut points for MVPA and ST, finding of MVPA (minutes/day) and ST (minutes/day or %) data, summary and author conclusions. International recommendations usually recommend the achievement of at least 60 min of MVPA every day, but in the eligible studies the achievement of MVPA recommendations was never operationalised in this way. In most studies that referred to the achievement of MVPA recommendations, the mean or median daily MVPA (minutes/day) was provided, and so this was used as a proxy for achievement of recommendations in the present study.

4.2.7. Data Analysis and Synthesis

We considered the data for meta-analysis but identified a substantial level of statistical heterogeneity between the studies (I^2 statistic > 70%) that led to the decision not to

present the combined results of individual studies. Hence, we performed a narrative synthesis of the data and present the findings in tabular, textual and graphical form. Data were synthesised by the age and sex of the subgroups as those are factors known to be strongly associated with both the exposure variable, obesity, and the outcomes, MVPA and ST, and so might explain some of the observed findings. The age subgroup was categorised according to the WHO definition of children and adolescence, i.e. as children aged 0 to 10 years old and adolescents aged 10.1 to 19 years old. Data for boys, girls and mixed-sex studies are reported separately where possible.

4.2.8. Quality Assessment

Eligible articles were assessed for methodological quality using a 15-item quality assessment scale as shown in Appendix I, collapsed to 6 items for scoring, with higher scores suggesting higher study quality. Each eligible study was assessed by RE, and any uncertainties resolved by discussion with JJR and JYP. The quality assessment scale was modified from the methodological quality assessment scale of Tooth et al. (352). This is a reliable and valid tool for assessing the quality of observational studies. It was considered initially for use in its original form, which consists of over 30 items. The modifications to the original scale were made to focus quality assessment on issues of particular importance to accelerometry measurement of physical activity. The modified Tooth et al. tool has been used in several recent systemic reviews of physical activity, all of which have reduced the number of items in the quality assessment to 8 to 17 items, which make up the quality score (54, 291, 353-355).

4.3. Results

4.3.1. Identification of Eligible Studies

The PRISMA flow diagram with the numbers of included and excluded articles at each step of the review process is provided in Figure 4.1. Table 4.2 and 4.3 provide a brief summary of all studies included in this systematic review. Of 1503 papers identified in the initial review of the five databases, 467 were selected for full-text screening and of these, 22 met the inclusion criteria. A further four eligible studies were identified from searching reference of included studies and of previous reviews, giving a total of 26 studies which met the inclusion criteria.

4.3.2. Studies Characteristics

Of the 26 included studies: six studies involved children, 18 studies involved adolescent and two studies involved both children and adolescents. Further, 22/26 compared MVPA data in the obese with non-obese peers; 13/26 studies also provided data on accelerometer measured SB; 10/13 studies compared SB data in those with obesity with a non-obese peer. **Measurement protocol:** The ActiGraph was the most common accelerometer type used to measure habitual MVPA and/or SB, used in 20/26 studies, though with a variety of different ActiGraph models and approaches to data collection and reduction. Of the remaining six studies: three used the Actical accelerometer (397-399); two the Triaxial Research Tracker (RT3) accelerometer (400, 401); and one the Actiwatch accelerometer (402).

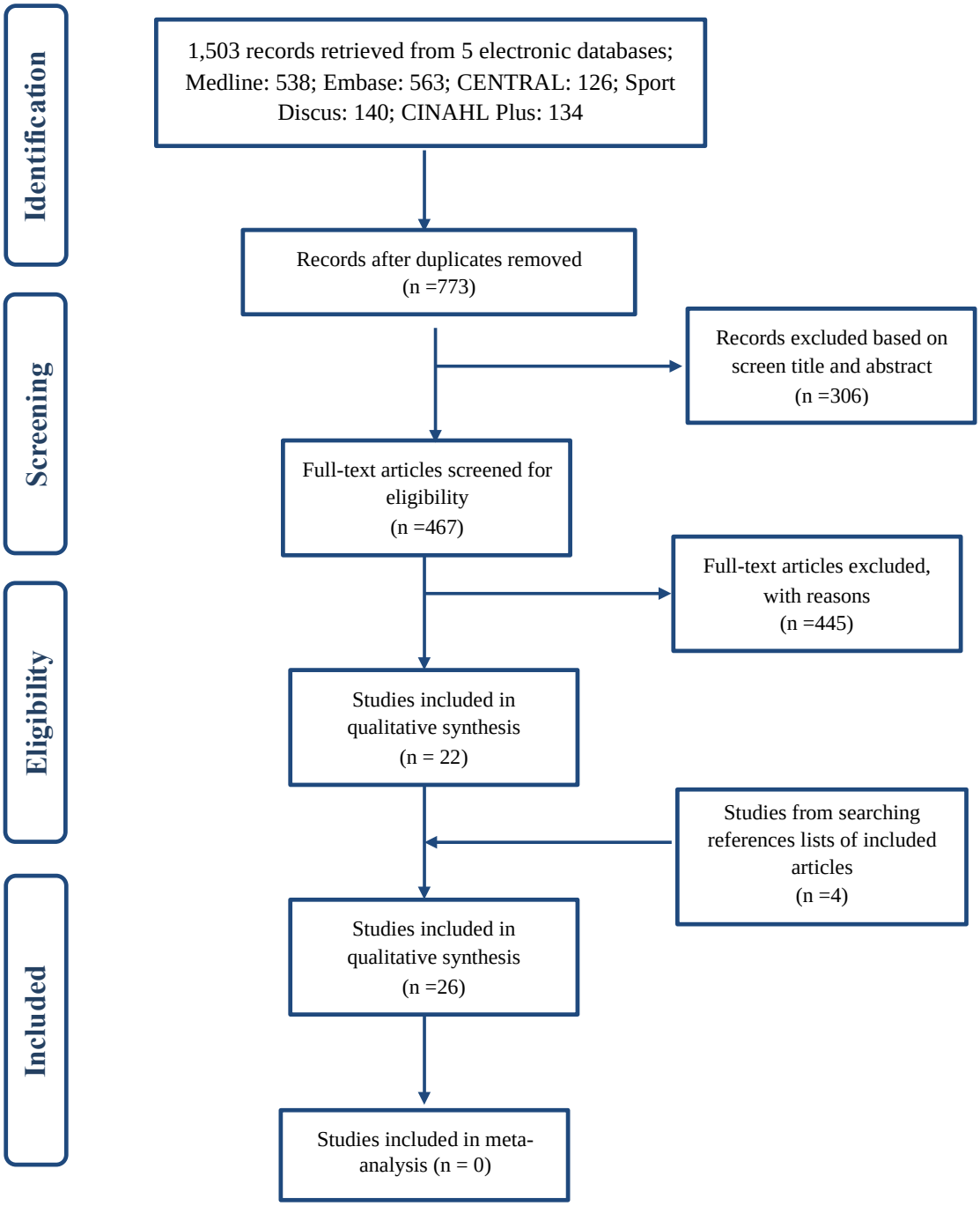


Figure 4.1: The PRISMA flow diagram with numbers of included and excluded articles at each step of the review process.

4.3.3. MVPA and SB in Obese Children

Eight eligible studies involved obese children, with a total sample size of 2138 children (478 obese; 131 boys, 136 girls and 211 no sex specified). Two of the eligible studies were clinical samples with study participants recruited from outpatient clinics. Eligible studies were from different nations with one study from Asia (403), three from Canada and USA (404-406) and four from Europe (222, 400, 407, 408), with the study characteristics summarised in Table 2. In four studies, MVPA data of boys and girls were reported separately while in the other four studies MVPA data were reported as mixed sex. 7/8 of eligible studies reported mean daily time spent in MVPA in minutes and in four studies time spent in MVPA was < 60 minutes/day. Furthermore, 2/7 of eligible studies obese children reached or exceeded 60 minutes of MVPA per day (405, 406), while in one study they came close to meeting the recommendations of 60 minutes/day of MVPA (404).

In all cases time spent in MVPA in the children who were obese was compared to the comparison peers. In only one study was the mean time spent in MVPA similar in both groups (405); in three studies, time spent in MVPA was significant lower in obese children than in the comparison group (403, 404, 407), while in two studies time spent in MVPA of obese children was lower than comparison group but differences were not significant (222, 406). In the other 2 studies time spent in MVPA of obese children was different in terms of gender compared to the comparison group: Hussey et al reported that mean MVPA was significantly lower in obese boys but not in girls (400); while Vale et al reported that mean time spent in MVPA was significantly lower in obese girls but not in boys (408) compared to the comparison groups.

With respect to SB, 4/8 eligible studies reported on accelerometer-measured time spent in SB of obese children with a total sample size of 536 children (191 obese; 28 boys, 32 girls and 131 no sex specified). In one study SB data of boys and girls was reported separately while in other the data were reported as mixed sex. Across all four eligible studies, mean time spent in SB was >70% of waking time (222, 400, 403, 407). In 3/4 of the studies time spent in SB was significantly higher in the obese than the non-obese groups, although, in one study it was significantly higher in obese boys but not in girls (400). In one study time spent in SB was similar in both groups (407).

4.3.4. MVPA and SB in Obese Adolescents

Twenty of the eligible studies involved adolescents, with a total sample size of 12601 adolescents (3045 obese; 1615 boys, 1575 girls and 195 no sex specified). Four of the eligible studies were clinical samples with participants recruited from outpatient clinics. Eligible studies were from different nations with one study from Asia (409), 11 from Canada and USA, and eight from Europe, with the study characteristics summarized in Table 3. In 12/20 studies, MVPA data of boys and girls were reported separately; in 6/20 studies MVPA data were reported as mixed sex, while the other two studies involved only adolescent girls. All 20 eligible studies reported mean daily of time spent in MVPA in minutes and in these studies it ranged from a low of 16 (SD 4) minutes/day (404) to a high of 140 (SD 47) minutes/day (410). In only 2/ 20 studies did daily time spent in MVPA reach an average of at least 60 minutes (410, 411) in the adolescents who were obese. A total of 16/20 eligible studies compared time spent in MVPA of those with obesity with a comparison group: in 3/16 time spent in MVPA was similar between obese and non-obese groups, while in 10/16 mean time spent in MVPA was significantly lower in obese adolescents than in non-obese peers.

Regarding time spent in SB, nine out of the 20 eligible studies reported on accelerometer measured time spent in SB in obese adolescents with a total sample size of 5484 adolescents (1101 obese; 546 boys and 555 girls), as summarised in Table 4.2. In 8/9 studies, SB data of boys and girls were reported separately, and 1/9 study involved only adolescent girls. In 7/9 studies, mean daily time spent in SB was reported in minutes and in these studies it ranged from a low of 345 (SD 122) minutes/day (402) to a high of 731 (SD 110) minutes/day (398). In 6/9 studies there was a comparison group; in 2/6 studies mean daily time in SB was similar in obese and non-obese groups (409, 412); in 2/6 studies time spent in SB was significantly higher in those with obesity than in the non-obese comparison groups (402, 413), while in the other 2/6 studies it was higher in the obese adolescents, but not significantly so (414, 415).

A graphical synthesis of the mean differences and 95% CI of time spent in MVPA by sex for both obese and non-obese children and adolescents is shown in Figure 4.2. A summary of the mean differences and 95% CI of time spent in SB by sex for both obese and non-obese children and adolescents is shown in Figure 4.3.

4.3.5. Study Quality Assessment

Study quality assessment summaries are given in Table 4.4. One study scored 4/6. Twelve studies scored 5/6 while 13 scored 6/6 on study quality.

Table 4.2: Overview of relevant characteristics and results of the included studies that involved child participants

Reference *	Place and publication year	Study design	Sample group	Comparison group	Measurement	Accelerometry methods	Finding	Meet 60min/day of MVPA (%) and Author Conclusions
Chung et al **(404)**	United States, 2012	Data of NHANES 2003-04 and 2005-06) surveys	n: 95 (47 boys, 48 girls) obese participants with BMI ≥95th to 99th centile Age: range 6-8 years	n: 514 (253 boys, 261 girls) participants with BMI ≥ 5th to 85th centile Age: range 6-8 years	Actigraph 7164 worn on the right hip for 7 consecutive days during waking hours	Epoch = 1min MVPA using Freedson cut-point (362)	Obese group mean (boys 118 (SD 6) and girls 83 (SD 10) min/day on MVPA. Comparison group mean (boys 129 (SD 4) and girls 104 (SD 4) min/day on MVPA	97, 70 % of obese boys and girls achieved an average of 60 min/day of MVPA. 98, 90% of the comparison boys and girls achieved an average of 60 min/day MVPA. MVPA was significantly lower in obese than comparison group ($p < 0.05$)
Hughes et al **(407)**	United Kingdom, 2006	Pairwise comparison study.	n: 53 (25 boys, 28 girls) obese participants with BMI ≥ 98th centile "Clinical sample" Age: mean 8.6 (SD 2)	n: 53 (25boys, 28 girls) participants with BMI < 85th centile. Age: mean 8.7 (SD 2.1) years	CSA/MTI, 7164 worn on right hip for 7 consecutive days.	Epoch = 1min MVPA > 3200 cpm Sedentary time < 1100 cpm	Obese group median 16 (range 2 -72) min/day on MVPA. Comparison group median 23 (range 7 - 77) min/day on MVPA. Obese group mean of 81 (SD 7) % sedentary. Comparison group mean of 79 (SD 6) % sedentary.	Obese participants failed to achieve an average of 60 min/day of MVPA. MVPA was significantly lower in obese than comparison group ($p < 0.001$). Sedentary time was similar in obese and comparison group

Hussey et al **(400)**	Dublin, 2007	Cross sectional study	n: 7/152 (3 boys, 4 girls) obese; with BMI > 97th centile. Age: range 7-10 years.	n: 121/152 (43 boys, 78 girls) pwith BMI > 75th to 91th centile. Age: range 7-10 years.	RT3Triaxial accelerometer, worn for 4 days.	Epoch = 1min MVPA > 3500 cpm Sedentary time cut-points not clearly reported	Obese participants mean (boys 14 (95%, CI- 11, 17) and girls 29 (95%, CI- 14, 43) min/day on MVPA. Comparison group mean (boys 39 (95%, CI-33, 45) and girls 24 (95%, CI- 22, 27) min/day on MVPA. Obese participants mean of (boys 1046 (95%, CI- 934, 1157) and girls 935 (95%, CI- 795, 1075) min/day sedentary. Comparison group spent mean of (boys 928 (95%, CI-901, 955) and girls 963 (95%, CI- 941,985) min/day sedentary.	Obese participants failed to achieve an average of 60 min/day of MVPA. MVPA was significantly lower in obese boys than comparison group (p <0.05). Sedentary time was significantly higher in obese boys than comparison group (p <0.05).
Maggio et al **(222)**	Switzerland, 2010	Cross sectional study	n: 45/209 obese participants with BMI > 97th centile "Clinical sample" Age: mean 9.1 (SD 0.3) years	n: 85 participants with BMI <90th centile Age: mean 10 (SD 0.3) years	Actigraph 6471, worn on right hip for 7 consecutive days	Epoch not clearly reported MVPA > 2000 cpm Sedentary time < 500 cpm	Obese group mean 60 (SD 3) min/day on MVPA. Comparison group mean 71 (SD 5) min/day on MVPA.	52% of the obese participants achieved an average of 60 min/day of MVPA. 60% of the comparison group achieved an average of 60 min/day MVPA.

							Obese participants mean 71% of time sedentary Comparison group mean of 70 % of time sedentary	MVPA was lower in obese than comparison group, but not significantly (p=0.07). Sedentary time was significantly higher in obese than comparison group ($p < 0.01$).
Metallinos-Katsaras et al **(406)**	United States, 2007	Cross sectional study	n: 21 obese children with BMI $\geq 95^{th}$ centile Age: range 2-5 years	n: 35 children; BMI $< 95^{th}$ centile Age: range 2-5 years	CSA 7164, worn on the hip for 7 consecutive days	Epoch= 1 min MVPA cut-points not clearly reported	Obese group mean 269 (SD not given) min/day on MVPA. Comparison group mean of 277 (SD not given) min/day on MVPA.	Obese participants exceeded an average of 60 min/day of MVPA. MVPA was lower in obese than comparison group but, not significant ($p > 0.05$
Thompson et al **(405)**	Canada, 2005	Cross sectional study	n: 112 (56 boys, 56 girls) obese participants with BMI $\geq 95^{th}$ centile Age: mean 8 (SD 0.3) years	n: 341 (177 boys, 164 girls) participants with BMI $\leq$ 85th centile Age: 3, 7 and 11 years old	Actigraph 7164, worn on the hip for 7 consecutive days	Epoch = 1min MVPA using Freedson cut-point (362)	Obese group mean (boys 172 (SD 58) and girls 157 (SD 52) min/day on MVPA. Comparison group mean (boys 179 (SD 63) and girls 165 (SD 51) min/day on MVPA.	Obese participants and comparison group exceeded an average of 60 min/day of MVPA. MVPA was similar in obese and comparison group.
Vale et al **(408)**	Portugal, 2013	Cross sectional study	n: 59/607 obese children with BMI defined according to the IOTF criteria Age: mean 5.1 (SD 0.8) years	n: 425/607 children with BMI defined as non-overweight, non-obese according to the IOTF criteria Age: range 4-6 years	ActiGraph GT1M, worn on the hip for 7 consecutive days	Epoch = 5 s MVPA $\geq$ 1680 cpm	Absolute MVPA not clearly given	MVPA was significantly lower in obese girls than comparison group ($p < 0.01$), but not in boys

Wafa et al **(403)**	Malaysia, 2014	Cross sectional study	n: 86 obese participants with BMI ≥ 95th centile Age: median 9.5 (IQR 8,11) years	n: 86 participants with BMI < 85th centile matched for age and gender	ActiGraph GT1M, worn for 5 consecutive days	Epoch not reported MVA >3200 cpm Sedentary time <1100 cpm	Obese group median 5 (IQR – 0, 32) min/day on MVPA. Comparison group median 9 (IQR – 0, 55) min/day on MVPA. Obese group spent an average of 90 % of time sedentary. Comparison group spent an average of 88 % of time sedentary	Obese participants failed to achieve an average of 60 min/day of MVPA. Comparison group failed to achieve an average of 60 min/day of MVPA. MVPA was significantly lower in the obese than in the comparison group ($p < 0.001$) Sedentary time was significantly higher in the obese group than in the comparison group ($p < 0.001$)

BMI – body mass index; cpm – counts per minutes; IOTF – International Obesity Task Force criteria; MVPA – moderate- vigorous physical activity; n – number; S – second. Data are expressed as mean, (SD) unless otherwise.
Freedson MVPA cutpoint (362) using the following equation: METS = 2.757 + (0.0015 x counts/min) – (0.08957 x age (yr)) – (0.000038 x counts/min x age (yr)). * Studies are listed in alphabetic order.

Table 4.3: Overview of relevant characteristics and results of the included studies that involved adolescent participants

Reference *	Place and publication year		Sample group	Comparison group	Measurement	Accelerometry methods	Findings	Meet 60min/day of MVPA (%) and Author Conclusions
Butte et al **(402)**	United States, 2007	Cross sectional study.	n: 473 (247 boys, 226 girls) obese participants with BMI ≥ 95th centile Age: mean 10.8 (SD 3.8) years	n: 424 (194 boys, 230 girls) participants with BMI <95th centile Age: mean 10.8 (SD 3.8) years	Actiwatch, worn on the right hip for 24 hours for 3 consecutive days	Epoch = 1min. Sedentary time and MVPA cut-points not clearly reported	Obese mean (boys 88 (SD 50) and girls 74 (SD 46) min/day on MVPA. Comparison group spent mean of (boys 96 (SD 57) and girls 79 (SD 57) min/day on MVPA. Obese group spent mean of (boys 357 (SD 118) and girls 345 (SD 122) min/day) sedentary Comparison group spent mean of (boys 305 (SD 121) and girls 308 (SD 131) min/day) sedentary.	62% of all participants (obese and comparison group) achieved an average of 60 min/day of MVPA. MVPA was lower in obese than comparison group but not significant Sedentary time was significantly higher in obese than comparison group (P = 0.001)
Chung et al **(404)**	United States, 2012	Data of NHANES 2003-04 and 2005-06) surveys	n: 185 (92 boys, 93 girls) obese participants with BMI ≥95th to 99th centile Age: range 12-17 years	n: 987 (489 boys, 498 girls) participants with BMI ≥ 5th to 85th centile Age: range 12-17 years	Actigraph 7164 worn on the right hip for 7 consecutive days during waking hours	Epoch = 1min MVPA used Freedson cut-point (362)	Obese group mean of (boys 34 (SD 4) and girls 16 (SD 4) min/day on MVPA. Comparison group mean (boys 40 (SD 3)	Obese participants failed to achieve an average of 60 min/day of MVPA. MVPA was significantly lower

							and girls 22 (SD 2) min/day on MVPA.	in obese than comparison group ($p < 0.05$)
Decelis et al **(414)**	Malta, 2012	Cross sectional study.	n: 34/187 (19 boys, 15 girls) obese participants with BMI defined according to the IOTF criteria Age: range 11-12 years	n: 106/187 (53 boys, 53 girls) participants with BMI defined as non-overweight and non-obese according to the IOTF criteria. Age: range 11-12 years	Actigraph GT3X, worn on right hip for 5 days during waking hours	Epoch not defined. Sedentary time ≤ 727 cpm and MVPA ≥ 2912 cpm	Obese group mean (boys 30 (SD 13) and girls 19 (SD 8) min/day) on MVPA. Comparison group mean (boys 44 (SD 16) and girls 26 (SD 9) min/day) on MVPA. Obese group mean (boys 638 (SD 95) and girls 619 (SD 106) min/day) sedentary Comparison group mean (boys 654 (SD 93) and girls 664 (SD 93) min/day) sedentary.	Obese participants failed to achieve an average of 60 min/day of MVPA. 11% of comparison group achieved an average of 60 min/day MVPA MVPA was significantly lower in obese than comparison group ($p < 0.05$) Sedentary time was higher in obese than comparison group, but not significant.
Decelis et al **(415)**	Malta, 2014	Cross sectional study.	n: 113/810 (59 boys, 54 girls) obese participants with BMI defined according to the IOTF criteria Age: range 10-11 years	n: 534/810 (254 boys, 280 girls) participants with BMI defined as non-overweight and non-obese according to the IOTF criteria Age: range 10-11 years	Actigraph GT3X, worn on right hip for 5 days during waking hours	Epoch = 10 s. Sedentary time < 100 cpm and MVPA > 2296 cpm.	Obese group mean boys 49 (SD 19) and girls 38 (SD 12) min/day on MVPA. Comparison group mean boys 61 (SD 22) and girls 44 (SD 15 min/day on MVPA. Obese group mean boys 553 (SD 94) and	Obese participants failed to achieve an average of 60 min/day of MVPA MVPA was significantly lower in obese than comparison group ($p < 0.05$).

							girls 610 (SD 125) min/day sedentary. Comparison group mean boys 582 (SD 113) and girls 603 (SD 97) min/day sedentary.	Sedentary time was higher in obese than comparison group, but not significant
Ekelund et al **(412)**	Sweden, 2002	Case control, cross sectional design study.	n: 18 (8 boys, 10 girls) obese participants with BMI defined according to the IOTF criteria Age: mean (boys 18.1 (SD 1.1), girls 17.3 (SD 1.9) years	n: 18 (8 boys, 10 girls) participants with BMI defined as non-overweight and non-obese according to the IOTF criteria. Age: mean (boys 18.2 (SD 1.1), girls 17.3 (SD 1.9) years.	CSA 7164, worn on lower part of the back (L 4–5) for 14 days.	Epoch= 15s Sedentary time <100 cpm and MVPA cut-points not clearly reported	Obese group mean boys 58 (SD 30) and girls 60 (SD 28) min/day on MVPA. Comparison group mean boys 82 (SD 36) and girls 98 (SD 58) min/day on MVPA. Obese group mean boys 421 (SD 33) and girls 465 (SD 132) min/day sedentary. Comparison group mean boys 414 (SD 81) and girls 397 (SD 69) min/day sedentary.	MVPA was significantly lower in obese than comparison group ($p < 0.05$). MVPA was similar in obese girls and boys ($p < 0.05$) Sedentary time was similar in obese and comparison group.
Gyllenham-mer et al **(416)**	United States, 2013	Cross sectional study.	n: 37 obese girls with BMI ≥ 95th centile Age: mean 15.5 (SD 1.1) years.	No comparison group	Actigraph GT1M, worn on the right hip for 7 consecutive days.	Epoch = 1min, SB =100 cpm and MVPA cut-points not clearly reported.	Obese girls mean 28 (SD 18) min/day on MVPA. Obese participants spent 63% (SD 7.) sedentary.	Obese girls failed to achieve an average of 60 min/day of MVPA. MVPA was lower in obese girls compared to

								published data from healthy adolescents.
Kitzman-Ulrich et al **(399)**	United States, 2010	Randomized trial ACT (Active by Choice Today) data at baseline used here.	n: 242/669 (98 boys, 144 girls) obese participants with BMI > 95th centile Age: mean 11.4 (SD 0.7) years.	n: 314/ 669 (138 boys, 176 girls) participants with BMI < 85th centile Age: mean 11.4 (SD 0.7) years.	Actical, worn on the right hip for 7 days all day	Epoch = 1 min. Sedentary time and MVPA cut-points not clearly reported.	Obese participants mean boys 46 (SD 20) and girls 36 (SD 15) min/day on MVPA. Comparison group mean boys 65 (SD 27) and girls 46 (SD 20) min/day on MVPA.	Obese participants failed to achieve an average of 60 min/day of MVPA. MVPA was significantly lower in obese than comparison group ($p<0.05$).
Maggio et al **(417)**	Switzerland, 2014	Case control study	n: 24 (12 boys, 12 girls) obese participants with BMI ≥ 97th centile. "Clinical sample" Age: mean 13.9 (SD 1.2) years	n: 25 (12 boys, 13 girls) participants with BMI <90th centile Age: mean 13.2 (SD 1.7) years.	Actigraph GT1M, worn for at least 4 days.	Epoch, MVPA cut-points not clearly reported, and Sedentary time <500 cpm	Obese participants mean 43 (SD 19) min/day on MVPA. Comparison group mean 58 (SD 30) min/day on MVPA.	Obese participants failed to achieve an average of 60 min/day of MVPA. MVPA was significantly lower in obese than comparison group ($P = 0.01$) MVPA was similar in obese girls and boys ($p < 0.05$).
Martins et al **(418)**	Portugal, 2015	Cross sectional baseline study.	n: 131 (48 boys, 83 girls) obese participants with BMI defined according to the IOTF criteria Age: mean 10.3 (SD 3.6) years.	No comparison group	Actigraph GT3x, worn for 7 consecutive days.	Epoch= 1 min. Sedentary time =0-100 cpm and MVPA cut-points not clearly reported.	Obese participants mean boys 65 (SD 28) and girls 51 (SD 22) min/day on MVPA. Obese participants mean boys 575 (SD 108) and girls 562 (SD 82) min/day on MVPA.	Obese participants failed to achieve an average of 60 min/day of MVPA MVPA was lower in obese participants compared to published data from healthy children and adolescents.

								MVPA was significantly lower in obese girls than obese boys ($p < 0.05$)
McMurray et al **(419)**	United States, 2008	Baseline data of Randomized controlled TAAG "Trial of Activity for Adolescent Girls"	n: 184/1021 obese girls with BMI ≥ 95th centile Age: range 11-14 years	n: 645/1021 participants with BMI < 85th centile Age: range 11-14 years	Actigraph MTI, worn for 6 consecutive days	Epoch = 30 s. MVPA cut-points not clearly reported	Obese girls mean 21 (SD 2) min/day on MVPA. Comparison group mean 25 (SD 1) min/day on MVPA.	Obese participants failed to achieve an average of 60 min/day of MVPA. MVPA was significantly lower in the obese than the comparison group (p=0.01).
Page et al **(410)**	United Kingdom, 2005	Cross sectional study.	n: 25 (14 boys, 11 girls) obese participants with BMI ≥ 99th centile. "Clinical and non clinical sample" Age: mean 10.5 (SD 0.8) years	n: 108 (54 boys, 54 girls) participants with BMI < 99th centile. Age: mean 10.5 (SD 0.8) years	Actigraph 7164, worn on the waist for 7 consecutive days	Epoch and MVPA cut-points not clearly reported.	Obese participants mean boys 140 (SD 47) and girls 105 (SD 48) min/day on MVPA. Comparison group mean boys 176 (SD 52) and girls 149 (SD 52) min/day on MVPA.	Obese participants exceeded an average of 60 min/day of MVPA MVPA was significantly lower in obese compared to comparison group (p=0.02)
Peart et al **(420)**	United States, 2011	Combined data of cross sectional NHANES (2003-04, 2005-06) surveys	n: 434/2368 (217 boys, 217 girls) obese participants with BMI ≥ 95 centile Age: mean 15.4 (SD 2.2) years	n: 1469/ 2368 (749 boys, 720 girls) participants with BMI < 85th centile Age: mean 15.4 (SD 2.2) years	Actigraph 7164, worn on hip over 7 day.	Epoch= 1 min MVPA≥ 1500 cpm.	Obese participants mean 28 (SD 35) min/day on MVPA. Comparison group mean 32 (SD 29) min/day on MVPA.	Obese participants failed to achieve an average of 60 min/day of MVPA. MVPA was lower in obese than comparison group

								but not significantly (p >0.05). MVPA was similar in obese boys and girls.
Ruiz et al **(413)**	10 centers in 9 European countries, 2011	Cross sectional study.	n: 104/2200 (45 boys, 59 girls) obese participants with BMI ≥ 95th centile Age: median 14.9 (IQR 12.8 – 15.8) years.	n: 1592/2200 (870 boys, 722 girls) participants with BMI < 85th centile Age: median 14.9 (IQR 12.8 – 15.8) years.	Actigraph GT1M, worn lower back for 7 consecutive days.	Epoch= 15 s Sedentary time < 100 and MVPA ≥ 2000 cpm.	Obese participants mean boys 60 (95%, CI- 53, 68) and girls 44 (95%, CI- 38,50) min/day on MVPA. Comparison group mean boys 67, (95%, CI- 65, 69) and girls 51 (95%, CI- 49,52) min/day on MVPA. Obese participants mean boys 68% and girls 71%) sedentary. Comparison group mean boys 69% and girls 72%) sedentary.	MVPA was significantly lower in obese boys than comparison boys group (p=0.002). Sedentary time was significantly higher in obese girls than comparison girls group (p=0.006)
Shoup et al **(421)**	United States, 2008	Cross sectional study.	n: 85 obese participants; BMI ≥ 99th centile "Clinical sample" Age: mean 10.6 (SD 1.4) years	n: 92 participants with BMI ≥85th and <95th centile matched for age	Actigraph 7164, worn on waist for 7 consecutive days	Epoch and MVPA cut-points not clearly reported	Obese participants mean 54 (SD 22) min/day on MVPA. Comparison group mean 59 (SD 30) min/day on MVPA.	40% (n = 34) of the obese group achieved an average of 60 min/day on MVPA 40% (n=35) of the comparison group achieved 60 min/day of MVPA.

								MVPA was similar in obese and comparison group.
St George et al **(397)**	United States, 2013	Baseline data of ACT Randomized trial (Active by Choice Today).	n: 484/1,422 (203 boys, 281 girls) obese participants with BMI ≥ 95th centile Age: mean 11.3 (SD 0.6) years	n: 684/1,422 (321 boys, 363 girls) participants with BMI < 85th centile Age: mean 11.4 (SD 0.6) years	Actical, worn on the right hip for 7 consecutive days	Epoch= 1 min MVPA used Puyau cut-point (384)	Obese participants spent mean of 37 (SD 22) min/day on MVPA. Comparison group spent mean of 47 (SD 28) min/day on MVPA.	Obese participants failed to achieve an average of 60 min/day of MVPA. MVPA was significantly lower in obese than comparison group ($p<0.01$)
Starkoffet al **(398)**	United States, 2014	Cross sectional study.	n: 16 (5 boys, 11 girls) obese participants with BMI ≥ 95 centile "Clinical sample" Age: mean 14.8 (SD 1.5) years.	No comparison group	Actical, worn on the right hip for 5 days during waking time	Epoch = 1min Sedentary time and MVPA cut-points not clearly reported	Obese participants mean (boys 26 (SD 36) and girls 19 (SD 17) min/day on MVPA. Obese participants mean boys 731 (SD 110) and girls 726 (SD 98) min/day) on sedentary.	12.5% of the obese group achieved an average of 60 min/day of MVPA. MVPA was lower in obese participants compared to published data from healthy adolescents.
Thompson et al **(405)**	Canada, 2005	Cross sectional study.	n: 171 (93 boys, 78 girls) participants with BMI ≥ 95th centile Age: range 12-16 years	n: 716 (327 boys, 389 girls) participants with BMI ≤ 85th centile Age: range 12-16 years	Actigraph 7164, worn on the hip for 7 consecutive days.	Epoch = 1min MVPA used Freedson cut-point (362)	Obese group mean boys 53 (SD 26) and girls 48 (SD 25) min/day on MVPA. Comparison group mean boys 58 (SD 30) and girls 47 (SD 24) min/day on MVPA.	Obese participants failed to achieve an average of 60 min/day of MVPA. Comparison group failed to achieve an average of 60 min/day of MVPA

								MVPA was similar in obese and comparison group.
Trost et al (43)	United States, 2001	Cross sectional study.	n: 54 obese participants with BMI ≥ 95th centile Age: mean 11.4 (SD 0.6) years	n: 133 non obese with BMI< 95th centile Age: mean 11.4 (SD 0.6) years	CSA 7164, worn on right hip for 7 consecutive days	Epoch = 1min MVPA used Freedson cut-point (362)	Obese participants mean 70 (SD 6) min/day on MVPA. Comparison group mean 82 (SD 4) min/day on MVPA.	Obese participants achieved an average of 60 min/day of MVPA. Comparison group achieved an average of 60 min/day of MVPA. MVPA was significantly lower in obese than comparison group ($p < 0.001$).
Vanhelst et al **(401)**	France, 2013	Cross sectional study.	n: 56 obese participants with BMI ≥ 97th centile "Clinical sample" Age: mean 12.8 (SD 2.9) years.	No comparison group	RT3 worn on right hip up to 21 consecutive days	Epoch = 1min Sedentary time = 0 - 40 cpm and MVPA cut-points not clearly reported	Participants mean 22 (SD 12) min/day on MVPA.	Obese participants failed to achieve an average of 60 min/day of MVPA. MVPA was lower in obese participants compared to published data from healthy children and adolescents.
Wang et al **(409)**	Chine, 2013	Cross sectional "large-scale study"	n: 175/2163 (115 boys, 60 girls) obese participants with BMI defined	n: 1709/2163; 808 boys; 901 girls with BMI defined as non-overweight, non-obese according	ActiGraph GT3X, worn on right hip for 7 consecutive days	Epoch = 1min. Sedentary time < 100 cpm and MVPA cut-points not clearly reported	Obese group mean boys29 (SD 18) and girls 24 (SD 13) min/day on MVPA.	7 % of obese boys achieved 60 min/day of MVPA. 10 %, 2 % of comparison boys

			according to the IOTF criteria Age: mean 13.41 (SD 2.25) years.	to the IOTF criteria Age: mean 13.41 (SD 2.25) years	Comparison group mean of boys 35(SD 19) and girls 22 (SD 14) min/day on MVPA. Obese group spent mean of (boys 480 (SD 107) and girls 490 (SD 89) min/day) sedentary. Comparison group spent mean of (boys 521 (SD 113) and girls 533, (SD 103) min/day) sedentary.	and girls achieved an average of 60 min/day of MVPA MVPA was similar in obese and comparison groups Sedentary time was similar in obese and comparison groups

BMI – body mass index; cpm – counts per minutes; IOTF – International Obesity Task Force criteria; MVPA – moderate- vigorous physical activity; n – Number; S – Second.
Data are expressed as mean, (SD) unless otherwise stated.
Freedson MVPA cutpoint (362) using the following equation: METS = 2.757 + (0.0015 x counts/min) – (0.08957 x age (yr)) – (0.000038 x counts/min x age (yr)).
*** Studies are listed in alphabetic order.**

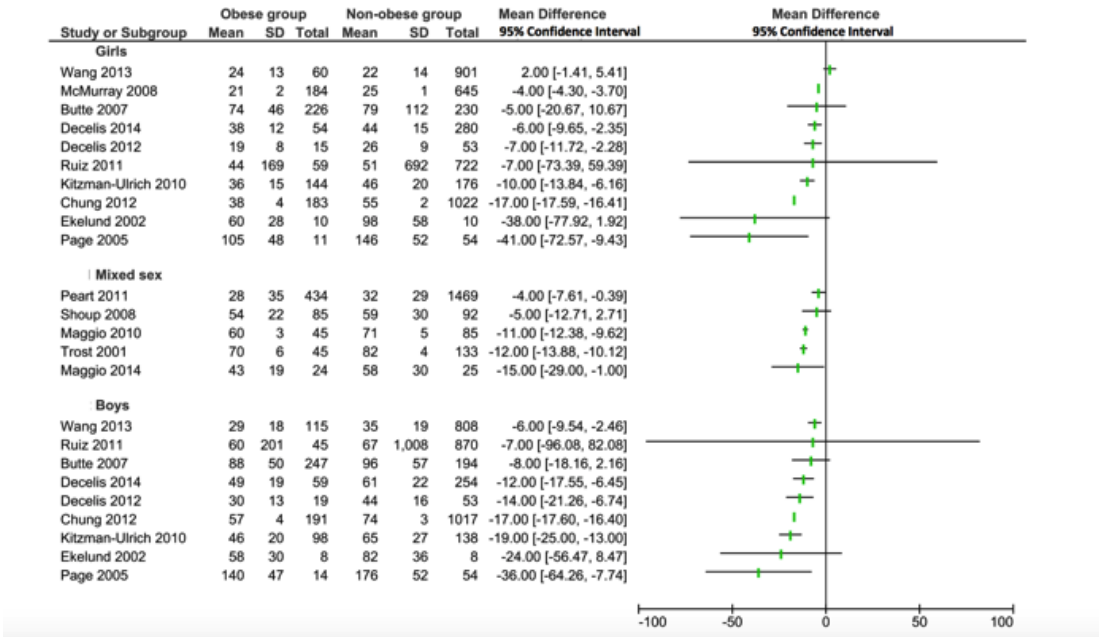


Figure 4.2: Forest plot of the comparison of moderate-to-vigorous intensity physical activity between children and adolescents with obesity and non-obese participants by sex.
SD: standard deviation; CI: 95% Confidence interval (Forest plot is kindly supplied by Dr Anne Martin).

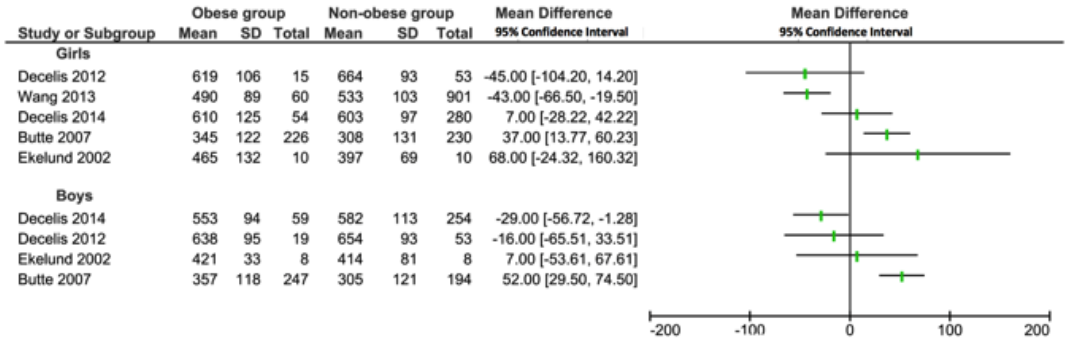


Figure 4.3: Forest plot of the comparison of sedentary time between children and adolescents with obesity and non-obese participants by sex.
SD: standard deviation; CI: 95% Confidence interval (Forest plot is kindly supplied by Dr Anne Martin).

Table 4.4: Methodological quality assessment of the included studies

	Quality Assessment Criteria, Items 1-6						
Study, year*	**1**	**2**	**3**	**4**	**5**	**6**	**Total score**
Butte et al, 2007	+	+	+	+	+	+	**6/6**
Chung, 2012	+	+	+	+	+	+	**6/6**
Decelis, 2012	+	+	+	+	+	+	**6/6**
Decelis, 2014	+	+	+	+	+	+	**6/6**
Ekelund, 2002	-	+	+	+	+	+	**5/6**
Gyllenhammer, 2013	-	+	+	+	+	+	**5/6**
Hughes, 2006	-	+	+	+	+	+	**5/6**
Hussey, 2007	+	+	+	+	+	+	**6/6**
Kitzman-Ulrich, 2010	+	+	+	+	+	+	**6/6**
Maggio, 2014	+	+	+	+	+	+	**6/6**
Maggio, 2010	-	-	+	+	+	+	**4/6**
Martins, 2015	-	+	+	+	+	+	**5/6**
McMurray, 2008	+	+	+	+	+	+	**6/6**
Metallinos-Katsaras, 2007	+	+	+	+	+	+	**6/6**
Page, 2005	-	+	+	+	+	+	**5/6**
Peart, 2011	+	+	+	+	+	+	**6/6**
Ruiz, 2011	+	+	+	+	+	+	**6/6**
Shoup, 2008	-	+	+	+	+	+	**5/6**
St George, 2013	-	+	+	+	+	+	**5/6**
Starkoff, 2014	-	+	+	+	+	+	**5/6**
Thompson, 2005	-	+	+	+	+	+	**5/6**
Trost, 2001	-	+	+	+	+	+	**5/6**
Vale, 2013	+	+	+	+	+	+	**6/6**
Vanhelst, 2013	-	+	+	+	+	+	**5/6**
Wafa, 2014	-	+	+	+	+	+	**5/6**
Wang, 2013	+	+	+	+	+	+	**6/6**

+ Indicates that a criterion was satisfied; − indicates that a criterion was not satisfied. 1, described of Sample recruitment?; 2, description of the sample.?; 3, Attrition of sample?; 4, Data collection and reduction?; 5, MVPA definition given?; 6, MVPA Results given?;

*** Studies are listed in alphabetic order.**

4.4. Discussion

4.4.1. Main Findings and Study Implications

Our systematic review provided evidence that is both clear and fairly consistent, and from relatively high study quality accelerometer-based studies that obese children and adolescents spend lower daily amounts of time spent in MVPA than non-obese peers. In most of the eligible studies, daily time spent in MVPA averaged less than the 60 minutes/day recommended in many guidelines.

In the methodology of the studies, it is noteworthy that the precise accelerometer methodology was often not stated clearly, or sometimes not stated at all, in the eligible studies particularly in the cut-off to define MVPA (Table 4.2 and 4.3). However, mean of time spent in MVPA were broadly similar within studies that employed comparable accelerometer methods. For example, in the two eligible Actigraph studies which used a cut-off of 2000 counts per minutes (cpm) to define MVPA (Maggio et al (222) , age 4-17 years old, and Ruiz et al (413), age 12-17 year olds) mean daily time spent in MVPA was 60 minutes/day in the obese boys in the sample studied by Ruiz et al (413), and 60 minutes/day in the obese boys studied by Maggio et al (222). Both of these studies might suggest the tentative conclusion that time spent in MVPA is relatively high in adolescents who are obese, possibly suggesting that adolescence and/or obesity do not present major barriers to MVPA. In contrast, three of the eligible Actigraph studies used higher MVPA cut-offs which ranged between 2912cpm in 11-12 year olds (Decelis et al (414)); 3200cpm in 8 and 9 year olds respectively (Hughes et al (407) and Wafa et al (403)). These studies found mean daily time spent in MVPA was 30 minutes in obese boys and 19 minutes in obese girls (414) and a median of 16 minutes for both sexes combined in the study by Hughes et al (407) and 5 minutes/day in the

study by Wafa et al (403). The majority of obese children and adolescents achieved means of < 30 minutes of daily time spent in MVPA in studies with cut-offs of ≥ 2912 cpm (400, 406, 407, 410, 411).

Further, it should be noted that recommendations for MVPA state that 60 minutes per day is a minimum every day (e.g. usually operationalized as 7 days in a week) (39, 281, 422), but adherence to recommendations was never operationalized in this way in any of the 26 eligible studies. We therefore used a mean or median daily MVPA of 60 minutes as a proxy for adherence, though this is conservative because in many individuals where 60 minutes MVPA/day was reached as an average, time spent in MVPA would have fallen below 60 minutes/day on at least one of the monitored days.

With respect to ST the present review found that studies fairly consistently reported that obese children and adolescent accumulated a high amount of sedentary time during their waking hours, ranging typically between 65-90 % of their monitoring time: 10 hours was the mean daily sedentary time in all 13/26 studies, which reaches or exceeds typical Actigraph measured levels of sedentary time in North-American adults from surveys such as NHANES. All eligible studies, which had comparison groups found sedentary time, were fairly consistent with no marked differences between obese and non-obese peers.

In the present systematic review, the level of heterogeneity between eligible studies made it impossible to combine data in a meta-analysis. The heterogeneity noted could be due to differences in place of the studies, differences in the way obesity was defined (different BMI cut-off points and different reference data), or differences in accelerometer models and methodology. Therefore, we narratively synthesized the

differences in the time spent in MVPA and ST between obese and control groups by age and sex.

4.4.2. Comparisons with Other Studies

We believe that the present study is the first systematic review to ask whether or not levels of accelerometer measured MVPA are adequate in obese children and adolescents, and whether time spent in MVPA and sedentary time differed between obese and comparison groups based on accelerometer data. There are therefore no directly comparable studies. However, our findings are consistent with some studies on the correlates and determinants of objectively MVPA (423, 424), and consistent with a growing belief that obesity is associated with reduced MVPA. Low MVPA is probably both a cause of obesity (low activity increases risk of the obesity) and a consequence of obesity (obesity lowers activity level), i.e., “bidirectional causation”, (65, 66, 396).

4.4.3. Review and Evidence Strengths and Weaknesses

The evidence considered by our review had a number of strengths. Firstly, it investigated the accelerometer-measured time spent in MVPA and SB of obese children and adolescents, with clear definitions of obesity so that samples included in the review were not contaminated by the inclusion of overweight but non-obese individuals. Secondly, there are several methodological strengths to this study. Studies were identified from an extensive search of the published literature conducted in a range of databases, over the last 15 years, covering the time when accelerometers started to become available and popular in PA research and more recently SB research. The broad definition of search terms applied across multiple databases enabled the

searching and identification across many potential studies with no limitations on place of publication, sample size or country of origin. Restricting eligibility to studies using accelerometry was important in increasing confidence in the measurement of MVPA (348, 380-382). The included studies were in general rated as being of high or very high methodological quality with respect to their accelerometry methods. Also, in some cases the eligible studies were based on large, nationally representative samples or surveys another strength in terms of generalizability.

There were some sources of weakness in our systematic review. Firstly, since studies had to be published in peer-reviewed journals in English, this may have excluded relevant evidence. The generalisability of review results is subject to certain limitation; for instance, eligible studies in our systematic review were from high-income nations, and we lack data from low-middle income countries. Most of the included studies were based on relatively small samples of obese children and adolescents with a total (n = 14739 participants; n = 3523 obese) and their power to estimate habitual MVPA might have been limited, and thus the extent to which the results observed are generalizable to the general obese paediatric population is unclear. Our method for assessing the quality of eligible studies has been used in variously adapted forms in a number of other recent accelerometry systematic reviews (54, 353-355) and used 15 items, but the process of collapsing these 15 items to a six-item scale might have reduced the possibility of identifying differences in quality between studies.

Eligible studies generally obtained MVPA and ST data using the ActiGraph accelerometer, but methods used varied between studies. Methodological differences include: the definition of epoch, the number of hours and days of data constituting a valid/acceptable data set, MVPA and ST cut-points, and the choice of non-wear

criteria. These methodological variation tends to produce meaningful differences in MVPA and ST estimates between studies (346) and also make it difficult to compare across studies. However, while there were multiple differences between studies in accelerometry methodology (e.g. in epochs, cut-points, handling of non-wear time, duration of accelerometry monitoring), in all cases the methods were the same within studies between the obese and non-obese comparison groups, so these methodological differences probably had limited effect on the ability of studies to identify differences in MVPA and ST between the obese and non-obese. Finally, the validity of accelerometry (in particular hip-worn accelerometry, the method in almost all eligible studies) to determine ST is less well established than the validity of this placement for measurement of MVPA (425). Hip-worn accelerometers are not generally designed to measure posture, and devices which include inclinometers may provide improved measurement. Accelerometers are used widely to measure ST though, and there is some evidence of validity for group-comparisons as here (obese vs non-obese comparisons) (30, 346).

4.5. Conclusions

In summary, the data presented in our review demonstrated that a high percentage of obese children and adolescents do not achieve the minimum amount of 60 minutes per day MVPA that is recommended in guidelines and tended to spend what appears to be the vast majority of their waking hours in SB. Obese children and adolescents were less physically active and more sedentary compared to comparison groups. The present review supports the hypotheses that the obese children and adolescents are both less physically active and more sedentary than the non-obese peers (though cannot test whether they were less active or more sedentary before becoming obese).

Given the many and varied health and non-health benefits of MVPA in children and youth (20, 38) and emerging evidence that ST influences health outcomes in children and adolescents (426, 427), the present review highlights the need to focus on increasing MVPA and reducing ST among obese children and adolescents, and the importance of raising these issues in clinical settings as part of treatment for obesity. However, there is a need for more research on children, and for more 'dose-response' evidence. As well, more intervention studies were warranted to examine the treatment of childhood and adolescent obesity should clearly involve a focus on increasing MVPA and reducing SB as recommended in multiple evidence based treatment and prevention guidelines published in recent years.

CHAPTER V

24-Hour Movement Behaviours in Children with Chronic Disease Compared to Healthy Children

Manuscript in under review in PLoS One 2018

5.1. Introduction and Aim

There is growing concern about low level of PA in children and adolescents (14, 150, 347, 428). Many fail to meet current recommendations for a minimum of 60 minutes of MVPA daily (79). In addition to low PA, there is increasing concern that high level of SB may also be common. Both low PA and high SB are important risk factors for cardiovascular disease, chronic diseases and mortality in adults (342, 344, 429, 430), as well associated with cardiovascular disease risk factors in children and adolescents, especially in their obesity (431) and metabolic risk profile (432). Most previous research on levels of PA and SB has focused on healthy children. Children with chronic disease have often been excluded from such research, with presence of a chronic disease being a common exclusion criterion, and they have either been excluded from or under-represented in public health surveillance of physical activity (291).

Our recent systematic review of objectively measured MVPA in children with chronic disease found a relatively small amount of evidence (25 eligible studies across all groups with chronic disease and across all of childhood and adolescence). Habitual MVPA in children with chronic disease was consistently well below the recommended minimum of 60 minutes per day and they accumulated a high amount of ST. However, MVPA in children with chronic disease though was not very much lower than in healthy control or comparison groups with the exception of children being treated for malignancy.(291).

It is clear that there are no easy solutions to these serious and interlinked public health issues of low PA and increased SB and it is acknowledged that a range of strategies is likely

to be required. One commonly used strategy has been to try to find ways to increase overall PA and reduced ST.

Recently, Chaput et al, have argued that focusing on MVPA while ignoring other components of movement behaviours limits our understanding of how various 'activities' interact together to impact children's health (22). This has led to a growing realisation that an integrated approach that includes all movement/non-movement behaviours extending from sleep through to MVPA ("24-Hour movement behaviours") might be a better way forward. Each of these behaviours may interact with PA and each may have an important influence on child health, development, and well-being (131, 132). This developing realisation has led to national Canadian and Australian evidence-based guidance for 24-hour movement behaviours in children and adolescents published in 2016 and 2017 (131, 132, 322). International (WHO) evidence-based guidance for the under 5s is currently under development and should be published in early 2019 (83).

The 24-hour movement behaviours concept is so new that it has not been applied to studying children with chronic disease to date. In order to start to address this research deficit, we aimed carry out a case-control observational study to investigate 24-hour movement behaviours (sitting/lying, PA, standing, and sleep) for 5-7 days in children with common chronic childhood disease and test whether there are differences between children with chronic disease and their healthy peers.

5.2. Methods and Participants

The methods and participant recruitment procedures were described in detail in Chapter II. In brief, the sample comprised 160 participants in total: children with chronic disease (n=80) and healthy controls (n=80) matched for age and sex. We investigated children with four common chronic diseases: 20 with TIDM, 20 with JIA, 20 with CHD, and 20 with CF as described in Chapter II. Patients were recruited from the outpatient clinics at Royal Hospital for Children, Glasgow, UK. Our healthy control children were obtained from nursery/schools, and children of staff members and friends.

The study was approved by West of Scotland Research Ethics Committee 1 (Reference number 16/WS/0126) and NHS Greater Glasgow and Clyde Health Board (Appendix II). Parents of all participants provided informed written consent, and their children provided their informed assent - if applicable - to participate in the study prior to collection of any study data.

Sex, age, height, weight, disease duration and a number of clinical variables related to each disease were recorded at the start of the study. BMI was then calculated from the height and weight measures (kg/m^2). Anthropometric measurements and clinical variables were described in details in Chapter II.

5.3. Statistical Analyses

In this study, all variables (anthropometric data, sitting/lying, PA, standing, and sleep behaviours) were checked for normality. Normally distributed data were summarised using mean (SD), while median and interquartile range were used for any data that were not normally distributed. Since children with chronic disease were matched pairwise with healthy controls (for age, sex, and time of year), and data on differences between pairs were normally distributed. Paired t-tests were used for the primary analysis that examined the significance of any differences between children with each particular illness vs their healthy controls for each of the 24-hour movement behaviours. As a secondary analysis we also compared the results in all children with chronic disease as a group with all healthy controls as a group using a t-test. Statistical significance was set at a cut-off value of $\leq$ 0.05. Details of the study power calculation are described in detail in Chapter II section 2.2.4.

5.4. Results

The details of the recruitment process, accelerometer results, characteristics of participants and summary details of the study participants are described in Chapter II Section 2.6.

5.4.1. 24-Hour Movement Behaviours in Children with Chronic Disease and Healthy Controls

Tables 5.1 and 5.2 and Figures 5.1, 5.2, 5.3 and 5.4 show summarised 24-hour movement behaviours (PA, standing, sedentary “sitting”, and sleep behaviours) for the children with chronic disease compared to healthy controls.

5.4.1.1. Sedentary Time in Children with Chronic Disease and Healthy Controls

All ST components (total sitting time, sitting percentage per 24 h period, and number of breaks (Up transitions) which reflected the number of sitting bouts) are shown in Table 5.1 and Figures 5.1, 5.2, 5.3 and 5.4.

Children with T1DM and their healthy controls group: there was no significant difference in sitting time between the two groups (paired t-test p = 0.33), as shown in Figure 5.1-A. The mean (SD) of total number of breaks (Up transitions) which reflected to total number of sitting bouts in children with T1DM was lower compared to healthy peers, a difference that was close to significance (paired t-test p = 0.08).

Children with JIA and their Healthy Controls: again there was no significant difference in sitting time between the two groups (paired t-test p = 0.77), as shown in Figure 5.1-B. Children with JIA had significantly lower of total number of breaks (Up transitions) compared to healthy controls (paired t-test p = 0.002).

Children with CHD and their healthy controls group: there was no significant difference in sitting time between the two groups although the difference was close to significance (paired t-test p = 0.06), as shown in Figure 5.1- C. Those with CHD had a lower number of breaks (Up transitions) which compared to healthy controls, but this difference in the number of breaks was not significant (paired t-test p = 0.36).

Children with CF and healthy controls group: There was a significant difference in sitting time between the two groups (paired t-test p = 0.02), as shown in Figure 5.1-D. The number of breaks (Up transitions) which reflected to number of sitting bouts per 24 h in

children with CF was lower compared to healthy peers, but this difference in the number of breaks (Up transitions) was not significant (paired t-test p = 0.52).

All Children with Chronic Disease (n=80) Compared with Healthy Controls (n=80)

Finally, as a secondary analysis we compared children in the chronic disease group with their matched healthy control group. There was a significant difference in sitting time between the two groups (paired t-test p = 0.01), as shown in Figure 5.2. The total number of breaks in sitting (posture transitions) was lower compared to healthy peers, a difference that was significance (paired t-test p = 0.001). Thus, children with chronic disease sat for longer with more prolonged periods of sitting than their healthy controls.

5.4.1.2. Standing in Children with Chronic Disease and Healthy Controls

Standing time was expressed as total amount of time spent in standing. Standing time and standing as a percentage per 24 h period are shown in Table 5.1 and Figures 5.1, 5.2, 5.3 and 5.4.

Children with T1DM and their healthy controls groups: the time spent in standing was lower in diabetic children compared to healthy peers, but the difference was not statistically significant (paired t-test p = 0.15).

Children with JIA and their healthy controls groups: Children with JIA spent lower time in standing compared to their healthy peers spent. The difference between children with JIA and healthy controls for standing time was significant (paired t-test p =0.02).

Children with CHD and their healthy controls groups: the time spent in standing was lower in children with CHD than healthy peers, but the difference between two groups was not significant (paired t-test p =0.22).

Children with CF and their healthy controls groups: The standing time was lower in children with CF compare to healthy. There was a significant difference in the time spent standing between two groups (paired t-test p = 0.0002).

All Children with Chronic Disease (n=80) Compared with Healthy Controls (n=80): Children with chronic disease spent lower time in standing and the difference between two groups was statistically significant (paired t-test p = 0.0001).

5.4.1.3. Physical Activity in Children with Chronic Disease and Healthy Controls

PA data expressed in two ways: 1) total amount of time spent in PA; 2) PA percentage per 24 h period and 3) number of steps per day as shown in Tables 5.1 and 5.2 and Figures 5.1, 5.2, 5.3 and 5.4.

Children with T1DM and their healthy controls groups: the difference in time spent in PA between children with T1DM and healthy control groups was significant (paired t-test p =0.04). Further, the activPAL measured step counts per 24 h period in children with T1DM compared with healthy controls and difference in step count between the groups was close to being significant (paired t-test p = 0.09).

Children with JIA and their healthy controls groups: Children with JIA spent lower time in PA compared to healthy peers, a difference that was not statistically significant (paired t-test p = 0.16). Steps measured by the activPAL in children with JIA and healthy controls group and the difference in step count between the groups was not significant (paired t-test p = 0.26).

Children with CHD and their healthy controls groups: The difference in the time spent in PA was significant (paired t-test p = 0.01) between two groups. While, the difference in step count between the groups was significant (paired t-test p = 0.02).

Children with CF and their healthy controls groups: There was no significant difference between the two groups in the time spent in PA (paired t-test p = 0.73). Also, the difference in step count between the groups was not significant (paired t-test p = 0.84).

All Children with Chronic Disease (n=80) Compared with Healthy Controls (n=80): The difference in time spent in PA between children with chronic disease and healthy controls was significant (paired t-test p =0.001). Further, the difference in step count between the groups was also significant (paired t-test p = 0.01). This overall, children with chronic diseases had lower PA levels and lower measured step count levels.

5.4.1.4. Sleep Duration in Children with Chronic Disease and Healthy Controls

Tables 5.1 and 5.2 and Figures 5.1, 5.2, 5.3 and 5.4 summarises sleep time variables in children with chronic disease compared to healthy controls. Other sleep variables are presented in chapter VI.

Children with T1DM and their healthy controls groups: The difference in sleep duration between children with T1DM and healthy controls was not significant (paired t-test, p=0.12). **Children with JIA and their healthy controls groups:** The difference in sleep duration between children with JIA and healthy controls was significant (paired t-test p = 0.0007). **Children with CHD and their healthy controls groups:** The difference in sleep duration of children with CHD and healthy controls was not statistically significant (paired t-test p =0.52). **Children with CF and their healthy controls groups:** The difference in sleep duration between-groups was not significant (paired t-test p =0.30). It was noted that this was the only chronic disease group where sleep duration was slightly shorter than controls. **All Children with Chronic Disease (n=80) Compared with Healthy Controls (n=80):** The difference in sleep duration between children with chronic disease and healthy controls was significant (paired t-test, p=0.001). This overall, children with chronic diseases had significant prolonged sleep duration than healthy controls.

5.4.2. 24-Hour Movement Data Comparisons with Recommendations

The activPAL can make objective measures of the amount of time spent in PA, of the number of steps per day (as a proxy for physical activity), of the time spent in sleep, and

of the time spent sedentary (sitting/lying down), and time spent standing but not moving. Of these behaviours, there are currently paediatric guideline recommendations only for number of steps per day and time spent in sleep. Number of steps per day and time spent asleep were therefore compared against the appropriate age-specific recommendations: in children aged 4-6 years for steps per day the recommendation is 10,000 - 14,000 steps/day; In boys aged 6-11years 13,000 - 15,000 steps per day and in girls 6-11years 11,000 - 12,000 steps per day in girls to achieve an average of 60 minutes per day of MVPA (86). For sleep duration, the recommendation in children aged 3-4 years is 10-13 h per night, and in children aged 5-13 years 9-11 h per night, with consistent bed and wake-up times (131, 132).

In both our chronic disease and healthy control groups mean steps per 24h period were below the recommendations. A total of 49/160 participants (n=20 in children with chronic disease and 29 in healthy control groups) met the step count recommendations. From each group the number of individuals who met the step count recommendations was as follows three (one boy and two girls) in children with T1DM and four girls in their healthy peers; eight (four boys and four girls) in children with JIA and nine (two boys and seven girls) in their healthy control group; four (one boy and three girls) in children with CHD and eight (three boys and five girls) in their healthy control group; and five (one boy and four girls) children with CF and eight (five boys and three girls) in their healthy control group, as summarised in Table 5.4.

Mean duration of sleep was within recommendations for all four-groups both for the children with chronic diseases and for their four healthy control groups. For the individual

level data, a total of 23 participants (n=10 in children with chronic disease and 13 in healthy control groups) were below the sleep recommendation. For each group the numbers not meeting the sleep recommendations were as follows three (one boy and two girls) in children with T1DM; and four (two boys and two girls) in their healthy peers, five (two boys and three girls) in healthy control of JIA group, three (two boys and one girl) in CHD and two (one boy and one girl) in their healthy peers, four (two boys and two girl) in CF and two (one boy and one girl) in their healthy control groups; were had short sleep duration "below" the sleep recommendation as summarised in Table 5.4.

In Summary,

In children with T1DM, although, there were no significant differences between patient and controls for sedentary, standing and sleep time, they had greater time spent sedentary with lower number of breaks (meaning more prolonged sitting bouts), less standing time with slightly longer sleep time than their healthy controls. While, time spent in PA was significant lower in children with T1DM, with lower step counts (but not significantly lower) compared to healthy controls.

Children with JIA had slightly greater sedentary time with significantly lower number of breaks in sitting (more prolonged sitting bouts), significantly lower standing time, and significantly longer sleep time than their healthy controls. Also, they were less physically active (in both time spent in PA and step counts) than their healthy controls although but the differences did not reach significance.

Children with CHD had greater ST lower number of breaks (i.e. prolonged sitting bouts) and less standing time with longer sleep time than their healthy peers, (but not significant). Children with CHD were significantly less physically active (in terms of both time spent in PA step counts) than healthy controls.

For children with CF there was little difference in terms of PA and step counts between them and their healthy controls. However, they were significantly more sedentary with lower number of breaks than their healthy controls and spent significantly less time standing than their healthy peer, Children with CF were the only chronic disease group to have slightly shorter sleep times compared to healthy controls.

These apparently small but consistent differences in the children within the individual chronic disease groups and their matched controls become more obvious when the children with chronic diseases are considered as a group. In children with chronic disease, there were significant differences between patients and controls for time spent sedentary, standing, PA and asleep. Patients had greater time spent sedentary with significantly lower number of breaks in sedentary time (meaning more prolonged sitting bouts), and less standing time with slightly longer sleep time than their healthy controls. Time spent in PA as measured by activPAL accelerometry was significantly lower in the children with chronic disease than the controls, and patients also had significantly lower step counts compared to healthy controls.

Table 5.1: 24-hour movement behaviours variables in children with chronic disease and their healthy control; data are presented as means and (SD)

Variables	CD (n=80)	HC (n=80)	T1DM (n= 20)	HC (n= 20)	JIA (n= 20)	HC (n= 20)	CHD (n= 20)	HC (n= 20)	CF (n= 20)	HC (n= 20)
Time spent sitting h	8.1 (1.4) *	7.4 (0.9) *	8.3 (1.7)	7.8 (0.8)	7.6 (1.1)	7.4 (1.0)	8.1 (1.7)	7.4 (0.9)	8.1 (1.0) *	7.2 (0.9) *
% of sitting per 24 h	33.3 (5.8)	30.8 (3.7)	34.5 (7.3)	32.6 (3.1)	31.5 (4.7)	31 (4.5)	33.9 (7.1)	30.9 (3.7)	33.7 (4.2)	30.0 (3.6)
No of sitting bouts	245 (68) **	277 (88) **	210 (56)	243 (93)	236 (75) **	319 (87) **	241 (61)	298 (82)	249 (31)	261 (83)
Time spent standing h	3.1 (0.7) ***	3.7 (0.7) ***	3.2 (0.7)	3.5 (0.6)	3.2 (0.9) *	3.8 (0.8) *	3.2 (0.8)	3.6 (0.5)	2.9 (0.5) ***	3.7 (0.7) ***
% of stand per 24 h	12.9 (3)	15.4 (2.9)	13.3 (3)	14.5 (2.3)	13.3 (3.8)	15.9 (3.2)	13.4 (3.2)	15 (2.1)	12.1 (2.1)	15.4 (3.1)
Time spent in PA h	2.1 (0.8) **	2.5 (0.4) **	1.7 (0.7) *	2.2 (0.4) *	2.3 (0.9)	2.6 (0.3)	1.9 (0.9) *	2.5 (0.4) *	2.4 (0.7)	2.4 (0.4)
% of PA per 24 h	8.7 (3.3)	10.4 (1.6)	7.2 (3)	9.1 (1.6)	9.5 (3.7)	10.8 (1.3)	8 (3.7)	10.4 (1.8)	10.0 (3.1)	10.2 (1.8)
No steps per 24h	9,485 (4,148) *	10,959 (2,024) *	8201 (3231)	9903 (1657)	10428 (4139)	11608 (1561)	8533 (4712) *	11249 (2320) *	11395 (4169)	11050 (2128)
Time spent in sleep h	10.1 (0.8) **	9.7 (0.6) **	10.2 (0.7)	9.7 (0.6)	10.4 (0.8) ***	9.5 (0.5) ***	10.2 (0.9)	9.7 (0.5)	9.7 (0.9)	9.9 (0.5)
% of sleep per 24 h	42.1 (3.3)	40.4 (2.8)	42.5 (2.9)	40.4 (2.8)	43.3 (3.2)	39.6 (2.1)	42.5 (3.9)	40.6 (2.1)	40.4 (2.8)	41.2 (2.2)

CD – chronic disease; CHD – congenital heart disease; CF – cystic fibrosis; JIA – juvenile idiopathic arthritis; h – hour; T1DM – type1 diabetes mellitus.
Combined data represented total children with chronic disease (CD n=80, mean age 6.9 years (SD=2.0), and F: M 43: 37) as one group and total healthy controls n=80, mean age 6.8 (SD=1.9) and F: M 43: 37) as one group. Further details of characteristics data in Chapter II and Table 2.1.
Data are presented as means and standard deviation SD unless otherwise specified.
Paired t test compared between children with chronic disease and healthy children control age and sex matched; * P=< 0.05, ** P=< 0.005 and ***P= <0.0005

Table 5.2: 24-hour movement behaviours variables comparisons with recommendations in children with chronic disease and healthy controls.

Variables	CD (n= 80)	HC (n= 80)	T1DM (n= 20)	HC (n= 20)	JIA (n= 20)	HC (n= 20)	CHD (n= 20)	HC (n= 20)	CF (n= 20)	HC (n= 20)
No. of participants meeting steps recommendation	20	29	3	4	8	9	4	8	5	8
No. of participants *NOT* meeting sleep recommendation	10	13	3	4	0	5	3	2	4	2

CHD – congenital heart disease; CF – cystic fibrosis; JIA, – juvenile idiopathic arthritis; T1DM – type1 diabetes mellitus.
Combined data represented total children with chronic disease (CD n=80, mean age 6.9 years (SD=2.0), and F: M 43: 37) as one group and total healthy controls n=80, mean age 6.8 (SD=1.9) and F: M 43: 37) as one group. Further details of Characteristics data in Chapter II and Table 2.1.
Steps recommendations per day 10,000- 14,000 steps/day in children aged 4-6 years, 13,000- 15,000 steps per day in boys and 11,000- 12,000 steps per day in girls aged 6-11 years old (86);
Sleep duration recommendations 10- 13 h per night in children aged 3-4 years, and 9- 11 h per night in children aged 5-13 years, with consistent bed and wake-up times (131, 132). Data are presented as number.

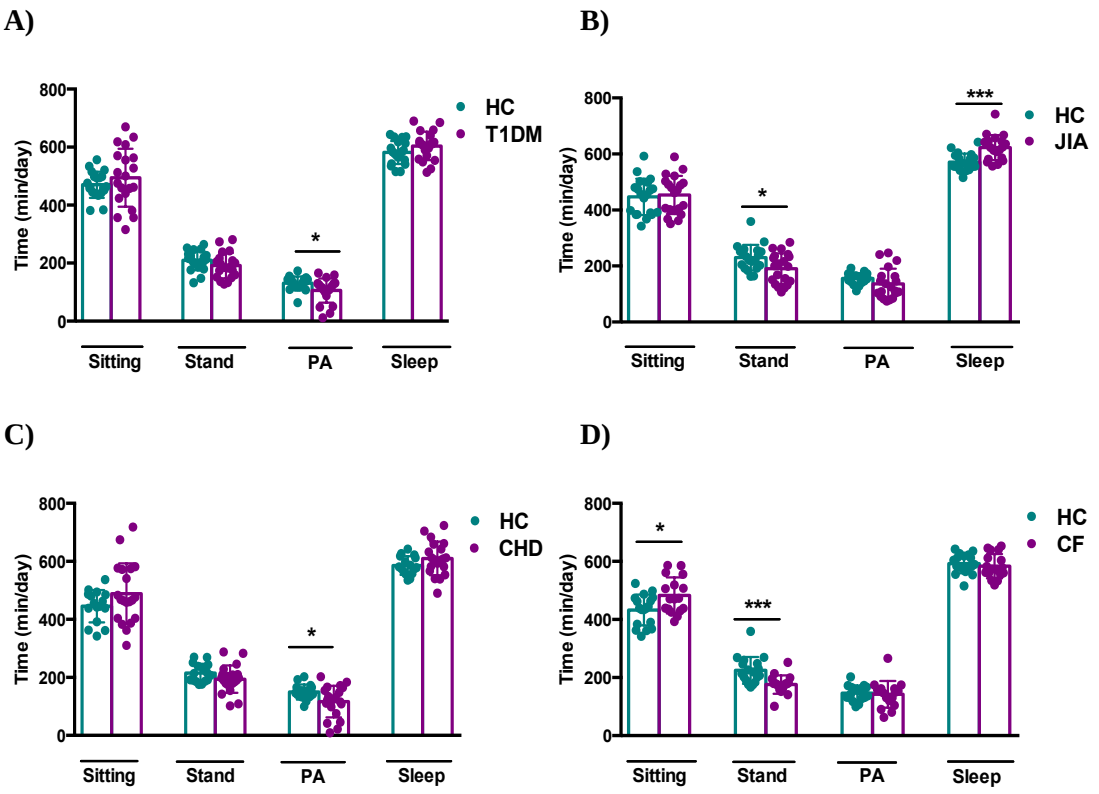


Figure 5.1: Difference in 24-Hour movement behaviours (Sitting/lying, PA; physical activity, stand, and sleep) variables for children with chronic disease compared to healthy controls.
A) Between children with T1DM (type 1 diabetes mellitus) (n=20) and their healthy control (n=20) groups;
B) Between children with JIA juvenile idiopathic arthritis (n=20) and their healthy control (n=20) groups;
C) Between children with CHD (congenital heart disease) (n=20) and their healthy control (n=20) groups;
D) Between children with CF (cystic fibrosis) (n=20) and their healthy control (n=20) groups;
Values presented with a mean ± SD and dots represent the participant. Paired t test compared between children with chronic disease and healthy children control age and sex matched; * significant difference and P=< 0.05, ** P=< 0.005 and ***P= <0.0005.

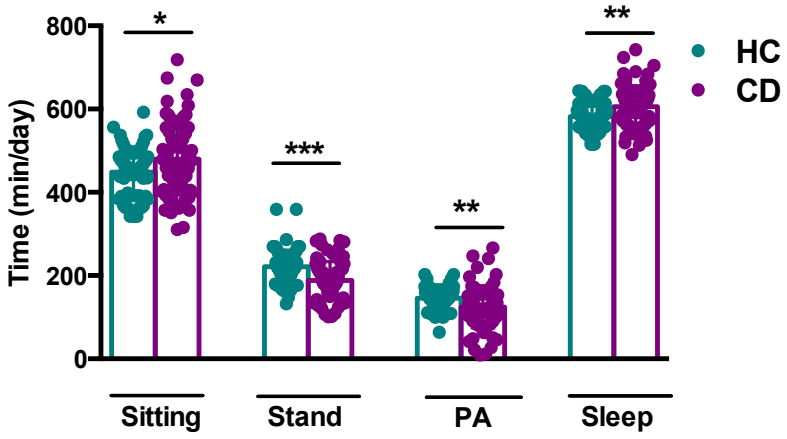


Figure 5.2: Difference in 24-Hours movement behaviours (Sitting/lying, PA; physical activity, stand, and sleep) variables for total children with chronic disease (CD n=80) compared to total healthy controls (HC n=80). Combined data represented total children with chronic disease (CD n=80, mean age 6.9 years (SD=2.0), and F: M 43: 37) as one group and total healthy controls n=80, mean age 6.8 (SD=1.9) and F: M 43: 37) as one group. Values presented with a mean (SD) and dots represent the participant. Paired t test compared between children with chronic disease and healthy children control age and sex matched; * significant difference and P=< 0.05, ** P=< 0.005 and ***P= <0.0005.

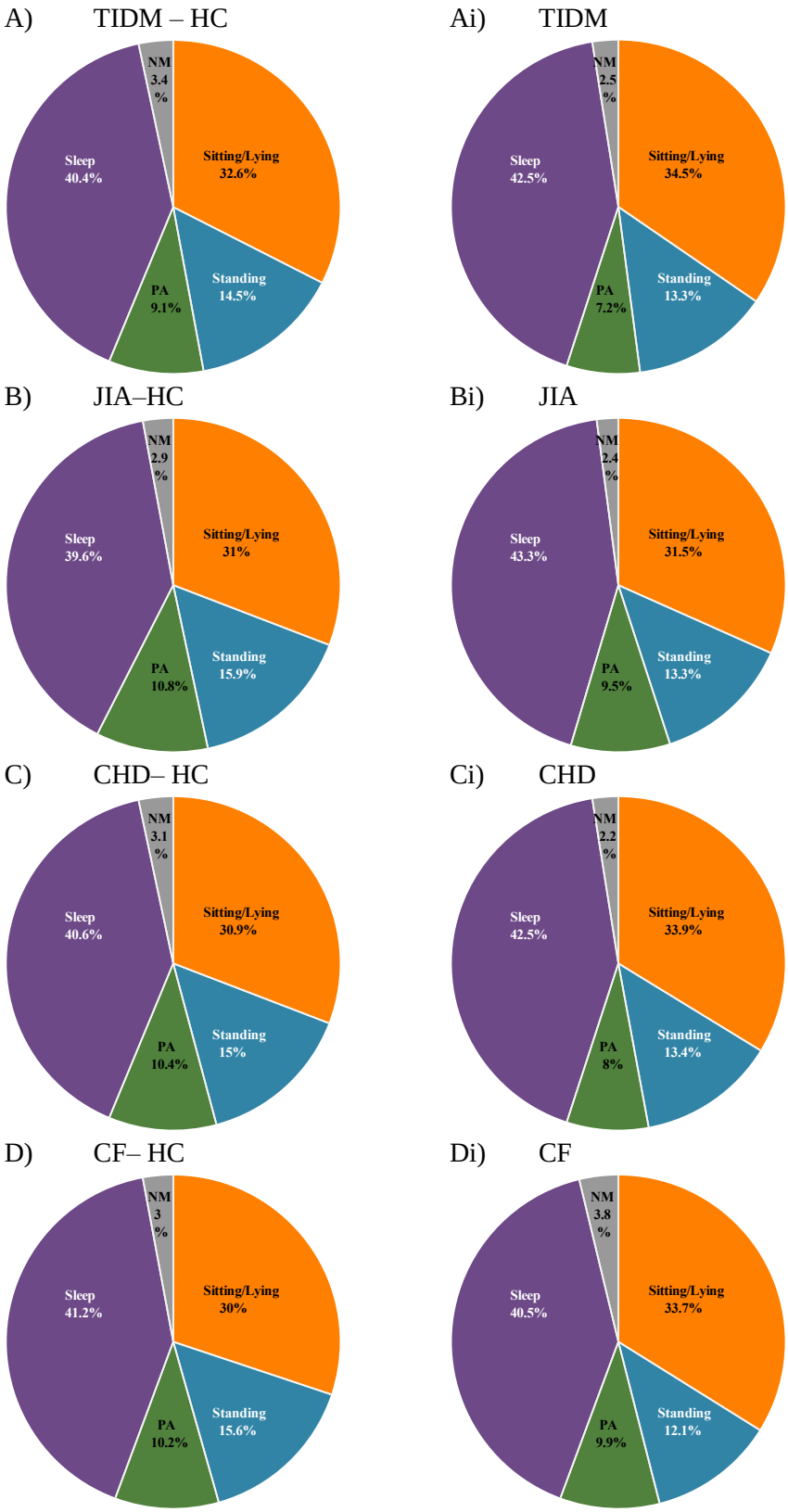


Figure 5.3: Pie chart represented the distribution of 24-hour movement behaviours in children with chronic disease and their healthy controls groups; A-D is healthy control groups (n=20/group) of TIDM; JIA; CHD and CF, while, Ai-Di is represent children with chronic disease (n=20/group) of TIDM; JIA; CHD and CF respectively. Abbreviations: CHD, congenital heart disease; CF, cystic fibrosis; JIA, juvenile idiopathic arthritis; T1DM, type1 diabetes mellitus; NM, non-wear time.

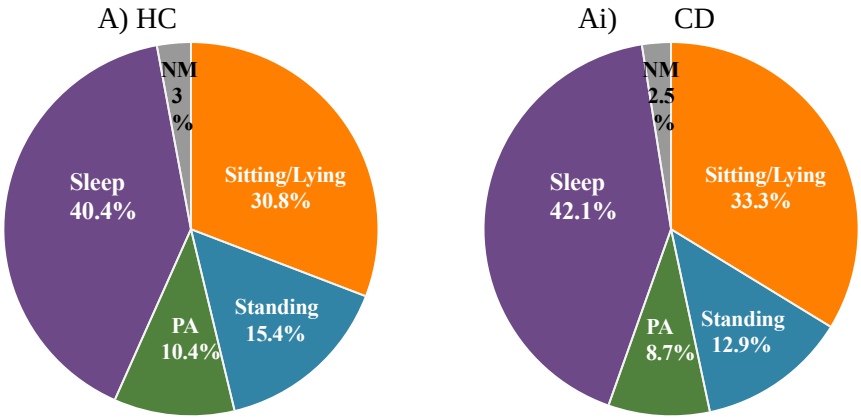


Figure 5.4: Pie chart represented the distribution of 24-hour movement behaviours in: A- total healthy controls (HC n=80, mean age 6.8 (SD=1.9) and F: M 43: 37) as one group, while, Ai- is represent total children with chronic disease (CD n=80, mean age 6.9 years (SD=2.0), and F: M 43: 37) as one group; NM - non-wear time. Further details of participants characteristics data in Chapter II and Table 2.1 Values presented with a mean (SD)

5.5. Discussion

5.5.1. Main Findings and Study Implications

The intense recent interest in the new paradigm of '24-hour movement behaviours' in children has not yet extended to children with chronic disease of childhood. There are currently few published data on these behaviours for children, particularly school-age children (132, 133) and even fewer data from children with any of the common chronic diseases of childhood. Since the release of the Canadian 24-Hour movement guidelines for children and adolescents in 2016 (school age children and adolescents) and 2017 (the under 5s) (131, 132), our study appears to be the first to quantify 24-hour movement behaviours in children with common childhood diseases, and to test for differences in the time spent in the behaviours between those children and healthy controls.

The present study suggests that for at least some groups with chronic disease 24-hour movement behaviours may differ substantially from recommendations and differ slightly but systematically from their healthy peers. The most obvious concerns in the present study relate to the greater ST in children with chronic disease, although the differences from healthy controls are small and were significant only in the CF group and nearly so in the CHD group. In addition, the number of breaks (Up transitions) was consistently lower in those with chronic disease compared to healthy controls, meaning that children with chronic disease had more prolonged sitting bouts compared to healthy control groups. Again differences between disease groups and healthy controls were small and here were only significant only in children with JIA and nearly so T1DM groups. Standing time was lower in children with chronic disease and significantly lower in those with JIA and CF than in their healthy controls.

Children with chronic disease were consistently less active than their healthy controls, in both the time spent in PA and step counts, although again the difference between chronic disease groups and controls were small with significantly lower time spent in PA in the T1DM and CHD groups, and significantly lower step counts in CHD. Except in children with CF, time spent in asleep was slightly greater in children with chronic disease compared to healthy peers but with a significant difference only in JIA and their healthy control groups.

When data from the four groups of controls and four groups with chronic disease were combined children with chronic disease had significantly greater time spent sedentary with significant lower number of breaks with significant less standing time with significant longer sleep time than their healthy controls. Children with chronic disease were significantly less active than their healthy controls, reflected both in the time spent in PA and step counts. Twenty-four hour movement behaviours were generally slightly more favourable in the healthy controls than in the patient groups.

The analysis combining data of the different patient groups is exploratory. The similarity in findings between patient groups and controls (e.g. generally slightly lower levels of PA and slightly higher levels of ST) across all four of the patient groups makes it tempting to conclude that any potential ‘effects’ of chronic disease may be similar, but further research would be needed to establish this. We combined data form four different disease groups all of whom were stable and free living at the time of recruitment. However, while it is important to acknowledge that different mechanism may be operating within the different groups, nevertheless they did all share the label and had the met the characteristics specified to be labelled as having a chronic illness

"*Chronic illness in children and adolescents could be defined as any physical, emotional, or mental health problem that lasts at least three months, and affects a child's physical appearance and/ or growth and daily normal activities and results in frequent hospitalisations with regular therapy and sometimes unpleasant procedures, with home and medical care (166).* "

There are no either evidence based or consensus expert opinion paediatric recommendations for total sedentary time and standing time. Lately, it is has become widely believed, based mostly on adult studies, that standing is better for cardiometabolic health than sitting, and breaking up long periods of sitting with standing is good for cardiometabolic health (433-435). It is not at present certain that these possible benefits of standing also apply to children. However, it is at least probable that underlying biological mechanisms are likely to apply to both children and adults, and behavioural norms around sitting and standing may be established in childhood. There is increasing interest in time spent standing in childhood, interest that includes a number of intervention studies where 'standing breaks' in the classroom have been the main intervention (436). Hopefully, this will result in a clearer and more substantial evidence base about whether time spent standing is indeed important for health outcomes in children.

Therefore, my study included time standing as an early empirical exploration of the topic. For example, it seemed potentially important to highlight that children stand for quite long periods in each 24-hour day, as shown by my study, yet most previous 24-hour movement behaviour studies in children have ignored/not presented time spent standing.

Hopefully, the significance of time spent standing might become clearer as more evidence comes to light on the possible benefits of standing (or at least not sitting) in children in future.

5.5.2. 24-Hour Movement Behaviours Data Comparisons with Recommendations

Whether children with chronic disease and their healthy peers meet 24-hour movement behaviours recommendation is an interesting and important question and deserves further investigations. As we noted above, currently there are no either evidence based or consensus expert opinion paediatric recommendations for total sedentary time and standing time. Therefore our study focused on step counts per day and sleep duration since these have widely used recommendations for children in the public domain (86, 131, 132). Our results showed that in all groups, both patients and controls, step counts were much lower than age-specific recommendations per day (86). Only 30.6% of participants (12.5% in children with chronic disease and 18.1% in healthy control groups) met the step count recommendations per day.

The next part of our study addressed meeting sleep duration recommendations. Here, in both chronic disease and healthy control groups mean duration of sleep was within the range 9-11 h of sleep per night with consistent bed and wake-up times, in accordance with what is recommended (131, 132). However, 14.4 % of participants (6.3 % in children with chronic disease and 8.1% in healthy control groups) did not meet the sleep duration recommendation, and they slept less than recommended.

5.5.3. Comparisons with Other Studies

As noted above, the novelty of the 24-hour movement behaviours paradigm, particularly as it applies to children with chronic disease, makes comparison between the present study and other studies problematic. We are unaware of any studies of compliance with new 24-hour recommendations in school-age children. Our recent systematic reviews found that levels of MVPA were lower than recommended in children with chronic disease, though typically not lower than control groups except in children with malignancy and children with obesity (291, 385).

The present study data on PA are broadly consistent with those findings, in that levels of PA (measured both as time spent moving by the activPAL and the step counts) in the patients were generally lower than those of the controls, though the differences were generally small and were not always significant in the sample size we used of n = 20 pairs.

Furthermore, our findings are somewhat consistent with previous research that examined these behaviours, particularly MVPA, in children with chronic disease. Our systematic review showed that children with chronic disease had more inactive lifestyles than their peers (i.e. spent less time in PA and more time in SB). As an example, one study included in our review was that of Maggio et al who carried out a cross-sectional study to examine MVPA and ST in children with childhood disease focused on obesity, JIA and T1DM groups compared to healthy children, with 209 children and adolescents aged 4.8 to 17.9 years: 45 were obese, 48 had T1DM, 31 had JIA and 85 were healthy. MVPA and ST were assessed by using an uniaxial accelerometer (Actigraph^{TM}). They found that ST was significantly greater in those

with chronic disease and MVPA was lower in children with childhood disease (but only significantly in JIA) compared to the healthy control group (222).

Taken together with our recent systematic reviews it seems likely that levels of objectively measured PA among many groups of children with chronic disease – at least for those who are relatively well - are lower than recommended, though probably not much lower than their healthy peers.

While the children recruited to patient groups in the present study were relatively well and living as outpatients, they and their families were presumably still living with a substantial burden imposed by their chronic disease. For example, in children with T1DM, although 60% (n=12) with good glycaemic control, there was 40% (n=8) were considered to have poor glycaemic control at the time of recruitment with an average of duration 2.1 years from diagnosis to the time of enrolment in the study. Further, 35% were on insulin pump therapy, a complex treatment, with the others on insulin multiple injections per day. All children with JIA had been receiving treatment with biological therapies with a mean 3.2 years disease duration from diagnosis to the time of enrolment. However, four out of the twenty of children with JIA were off treatment at the time of recruitment. All children in the group with CHD had received cardiac surgery, with a mean time from the last surgical procedure at the time of enrolment of 3.5 years (SD=2.2) years, while 55% (n=11) children had moderate-severe CHD and most had more than one cardiac operation. Further, forty per cent (n=8) of CHD children were still on medical treatment at the time of enrolment. Children with CF were on treatment with the mean time from diagnosis to study enrolment of 6.5 years (SD=2.0) years, where most of them had diagnosis with CF in early their life following

neonatal screening “within a few months after their birth” and were being frequently admitted to the hospital to receive systemic treatment.

While the disease severity ranged from mild/moderate to severe among the children with chronic disease in the present study, all were attending school and being treated as outpatients. Therefore, the lack of large differences in PA and the other 24-hour movement behaviours between chronic disease versus control groups is perhaps a reflection of the normalisation of low levels of PA and high levels of ST among healthy contemporary children rather than exceptionally impaired PA in the chronic disease group (156, 158, 437).

5.5.4. Study Strengths and Limitations

This study had several strengths and limitations that warrant discussion. The main interest of the present study was the novelty of the research questions and population, with a paucity of 24-hour movement data in general. This lack of data has been even greater in children with chronic disease. Further strengths were our ability to make objective measures of so many of the behaviours (time spent sitting, standing, moving, and sleeping), to control for the key known determinants of these behaviours at this age (age, gender, season (158, 289, 290)), and to make pair-wise comparisons of the behaviours with closely matched healthy controls. The participants were composed of boys and girls with children with chronic disease and their healthy control groups and they were closely matched for age and sex matched-to avoid influences of age and sex on PA and sedentary behaviours (289). Previous research reported that younger children are more active than older children, with a decline in activity with increasing age (289, 290). Evidence from longitudinal studies has shown that SB increases with

age and becomes less fragmented (longer bouts of sitting time), and also that the increase in sedentary time displaces time spent in PA (158, 438).

We were also able to allow for the fact that children spend a good deal of time standing and not moving. Time spent standing has generally not been considered in previous studies, and possibly misclassified as other forms of movement behaviour in previous studies. Furthermore, a highly standardised measurement protocol was used. In addition, the 24-hour movement behaviours were measured across a sufficient number of days and nights to obtain a reliable assessment of the participants' usual sedentary, standing, PA and sleep behaviours by using ActivPAL™ accelerometer, a small device that has been validated for such studies. Thus, we believe our results provide a valid and reliable picture of 24-hour movement for the children with chronic disease and healthy children across 7 days.

The limitations of the present study included the fact that children with chronic disease were recruited from a hospital setting. However, these children were attending routine follow-up appointments because of their chronic disease and were apparently fairly well at the time of recruitment. Our results focused on four of the chronic childhood chronic disease groups and their generalisability to other chronic disease groups in children is not yet known. It is not clear if differences in 24-hour movement behaviours could be detected among groups of children with other chronic diseases such as children with malignancies or another musculoskeletal disease, or with even more severe/advanced forms (or during disease exacerbations) of diseases in the present study, and this requires future work. Furthermore, in our study the participants aged range 3-10 years, a relatively young age when taking account of the fact that differences in activity are

only likely to increase as children move into adolescence. Thus additional research will be required to investigate whether similar findings are found in younger or older children with these or other chronic diseases.

The most important limitation was inability to measure MVPA in the present study, as there are currently no algorithms for converting activPAL-measured movement to MVPA in school-age children. Although a few studies in adults have suggested stepping cadence of >100 and >70 steps/min as equivalent to MVPA using the activPAL3 (439), there is no valid and reliable data that this would be suitable for children of mean age around 6 years. Janssen et al have provided evidence validity of using a cut-point ≥1418 counts per 15s to measured MVPA from activPAL in young children aged 4-6 years. Despite the broader age ranges in our study (from 3-10 years with mean age 6.9 and 6.8 for children with chronic disease and healthy peers), we initially thought the Janssen cut-point might be suitable to use with our participants to estimate MVPA levels. Unfortunately, the results show there was discrepancy between their MVPA level and number of steps/day. Since this means that the cut-points was not evidence based I did not present this result in the original thesis and presented in Appendix III Table 2.

A further weakness was our inability to measure screen-time – a subset of sedentary behaviour. Again, there are currently no objective methods available for measuring screen time exposure in children and the accuracy of subjective (parent-report) methods is unknown as suggested by the recent systematic review by Prince et al (312). If and when these methodological difficulties can be overcome, then more comprehensive experimental investigations of 24-hour movement behaviours will become possible.

The high degree of compliance with the activPAL measurement protocol in the present study suggests that future studies of time spent in PA, SB, and sleep, should be practical with a single device, but enhancements to our existing device-based approaches to reflect the limitations highlighted would be desirable.

The high degree of compliance with the activPAL measurement protocol in the present study suggests that future studies of time spent in PA, SB, and sleep, should be practical with a single device, but enhancements to our existing device-based approaches to reflect the limitations highlighted would be desirable.

Finally, in a post hoc analysis of our data we calculated using the data we collected that a minimum of 16-20 pairs would be required to have a 80% power of detecting a difference in PA and SB between children with chronic disease and healthy peers with a significance level of 5%, but in fact some of the differences between groups were relatively small and much larger studies may be required to determine the significance of differences between some of the groups in future studies. The statistical significance of some of the differences may in fact be of secondary importance - the main findings of the present study may be more relevant because of the biological/clinical significance of the observed low levels of PA, high levels of ST, with apparently adequate levels of sleep in children with and without chronic disease during early-mid childhood. If sustained, the tracking of such low levels may lead to cumulative effects in the longer term.

5.6. Conclusions

In conclusion, the present study suggests that 24-hour movement behaviours in children with chronic disease give cause for some cause for concern and may be generally slightly worse than in their healthy peers. Those with chronic disease tended to spend slightly more time sedentary with lower number of breaks in their sitting, and with less time standing and less time in PA with lower step counts per 24 h period but and with longer sleep duration than controls. The fact that the findings for sleep were different in children with CF who were only chronic disease group to have slightly shorter sleep duration then their healthy peers – suggests that individual characteristics of each chronic disease may have different impact on 24 hour movement behaviours.

Optimising levels of the 24-hour movement behaviours should potentially confer a number of benefits for child health, development, and wellbeing (132) and so improving 24-hour movement behaviours should be considered as part of the management of many common childhood chronic diseases in future. Methods to normalising 24-hour movement behaviours will require large scale empirical testing. At present, further, future research efforts should aim to examining 24-hour movement behaviours in larger sample sizes, should extend measures to screen time and MVPA if possible, and also children with other chronic diseases should be considered for future studies.

CHAPTER VI

Sleep Behaviour in Children with Chronic Disease Compared to Healthy Children

6.1. Introduction and Aim

Sleep is a ‘naturally recurring resting state in which the human body is not active and the mind is unconscious’ (109). During sleep, most human systems are in an anabolic state, building up the immune, nervous, skeletal and muscular systems (119). Sleep is also important for the mental processes of learning as well as the maintenance of emotional and mental wellbeing of the individual (112, 125). Healthy sleep requires adequate duration of sleep, appropriate timing of going to sleep (sleep onset) and waking (sleep offset), and freedom from disturbance during sleep (112). Like PA and nutrition, sleep has an important role in growth and physical and mental development and health in children and adolescents (114, 125, 440).

Lack of sleep (in terms of timing and duration) and poor sleep quality (in terms of sleep interruption by awake episodes) has been shown to have significant impacts on daytime functioning and mood in otherwise healthy children (441, 442). A number of epidemiological reports have linked inadequate sleep duration with increased risk of chronic disease and rate of premature mortality in adults (111). Part of this association might be mediated by obesity, as that has also been associated with short and long sleep duration (119, 443). Further, it is obvious from many observational studies that suboptimal sleep - insufficient or poor quality sleep - is associated with impairments in cognition, behaviour, performance, and well-being in children and adolescents (139, 442, 444, 445). It is also associated with poor physical health outcomes, including hypertension, cardiovascular disease, diabetes, obesity, and cancer in adults and children (121-123, 446-448).

In contemporary society, it is recognised that there has been a secular decline in sleep duration in children (449). However, the causes of this decline are not well understood. Later bedtimes with largely unchanged wake time are one possibility (118, 450). National and international bodies such as the National Sleep Foundation have recommended 10-13 hours of sleep per night for preschool children and 9–11 hours of sleep per night for school-aged children to maximise general health and well-being (451). These recommendations for the population are usually also considered to be applicable to children with chronic diseases (131, 132), Indeed, the United States Centres for Disease Control and Prevention in 2011 recommended 10 -12 hours of sleep per night for school-aged children with chronic disease (452).

Measurement of sleep in young children continues to be challenging. Subjective measures such as sleep diaries and parental questionnaires are widely used methods of assessing child and adolescent sleep and are relatively easy to use and inexpensive. Some clinical research has used objective methods such as polysomnography, considered the gold standard of objective sleep measurement, in children and adolescent. Because it is complex, time consuming and expensive, polysomnography is mainly used in experimental studies that include clinical populations. Alternative objective methods such as accelerometry currently represent a more readily available accurate and convenient objective tool for measuring sleep in terms of both quantity and quality of sleep (453). Accelerometry has been shown to produce more consistent and accurate measurement of sleep than subjective methods (138, 309).

While there have been many studies on sleep, both on quantity and quality, in healthy children (454, 455), there are surprisingly few studies in children with chronic disease

and so differences in sleep in children with chronic disease compared to healthy children particularly using objective methods of measurement such as accelerometry (128, 129). This part of our work was undertaken to investigate sleep quantity – particularly sleep timing (in terms of sleep onset/offset), and sleep duration - and sleep quality in children with chronic diseases. In particular, we wished to investigate whether children with chronic disease differed from healthy controls and whether both met the current sleep duration recommendations (131, 132) using objective measurements (activPAL^{TM} micro accelerometer).

6.2. Methods and Participants

6.2.1. Recruitment Process and Participants

The data used in this study were also collected in the 24-hour movement behaviours in children with chronic disease compared to healthy controls groups study described in Chapter V. The procedures for recruitment were described in chapter II. In brief, there were 160 participants in total: (n=80) children with chronic disease recruited from outpatient clinics at the Royal Hospital for Children, Glasgow, UK; and (n=80) healthy control group children recruited from local schools and nurseries. We investigated children from four groups of children with common chronic diseases: 20 with TIDM, 20 with JIA, 20 with CHD, and 20 with CF. The study had a paired design, with each patient matched with a healthy control child, matched for age, gender, and time of measurement as these have been identified in previous studies as the main influences on PA, SB and sleep in children. (289, 290).

The study was approved by West of Scotland Research Ethics Committee 1 (Reference number 16/WS/0126) and NHS Greater Glasgow and Clyde Health Board. Informed consent was obtained from the parents/guardians of all participants, and children provided their informed assent -if applicable - to participate in the study prior to collection of any study data.

Sex, age, disease duration and a number of clinical variables related to each disease were recorded at the start of the study. Height and weight were measured to 0.1cm and 0.1kg respectively, and Body Mass Index (BMI) was then calculated from the height and weight measures (kg/m^2) and expressed relative to age and sex using the UK 1990 BMI reference data (298, 299). Details of the anthropometric measurements and the clinical variables collected were described in detail in Chapter II.

6.2.2. Measurement of Sleep Behaviour Variables – Sleep Quantity and Quality - Using the ActivPAL

Sleep time was measured objectively using an activPAL™ micro monitor (PAL Technologies Ltd., Glasgow, UK). Children were asked to wear the monitor continuously for 24 h a day over seven consecutive days and nights. Data from the activPAL™ micro were downloaded using activPAL Professional (Version 7.2.32 software) and processed manually using the activPAL™ HSCPAL software files. To be included in our analysis, participants had to have ≥ 4 days with ≥ 10 hours of waking wear time in a 24-hour period including one weekend day, and have ≥ 3 valid nights (i.e. valid night having total sleep duration ≥ 160 minutes per night (326)) including one weekend night – either Friday or Saturday night. The reason for these inclusion criteria was to attempt to get a measure of usual sleep.

For each participant, information on sleep onset and offset, sleep time (duration) and sleep quality variables were extracted and calculated by using event file of the HSC PAL analysis software version 2.14, more details provided in Chapter II.

6.3. Statistical Analyses

All study variables were screened for normality, and normally distributed data summarised either as mean (SD) for normally distributed data or as median (interquartile range) for data that were not normally distributed. Since children with chronic disease were matched pairwise with healthy controls (for age, sex, and time of year), paired t-tests were used to test the significance of any differences between children with particular illness vs their healthy controls for each of the sleep behaviour (quantity and quality) components. Then all children with chronic disease were tested compared with their healthy controls for each of the sleep behaviour (quantity and quality) components.

Statistical significance was set at a cut-off value of ≤ 0.05. Details of the study power calculation are described in detail in Chapter II section 2.2.4.

6.4. Results

The details of the recruitment process, accelerometer results, characteristics of participants and summary details of the study participants are described in Chapter II Section 2.6.

6.4.1. Nocturnal Sleep Behaviour Variables in Children with Chronic Disease and Healthy Controls

Tables 6.1 and 6.2 summarises the nocturnal sleep behaviour (quantity and quality) variables measured objectively of children with chronic disease compared to healthy controls.

6.4.1.1. Sleep Quantity Variables in Children with Chronic Disease and Healthy Controls

Sleep quantity measures (Sleep onset, sleep offset, sleeping time "sleep duration per 24h period", sleep percentage per 24 h period and number of participants meeting the sleep recommendation per night) are shown Table 6.1.

The mean time of nocturnal sleep duration in children with chronic disease compared to healthy controls was significant in children with JIA was significant (paired t-test p = 0.0007), but the difference was not significant in children with T1DM (paired t-test p=0.12), in children with CHD (paired t-test p =0.52) and in children with CF (paired t-test p =0.30). As well, the difference between all children with chronic disease (n=80) compared with healthy controls (n=80) in sleep duration was significant (paired t-test p=0.001).

6.4.1.2. Sleep Quality in Children with Chronic Disease and Healthy Controls

Table 6.2 presents sleep quality-related variables obtained from 24 h thigh-worn accelerometry data in all children with chronic disease and healthy controls.

Children with T1DM and their Healthy Controls

Our results showed that, six (30%) children with T1DM accumulated sleep in a single episode, ten (50%) in two episodes, while four (20%) had three or more episodes per night. Thus six (30%) of children with T1DM had no wake episodes per night, ten (50%) had one wake episode per night and four (20%) of children had two or more wake episodes per night. In their matched controls, seventeen (85%) accumulated sleep in a single episode and the other three (15 %) had two sleep episodes per night. Thus, seventeen (85%) of healthy controls had no wake episodes, three (15 %) of the healthy control group had only one wake episode per night and none of the controls had more than one wake episode per night.

Next, we looked at quality of sleep in children with T1DM and control group in relation to duration of nocturnal sleep disruption per night (average total wake time per night). Mean total disrupted sleep duration in children with T1DM was 17 minutes (SD 20 minutes) per night compared to controls with an average 5 (SD 7 minutes) per night. The difference was significant (paired t-test $p = 0.03$).

Children with JIA and their Healthy Controls

Seven (35%) of children with JIA accumulated sleep in a single episode, eleven (55%) in two sleep episodes, and two (10%) in three sleep episodes per night. Thus seven

(35%) of the children with JIA had no wake episodes, eleven (55%) one wake episode, and two (10%) of JIA children had two wake episodes per night. In comparison, eighteen (90%) of healthy controls accumulated sleep in a single episode, and two (10%) in two sleep episodes and thus eighteen (90%) of healthy controls had no wake episode and two (10%) of them had one wake episode.

With regards to the duration of total sleep disrupted in children with JIA compared to healthy controls, children with JIA had an average of 13 minutes (SD 22 minutes) per night disrupted compared to healthy children who had an average of 7 minutes (SD 5 minutes) disrupted per night. This difference was not significant (paired t-test $p = 0.20$).

Children with CHD and their Healthy Controls

In children with CHD, two (10%) accumulated sleep in one episode, seven (35%) in two episodes and eleven (55%) in three or more sleep episodes. Thus, two (10%) children with CHD had no wake episodes per night, seven (35%) had one wake episode per night and eleven (55%) had two or more wake episodes per night. While in healthy controls, sixteen (80%) accumulated sleep in a single episode and four (20%) in two sleep episodes. Therefore, sixteen (80%) of the healthy controls had no wake episode and four (20%) of healthy controls had one wake episode per night.

In term of duration of total sleep disrupted in children with CHD and healthy control, there was a significant difference in total disrupted sleep duration, in children with CHD mean 24 minutes (SD 30 minutes) per night and healthy control group mean 6 minutes (SD 4 minutes) per night (paired t-test $p = 0.01$).

Children with CF and their Healthy Controls

Three (15%) of children with CF accumulated sleep in one episode per night, five (25%) in two episodes and twelve (60%) in three or more episodes per night. Only three (15%) of children with CF had no wake episodes, five (25%) had one wake episode and twelve (60 %) had two or more wake episodes per night. Seventeen (85%) of healthy controls accumulated sleep typically in a single episode and three (15%) in two episodes per night and thus seventeen (85%) healthy controls had no wake episodes and three (15%) had one wake episode.

Additionally, the duration of total sleep disrupted per night in children with CF was a mean of 24 minutes (SD 13 minutes) per night while in the healthy controls the mean was 5 minutes (SD 5 minutes) per night. The difference between the two groups was significant (paired t-test p = 0.0001).

All Children with Chronic Disease (n=80) Compared with Healthy Controls (n=80)

Our results showed that, eighteen (23%) children with chronic disease accumulated sleep in a single episode, thirty-three (41%) in two episodes, while sixteen (20%) had three episodes, thirteen (16%) had four or more episodes per night. Thus eighteen (23%) children with chronic disease had no wake episodes per night, thirty-three (41%) had one wake episode per night, sixteen (20%) of children had two and thirteen (16%) had three or more wake episodes per night. In their matched healthy controls, sixty-eight (85%) accumulated all sleep time in a single episode and eleven (14%) had two sleep episodes per night, the other one (1%) had three sleep episodes per night. Thus, sixty-eight (85%) of healthy controls had no wake episodes per night, eleven (14%) of the

healthy control group had only one wake episode per night and one (1%) of the controls had two wake episodes per night.

Next, we evaluated the quality of sleep in children with chronic disease and controls as measured by the duration of nocturnal sleep disruption per night (average total wake time per night). Mean total disrupted sleep duration in children with chronic disease was 20 minutes (SD 22 minutes) per night compared to controls with an average 6 (SD 5 minutes) per night. The difference between groups was significant (paired t-test p = 0.0001).

6.4.2. Comparisons of Sleep Duration with Recommendations

As noted in Chapter V, on average the sleep duration across all groups – children with chronic disease and healthy control groups - was within current guideline recommendations (i.e. sleep duration 10 - 13 h per night in children aged 3-4 years, and 9 - 11 h per night in children aged 5-13 years, with consistent bed and wake-up times (131, 132)). However, 23 participants (n=10 in children with chronic disease, and (n=13) in healthy control groups) did not meet the sleep duration recommendation. From each group those not meeting the sleep duration recommendation were as follows: three (boy and two girls) in children with T1DM and four (two boys and two girls) in their healthy peers, five (two boys and three girls) in healthy control of JIA group, three (two boys and girl) in CHD and two (boy and girl) in their healthy peers, four (two boys and two girls) in CF and two (boy and girl) in their healthy control groups; was below the sleep recommendation as summarised in Table 6.1.

In summary, these observations suggest that sleeping time in children with chronic disease is generally longer and starts slightly earlier than in their healthy peers except in those with CF. There are also slightly more wake episodes due to disrupted sleep time in children with chronic disease compared to the healthy age and sex matched children and the amount of disturbed sleep in each group was significantly greater than in the healthy children except in JIA group. However, in the present study the overall duration of sleep was similar between the healthy control and chronic disease groups, and in the main children appeared to be meeting current sleep duration recommendations.

Table 6.1: Nocturnal sleep quantity-related variables based on 24-hour accelerometer data in children with chronic disease and healthy controls. Data are presented as means and standard deviation (SD)

Variables	CD (n=80)	HC (n=80)	T1DM (n= 20)	HC (n= 20)	JIA (n= 20)	HC (n= 20)	CHD (n= 20)	HC (n= 20)	CF (n= 20)	HC (n= 20)
Sleep onset hr:mm	21:16 (01:03)	21:45 (01:13)	21:32 (01:13)	21:41 (01:34)	20:54 (00:56)	22:17 (00:50)	20:43 (01:26)	21:23 (01:38)	21:57 (00:40)	21:40 (00:52)
Sleep offset hr:mm	07:45 (00:44)	07:53 (00:31)	07:59 (00:33)	07:52 (00:22)	07:34 (00:39)	07:50 (00:38)	07:42 (01:08)	08:04 (00:38)	07:45 (00:37)	07:48 (00:26)
Time spent in sleep h	10.1 (0.8) **	9.7 (0.6) **	10.2 (0.7)	9.7 (0.6)	10.4 (0.8) ***	9.5 (0.5) ***	10.2 (0.9)	9.7 (0.5)	9.7 (0.9)	9.9 (0.5)
% of sleep per 24 h	42.1 (3.3)	40.4 (2.8)	42.5 (2.9)	40.4 (2.8)	43.3 (3.2)	39.6 (2.1)	42.5 (3.9)	40.6 (2.1)	40.4 (2.8)	41.2 (2.2)
No of *Not* meeting sleep recommendation	10	13	3	4	0	5	3	2	4	2

CD – chronic disease; CHD – congenital heart disease; CF – cystic fibrosis; T1DM – type1diabetes mellitus; JIA – juvenile idiopathic arthritis.
Combined data represented total children with chronic disease (CD n=80, mean age 6.9 years (SD=2.0), and F: M 43: 37) as one group and total healthy controls n=80, mean age 6.8 (SD=1.9) and F: M 43: 37) as one group. Further details of participants characteristics data in Chapter II and Table2.1.
Data are presented as means and standard deviation SD unless otherwise specified.
Paired t test compared sleep period time between children with chronic disease and healthy children control age and sex matched; * significant difference and P< 0.05, ** P< 0.005 and ***P= <0.0005.

Table 6.2: Nocturnal sleep quality-related variables based on 24-hour accelerometer data in children with chronic disease and healthy controls. Data are presented as means and standard deviation (SD)

Variables	CD (n=80)	HC (n=80)	T1DM (n= 20)	HC (n= 20)	JIA (n= 20)	HC (n= 20)	CHD (n= 20)	HC (n= 20)	CF (n= 20)	HC (n= 20)
NO. of sleep episode **1 sleep episodes:** **2 sleep episodes:** **3 sleep episodes:** **≥ 4 sleep episodes:**	18 (23%) 33 (41%) 16 (20%) 13 (16%)	68 (85%) 11 (14%) 1 (1%) 0	6 (30%) 10 (50%) 2 (10%) 2 (10%)	17 (85%) 3 (15%) 0 0	7 (35%) 11 (55%) 2 (10%) 0	18 (90%) 2 (10%) 0 0	2 (10%) 7 (35%) 6 (30%) 5 (25%)	16 (80%) 3 (15%) 1 (5%) 0	3 (15%) 5 (25%) 6 (30%) 6 (30%)	17 (85 %) 3 (15%) 0 0
NO. of wake episode: **0 wake episode:** **1 wake episodes:** **2 wake episodes:** **≥ 3wake episodes:**	18 (23%) 33 (41%) 16 (20%) 13 (16%)	68 (85%) 11 (14%) 1 (1%) 0	6 (30%) 10 (50%) 2 (10%) 2 (10%)	17 (85%) 3 (15%) 0 0	7 (35%) 11 (55%) 2 (10%) 0	18 (90%) 2 (10%) 0 0	2 (10%) 7 (35%) 6 (30%) 5 (25%)	16 (80%) 3 (15%) 1 (5%) 0	3 (15%) 5 (25%) 6 (30%) 6 (30%)	17 (85 %) 3 (15%) 0 0
Duration of wake episode minutes	11.2 (13.2)	1.4 (2.1)	9.9 (13.8)	1.3 (2.0)	5.5 (9.2)	1.6 (2.5)	12.1 (17.6)	0.9 (1.8)	17.3 (12.5)	1.6 (1.9)
Duration of sleep episodemovement minutes/night	8.4 (13.1)	4.7 (4.3)	7.1 (8.9)	4.1 (5.6)	7.7 (20.1)	5.4 (3.7)	11.5 (16.4)	5.4 (3.9)	7.1 (7.1)	3.8 (4.0)
Total sleep disrupted minutes/ night	19.6 (21.9) ***	6.1 (5.4) ***	17 (20.8) *	5.4 (7.1) *	13.2 (22.9)	6.9 (5.0)	23.6 (30.7) **	6.4 (4.5) **	24.4 (13.3) ***	5.4 (5.1) ***

Abbreviations: CD – chronic disease; CHD – congenital heart disease; CF – cystic fibrosis; T1DM – type1diabetes mellitus; JIA – juvenile idiopathic arthritis.
Combined data represented total children with chronic disease (CD n=80, mean age 6.9 years (SD=2.0), and F: M 43: 37) as one group and total healthy controls n=80, mean age 6.8 (SD=1.9) and F: M 43: 37) as one group. Further details of participants characteristics data in Chapter V and Table 5.1.
Data are presented as means and standard deviation SD unless otherwise specified. Paired t test compared total sleep disrupted time between children with chronic disease and healthy children control age and sex matched; * significant difference and P< 0.05, ** P< 0.005 and ***P= <0.0005.

6.5. Discussion

6.5.1. Main Findings and Study Implications

Despite considerable recent interest in the sleep quantity and quality in children, there are currently few published data (453), and there are even fewer data from children with any chronic disease using objective measurement (128, 129). Thus, our study appears to be the one of the first to attempt to quantify sleep behaviour in children with common childhood diseases using accelerometry to provide an objective measure, and to test for differences in the quantity and quality of sleep between those children with chronic disease and healthy controls.

Our findings show that overall children with T1DM, JIA and CHD slept longer than age and sex matched healthy controls, though differences between groups were significant in only the JIA group. Differences between chronic disease and healthy control groups were fairly small and appear to have been due to differences in bedtimes, with healthy children apparently going to bed around forty minutes later than children with chronic disease, and with both groups waking up at around the same time. The cause of earlier sleep onset in children with chronic disease is not understood. It could be either a consequence of the disease itself or socially conditioned by the parents, questions which will require further research.

Taken together, these observations suggest that objectively measured overnight sleep duration differs slightly but significant between children with chronic disease and healthy These small and generally significant differences observed in the present study will have to be tested in larger studies to confirm if they are real and reproducible. In all groups recommended sleep times were achieved on average, so there was no major

concern over sleep duration.

The next part of our study addressed sleep quality in children with chronic disease compared to healthy controls. This study noted several striking findings regarding the difference in quality of sleep between children with chronic disease and healthy children control age and sex matched. First of all, although, the sleep duration in children with chronic disease was generally slightly longer than in control groups except in children with CF, in all groups it was more disrupted than in healthy children: eighteen (23 %) of the children with chronic disease compared with sixty-eight (85 %) of healthy controls accumulated sleep in a single episode. Thus, 77 % of children with chronic disease had at least one wake episode per night and most of them had more than two wake episodes per night, while 10 % healthy control had one wake episode and only 5 % had two wake episodes per night. Furthermore, children with chronic disease in the present study had longer duration of disruption than age and sex matched healthy controls, though differences between groups were significant only in the CHD and CF groups.

Previous studies of sleep and sleep disorders in children and adolescents suggested that causes of sleep disturbance can be emotional (e.g., anxiety) or behavioural dysregulation (e.g., bedtime refusal), interfering with sleep or further exacerbating underlying sleep disruption (113, 456). Our study suggests that children with chronic disease appear to have more sleep disturbances when compared to healthy controls. As noted briefly in Chapter I, these differences in the patients groups compared to the controls might relate to the disease itself and/or disease severity. In diabetic children with poor glyceamic control for example, the high level of blood sugar might affect sleep by dehydration prompting the child to get up for regular glasses of water, and

more frequent urination, also low blood sugar levels could cause shakiness, dizziness and sweating, and all these could affect their sleep quality. In children with JIA, pain might be the main contributor to sleep disturbance (200, 223), and the effects of medication might also have an influence (most of the participants with JIA in our study were on biological treatment (128)). In our study sample children with CF had stable lung disease with good lung function and nutritional status making it unlikely that gas exchange abnormalities were the main cause for sleep disruption. Whether nocturnal cough accounted for the disturbance will require further study (129). However, at present, all these possible reasons for the observed differences are hypothetical and will require furthermore detailed studies.

6.5.2. Comparisons with Recommendations

The mean sleep duration in children with chronic disease and healthy control groups was within the range 10 - 13 h per night in children aged 3-4 years, and 9 - 11 h per night in children aged 5-13 years, with consistent bed and wake-up times and in accordance with what is recommended for children (131, 132). However, 14.4 % of participants (6.3 % in children with chronic disease and 8.1% in healthy control groups) did not meet the sleep duration recommendation and slept less than recommended amount.

6.5.3. Comparisons with Other Studies

We believe that the present study is the first study to ask whether objectively measured levels of sleep are adequate in children with chronic childhood disease. Hence there are no directly comparable studies, but we note that our findings are somewhat inconsistent with previous research examining sleep timing and duration in healthy

children objectively. One particular example is in the International Study of Childhood Obesity Lifestyle and the Environment (326) study. ISCOLE was a cross-sectional study, which included 6106 children aged 9-11 years from sites in Australia, Brazil, Canada, China, Colombia, Finland, India, Kenya, Portugal, South Africa, United Kingdom and United States of America. Sleep duration was assessed by using 24-h waist-worn accelerometers (GT3X+, ActiGraph LLC) over seven consecutive days. They reported that average sleep onset was at 20:18, sleep offset at 07:07, with sleep duration averaging 8.8 hours per night. Fifty seven point seven per cent of the healthy children accumulated less than recommended sleep duration and 7.8% accumulated more than recommended sleep (326), so in total around two thirds of the ISCOLE participants did not meet sleep duration recommendations. The methodological difference between the present study (activPAL based) and the ISCOLE study (ActiGraph GT3X+ based) might be important, as well as differences in the ages of the samples in ISCOLE (9-11 years) and the present study (3-10 years).

Together, these data provide preliminary evidence that there may be a difference in sleep quantity and sleep quality between healthy children and those with chronic disease in mid-childhood. It is recommended that this be confirmed in different age groups, and different chronic diseases.

6.5.4. Study Strengths and Limitations

The main strength of the present study was in answering the research questions in a novel but important population vis. groups of children with common chronic disease. Further strengths are that our study investigated objective sleep behaviour (quantity and quality parameters) in children living with childhood chronic disease compared to

closely match healthy controls so that the main influences on the behaviours (age, sex, time of year) were all controlled for by the paired design.

In addition, there are several other methodological strengths to this study: the participants were diverse and were composed of children with chronic disease and healthy children, both male and female. Further, the measures of sleep were detailed and quantitative due to the objective measurement methods used, and our ability to make objective measures of sleep behaviours (quantity and quality parameters). The most practical method was used rather than a gold standard method. There were practical constraints on my time and the equipment available, and the issue of burden to participating families was important too. Polysomnography was not a feasible option in our study; and of the alternatives, objective measurements are more accurate than using a subjective methods (self-reports/parent reports) (286, 310, 311) (286, 310, 311); self-reports tend to underestimate night awakenings and overestimate sleeping time and thus might not convey as accurate or complete a picture of children's sleep (457). A highly standardised measurement protocol was used and the sleep behaviours (sleep quantity and quality) were measured across a sufficient number of nights to obtain a reliable assessment of the participants' usual sleep behaviours by using ActivPAL^{TM} accelerometer. Family and child compliance with the activPAL protocol was very high, at least for those families who met study inclusion criteria and whose data could be retained. Moreover, the methods used were the same between patient and control groups and so any methodological biases in sleep variables probably apply fairly equally to both groups so between-group comparisons can be made. Thus, we believe our results provide a reasonably valid and reliable picture of sleep behaviour for the children with chronic disease and healthy children across 7 days. However, the gold standard methods would be needed to confirm our conclusions.

The study also had some limitations. The study design was cross-sectional, and antecedent-consequent relationships could not be made in regards to the associations observed. Further, the combined analysis was exploratory data and can only provide preliminary evidence. However, these children were children with a history of a chronic disease who were attending follow-up appointments but were apparently healthy and living at home at the time of recruitment. It is also important to acknowledge the possibly limited generalisability of our findings to other groups of children with different chronic diseases, or to children with the same chronic diseases as recruited to the present study, but with more severe/advanced forms of disease (or during disease exacerbations) is not known at present. Although, in each group of children with chronic disease in our study there was a spectrum of illness with a number of children at the more severe end of the spectrum, in children with more severe chronic disease there might be significantly less sleep time and poorer sleep quality, than observed in the present study. In our study the participants age range-covered childhood did not include either adolescence or early childhood so generalisability to chronic disease effects on sleep in younger or older disease groups, or to different chronic diseases is not possible. To address this, it would be advisable to replicate this research with these methods in children from different age groups and with these and other chronic diseases. A further limitation included the fact that there is no currently available methodology that applies automated measurements to young school age children.

Finally, our power calculations suggested that 160 participants – 80 children with chronic disease and 80 children healthy controls would be sufficient, but in fact some of the differences within the individual disease categories when considered separately

were small. Larger studies may be required to determine the significance of differences between some of the groups. However, the statistical significance or otherwise of some of the differences may in fact be of secondary importance - the main findings of the present study probably relate to the biological/clinical significance of the observed in those with chronic disease had apparently adequate levels of sleep with slightly lower sleep quality than their peers due to more time in wakefulness during the night rather than less time spent in bed, at least during early-mid childhood. Small differences sustained over long time periods, as children get older may have a significant cumulative impact in relation to longer-term health.

6.6. Conclusions

In conclusion, the present study provides evidence that there may be slight but systematic differences in both sleep quantity and quality between children with chronic disease and healthy children. In children with chronic disease generally slept longer and started sleeping slightly earlier than in their healthy peers, except in children with CF. Sleep is also more disrupted sleep in those with chronic disease than healthy children. Future efforts aimed at examining sleep quantity and quality in children with other common chronic disease should be considered.

CHAPTER VII

GENERAL DISCUSSION

7.1. General Discussion

Recent evidence-based guidelines (131-133) have concluded that PA, SB and sleep have important roles in the physical development of children and impact on health outcomes in childhood and in adulthood (14, 112). Several epidemiological studies in children have reported that low levels of PA and insufficient sleep in children are linked with unfavourable health outcomes e.g. obesity and development of chronic diseases such as diabetes and cardiovascular diseases in later life (97, 440, 456, 458, 459).

Low levels of PA are associated with significant exposure to prolonged periods of SB, especially in relation to watching television or playing computer games. Increasing PA is often considered as the most important principal intervention for primary and secondary disease prevention. Some studies have even shown that regular PA during treatment for cancer may help adult patients better tolerate treatment-induced side effects with improved quality of life (75).

The developing paradigm of 24-hour movement behaviours suggests that the focus on PA needs to broaden to consider the whole 24-hour day even in interventions. Viewed like that other possibilities than just promoting PA emerge for consideration e.g. focusing on reducing SB by swapping some ST for PA and/or sleep (460). The paradigm is new and researchers have only recently begun to consider movement across the 24-hour period and so there is limited evidence on it, including how best to analyse 24-hour data (461).

In children with chronic disease, too, there is concern about the amount of PA, particularly MVPA, and ST. In our systematic review (Chapter III) across all of childhood and adolescence that children with chronic disease accumulated low level of MVPA, consistently below the recommended minimum level of 60 minutes per day in most of the eligible studies. Compared to healthy children, there were no marked differences for patients with T1DM, CVD and chronic respiratory diseases, while in those with leukaemia MVPA was significantly lower. Further, children with chronic disease accumulated a high amount of ST during their waking hours (291).

Levels of MVPA and ST are also important to health in children and adolescents, and unfavourable levels of MVPA and ST may be both causes and consequences of obesity. In our second systematic review (Chapter IV), a high percentage of obese children and adolescents did not achieve the minimum amount of 60 minutes per day MVPA (39), and MVPA levels in children and adolescents with obesity were consistently slightly lower than children from healthy control or comparison groups. Additionally, all eligible studies, which had comparison groups, found ST was fairly consistent, with no marked differences between obese and non-obese peers (385)

Our findings from both systematic reviews provided valuable information about levels of MVPA and ST in children and adolescent with chronic disease including in those with obesity that may help to stimulate improving PA guidelines, and improving PA level for these children. These reviews also call attention to focus on increasing MVPA and reducing ST among children and adolescents with chronic disease and those with obesity, and the importance of raising these issues in clinical settings as part of their treatment. Treatment of those children should clearly involve a focus on increasing

MVPA and reducing ST as recommended in multiple evidence based treatment and prevention guidelines published in recent years for healthy children (39, 281, 462).

In 2014, the concept of 24-hour movement behaviours began to be used. This sought to take account of the fact that only a small amount of any child's days is involved in MVPA – typically around 5%. Further, the different movement behaviours are believed to interact and impact on physical health and development in combination (22). A small body of research is emerging that quantifies all of the various movement behaviours (PA, SB, and sleep) in 24-hour period in healthy children, particularly in preschool and school age children (131-133). Collectively, some studies provided evidence on compliance of young children to the new 24-hour movement guidelines. These suggest that only a small proportion of young children meet the overall guidelines e.g. only 10-13% of preschool-aged children were found to meet the new 24-hour movement guidelines for the early years (133, 463-465). In the recent study by Walsh et al (461) of 4,500 United States children aged from 8-11years, only 5 % of primary school-age children met all three guidelines, 51% participants met the sleep recommendation while 18% met the PA recommendation, as measured by self/parent report (461). However, at present, there is very limited evidence about 24-hour movement behaviours in children with chronic childhood illnesses, and so the adequacy of levels of 24-hour movement behaviours in children with chronic disease is unknown.

In order to start to address this research deficit, our aim in (Chapter V) of the present thesis was to evaluate the 24-hour movement behaviours in children with chronic childhood diseases, focusing on four common chronic childhood disease groups. We also explored whether there are differences in levels of 24-hour movement behaviours

in those children and their healthy peers. We found that, there were small systematic differences between children with chronic diseases in their individual groups and healthy matched controls. These were made more obvious when the children with chronic disease were compared as a single group with their healthy controls. The most important finding obtained from this study was that there were significant differences between children with chronic disease and healthy controls for time spent sedentary, standing, PA and sleep. Those with chronic disease had greater time spent sedentary with significant lower number of sedentary breaks, less standing time with slightly longer sleep time than their healthy controls. Time spent in PA was significant lower (in both PA time and steps counts) in children with chronic disease compared to healthy controls. ST was consistently higher in children with chronic disease, though the number of breaks in sitting, reflecting the more prolonged sitting bouts was consistently lower in those with chronic disease compared to healthy controls. Standing time was also was consistently lower in children with chronic disease. The mean time spent in PA and step counts per day were consistently lower in the children with chronic disease compared to healthy controls, and 29/80 controls met the daily step count recommendations. Time spent asleep was slightly greater in the children with chronic disease.

The next study (Chapter VI) examined sleep behaviour (quantity and quality of sleep) in children with common chronic childhood diseases. In this study, possibly somewhat surprisingly, it was found that sleep duration was consistently slightly longer in those with T1DM, JIA and CHD than in age- and sex- matched healthy controls. This difference could be due to the time of the sleep onset. Children with chronic disease in the present study apparently started to sleep on average around forty minutes earlier than their healthy controls, with both groups waking up at around the same time. Sleep

disruption was consistently greater in those with chronic disease, reaching significance in T1DM, CHD and CF groups. However, mean sleep duration on a group level (both in in children with chronic disease and healthy control groups) was within usual recommendations (131, 132).

Taken together our activPAL-based studies suggest that among the children with the chronic diseases studied compared with matched controls there was a lower PA level, higher ST amount, but an apparently adequate amount of sleep although sleep was slightly more disrupted in those with chronic disease. In addition, levels of PA were lower than recommended in current guidelines for both groups.

Reasons for differences between patient and control groups are unclear. Several prior studies had suggested a number of reasons for lower levels of PA in children and adolescent with chronic disease including a relation to disease activity or cardiorespiratory functional disability (61). However, Fereday *et al*, had demonstrated that, the participation in PA in children with T1DM, with asthma and with cystic fibrosis was not hindered by the chronic condition itself (466).

In our studies, in all cases children with chronic disease were recruited while relatively well and clinically stable, free of acute illness, and living in the community and attending schools/pre-school. The disease severity in the sample ranged from mild/moderate to severe, and in the children who had disease for many years (or in those with CHD who had cardiac surgery), this could have affected the ability of those children to engage in PA (e.g. to play actively, or to be active in sport or during school physical education) and could theoretically lead to lowering PA levels, with reduced PA being replaced by more ST. Alternatively, lower levels of MVPA in children with

chronic disease might be due in part to parental over-protective care as they might see their child as especially “vulnerable”, leading to them not permitting their child with chronic disease to be engaged in PA to the same extent as their healthy peers (377, 378), or they may perceive that spending time indoors engaging in ST is a safer option and parents may encourage that. Also, at schoolteachers might be more concerned about children with chronic disease playing and engaging in activity programmes compared to their healthy peers. Indeed, a lack of supervised facilities and opportunities for PA, with insufficient knowledge about the suitable types of PA for the specific disease condition could be one reason for lowering the PA levels among children and adolescents with chronic disease (377, 378). It seems most likely that both physio-pathologic as well as issues of socialisation into sport and activity are active and contribute to the observed levels of activity.

The low levels of PA among the patient groups suggest that there is a need to address this, perhaps by providing disease-specific rehabilitation programmes aimed at increasing PA. Such programmes should involve children/adolescents, parents and other caregivers, General practitioner and other Healthcare professionals. It would probably be helpful if families and all health professionals were able to encourage and support children with chronic disease to engage in regular and appropriate PA.

As noted earlier in the thesis there has been a lack of attention in the PA research community on children and adolescents with chronic disease. For many years national and global Active Healthy Kids Report Cards (467) have attempted to report on and increase levels of PA among the general population of children and adolescents. Increasing PA levels in children with chronic disease could be achieved through a similar knowledge exchange effort aimed at children with chronic disease rather than

the general population. One very recent pioneering example of this –from 2018- can be found in the Dutch Active Healthy Kids Report Card for those with chronic disease (468). This sort of report card for children or adolescents with chronic disease would provide useful information for the clinician regarding recommendations and contraindications for PA, and both parents and affected children/adolescents could gain reassurance about PA, exercise and participation in sport (468). Further, the report card emphasises the important role, which parents and family have an increasing the PA levels and reducing ST in this group of children. Report cards and disease-specific rehabilitation programmes could help parents, family and other caregivers to improve their child's PA, possibly by including a simple 24-hour perspectives that provides examples such as the trading of indoor time for outdoor activity, so replacing SB with PA.

Further, the variety of childhood chronic diseases makes it difficult to speculate as to what future chronic disease guidelines might look like, or the extent to which they might need to be disease-specific. Even within childhood chronic disease there is such variety in disease severity and other factors (e.g. age) that developing disease specific guidance would not be easy also speculated that a good deal of evidence on associations between movement behaviours and health outcomes in chronic disease groups would be needed to establish if disease specific recommendations were needed. We are a long way from having that sort of evidence just now. most recent 24 hour movement guidelines and physical activity guidelines state that they are applicable for children with chronic disease, while recommending that a healthy professional should be consulted for additional guidance (132) such that (a) such children might have to reach recommendations gradually, and (b) the limitations of the chronic disease, and safety issues, should be considered when families are trying to reach the

recommendations. I hope this work will start to highlight that a more secure evidence base is needed for such recommendations

However, the thesis data shows that in healthy children too, there is high probability that levels of the 24-hour movement behaviours will get worse with age - PA declines and SB goes up with age and increasing SB displaces PA and eventually sleep too by the time of adolescence (156, 158, 437). Thus it is likely that levels of all the 24hour movement behaviours would be likely to change (at least on average) if the children with chronic disease studied in this thesis were studied again when older. Levels of movement behaviours in the present study may actually be relatively favourable because of the relatively young age of the study participants.

One of the implications from the present study is that it suggests that the activPAL^{TM} is a good tool for objective measurement of many of the 24hour movement behaviours and so could be more widely used in paediatric populations in future. The activPAL has not been used to any great extent to measure 24-hour movement behaviours previously. However, it cannot measure all of the 24-hour movement behaviours - as noted in the individual studies/chapters as it does not currently measure MVPA, screen time, and cannot differentiate between sitting and lying postures. These are important limitations and future studies should try to measure these behaviours, though methods to do so are not very practical at present. The validity of the simple and widely used self or parent report measures -e.g. parent reported screen time – is unclear at the moment. A further complication of interpretation of thesis findings is that there are no national or international guidelines for time spent in standing and total ST. However, thesis data provide preliminary evidence that there may be small but clear differences

in 24-hour movement behaviours between children with chronic childhood disease and their healthy peers.

As noted above, the field of 24 movement behaviours is quite new and there are new developments in data analysis as well as in measurement methods underway. In future studies we would like to consider use of 'compositional analysis'. This is a statistical approach that explores the integrated time spent in the 24-hour movement behaviours (sleep, sedentary behavior, physical activity – light, moderate and vigorous) (433, 469).

> *"Compositional analysis is about changing how we conceptualize data from the standard real space to the constrained simplex space perspective. This requires that we abandon thinking of each behavior as an independent variable and, instead, view them as relative to the other ones (470). "*

Compositional analysis provides a different approach to analysis, which might be informative, but as this approach is new and complex, and there was limited time, there was not the chance to use this analysis in the present thesis, so for the author this is a technique for the future.

For all the studies in this thesis, we instructed our participants to maintain their usual daily PA and sleep habits during the study, but they might have altered their habits as a consequence of taking part. It is currently not clear whether or to what extent children and families change their 24-hour movement behaviours when taking part in studies, but PA studies using accelerometry are not considered to be affected by 'reactivity' (471, 472).

The limited age range and number of chronic disease groups included in the thesis studies mean that to increase generalisability, further research with more participants and in different age group also with different chronic childhood diseases will be needed. Further, as disease activity and functional disability could be a reason for lower PA levels and sleep disturbance in those with chronic disease (and in our study disease activity was mostly mild/moderate), it would be advisable to replicate this work with patients with more active and more severe disease to increase understanding of the association between different disease severities and 24-hour movement behaviours. If the 24-hour movement behaviours deteriorate a lot in older children and/or as their disease progresses that might provide useful information, which could help in the clinical management of those children and could help them and their parents balance the disease burden with a healthier lifestyle.

Future research efforts should also include the possibility of interventions for some or all of 24h movement behaviours, and in a wider range of groups of children with chronic disease.

To gain a better understanding of 24-hour movement behaviours in children with chronic diseases to future reviews should consider other groups of disease such as musculo-skeletal and neurological disease, and also, should investigate the factors impacting on the behaviours in these populations (correlates or determinants of the 24-hour movement behaviours).

7.2. Conclusions and Relevance

Several conclusions can be drawn from this work. The systematic literature reviews showed that levels of MVPA in children and adolescents with chronic disease and in those with obesity appear to be well below recommendations, although similar to those of their contemporary healthy peers (except for children with malignancies and with obesity). Children with chronic disease tend to spend the majority of their waking hours sedentary and their ST is often higher than in their healthy peers. Thus, a substantial effort and appropriate disease intervention strategies are likely to be required to increase MVPA and reduce ST among children with chronic disease.

The systematic review findings were somewhat consistent with our finding in the studies of objectively measured 24-hour movement behaviours in children with chronic disease and their healthy peers. This study suggests that for at least some groups with chronic disease 24-hour movement behaviours may differ substantially from recommendations and differ slightly but systematically from their healthy peers.

The most obvious concerns in the present study arising from differences between patient and control groups relate to the greater ST in children with chronic disease, and the evidence that the number of sitting bouts was consistently lower (more prolonged sitting bouts) in those with chronic disease. Also, children with chronic disease were consistently less active than their healthy controls, operationalised both in the accelerometer-measured time spent in PA and in the step counts, and time spent in sleep was slightly longer in children with chronic disease. Sleep duration was generally within recommended values but there was evidence that sleep in children with chronic disease was slightly more disrupted compared to the healthy controls. Finally, it is becoming clear that optimising levels of 24-hour movement behaviours should confer

a number of benefits for child health, development, and wellbeing and so there is a need for further research with a clinical focus on these behaviours in those with chronic disease (131-133).

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APPENDIXES

APPENDIX I

Search strategies of systematic literature reviews

The search strategies that used to search in the electronic databases: Medline, Cochrane library, EMBASE, SPORT Discus and CINAHL

A. EMBASE (ovid):

1. exp Child/
2. exp Adolescent/
3. (child* or adolesc* or teen* or youth or girl* or boy*).tw.
4. (young adj1 (person or people)).tw.
5. 1 or 2 or 3 or 4
6. exp Exercise/
7. exp Motor Activity/
8. exp Sports/
9. exercis*.tw.
10. physical* activ*.tw.
11. (active adj2 (living or lifestyle)).tw.
12. sedentary behavi?r.tw.
13. exp Sedentary Lifestyle/
14. ((sedentary or sitting or screen or TV or television or computer or PC or video games) adj2 time).tw.
15. 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16. exp Obesity/ or exp Overweight/
17. (overweight or obes*).tw.
18. exp Accelerometry/
19. exp Actigraphy/
20. acceleromet*.tw.
21. actigraph.tw.
22. activity monitor*.tw.
23. (objective adj1 (measure* or monitor* or assess*)).tw.
24. 18 or 19 or 20 or 21 or 22 or 23
25. exp cardiovascular abnormalities/ or exp heart diseases/
26. exp Cardiovascular Abnormalities/
27. exp Heart Diseases/
28. "congenital heart disease".tw.
29. "Atrial Septal Defect".tw.
30. "Complete Atrioventricular Canal Defect ".tw.
31. "Ventricular Septal Defect".tw.
32. (Tetralogy adj2 Fallot).tw.
33. exp Asthma/
34. asthma.tw.
35. exp Respiratory Tract Diseases/
36. exp Respiratory Hypersensitivity/
37. exp Cystic Fibrosis/

38. (respiratory adj2 allerg*).tw.
39. "cystic fibrosis".tw.
40. wheez*.tw.
41. exp Bronchopulmonary Dysplasia/
42. lung diseases/ or exp alpha 1-antitrypsin deficiency/ or exp "cystic adenomatoid malformation of lung, congenital"/ or exp hepatopulmonary syndrome/ or exp hypertension, pulmonary/ or exp lung diseases, fungal/ or exp lung diseases, interstitial/ or exp lung diseases, obstructive/ or exp lung diseases, parasitic/ or exp lung injury/ or exp lung neoplasms/ or exp lung, hyperlucent/
43. "chronic lung disease".tw.
44. "chronic respiratory disease".tw.
45. exp diabetes mellitus, type 1/ or exp diabetes mellitus, type 2/
46. (diabetes adj1 mellitus).tw.
47. exp Leukemia/
48. Leukemia.tw.
49. exp Lymphoma/
50. Lymphoma.tw.
51. exp Neuroblastoma/
52. Neuroblastoma.tw.
53. "Wilms' tumor".tw.
54. exp Central Nervous System Neoplasms/
55. exp Sleep Apnea Syndromes/
56. "sleep apnea".tw.
57. 16 or 17 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56
58. 5 and 15 and 24 and 57
59. exp Adult/
60. 58 not 59
61. limit 60 to (english language and yr="2000 -Current")

B. Cochrane Central Register of Controlled Trials:

#1 MeSH descriptor: [Child] explode all trees
#2 MeSH descriptor: [Adolescent] explode all trees
#3 child* or adolesc* or teen* or boy* or girl* or youth:ti,ab,kw (Word variations have been searched)
#4 young near/1 (person or people):ti,ab,kw (Word variations have been searched)
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Motor Activity] this term only
#7 MeSH descriptor: [Exercise] explode all trees
#8 MeSH descriptor: [Sports] explode all trees
#9 MeSH descriptor: [Sedentary Lifestyle] explode all trees
#10 physical* activ*:ti,ab,kw (Word variations have been searched)
#11 exercis* or sport*:ti,ab,kw (Word variations have been searched)
#12 active near/2 (living or lifestyle):ti,ab,kw (Word variations have been searched)
#13 sedentary behavi?r:ti,ab,kw (Word variations have been searched)

#14 (screen or sedentary or sitting or TV or television or computer or PC or video games) near/2 time:ti,ab,kw (Word variations have been searched)
#15 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14
#16 MeSH descriptor: [Accelerometry] explode all trees
#17 acceleromet*:ti,ab,kw (Word variations have been searched)
#18 actigraph*:ti,ab,kw (Word variations have been searched)
#19 activity near/1 monitor*.:ti,ab,kw (Word variations have been searched)
#20 #16 or #17 or #18 or #19
#21 MeSH descriptor: [Overweight] explode all trees
#22 overweight or obes*:ti,ab,kw (Word variations have been searched)
#23 MeSH descriptor: [Heart Defects, Congenital] explode all trees
#24 "Congenital Heart Disease":ti,ab,kw (Word variations have been searched)
#25 "Atrial Septal Defect" or "Coarctation of the Aorta" or "Complete Atrioventricular Canal defect" or "Ventricular Septal Defect" or "Tetralogy of Fallot":ti,ab,kw (Word variations have been searched)
#26 MeSH descriptor: [Hypertension] explode all trees
#27 hypertension:ti,ab,kw (Word variations have been searched)
#28 high near/1 (blood pressure):ti,ab,kw (Word variations have been searched)
#29 MeSH descriptor: [Cardiomyopathies] explode all trees
#30 Cardiomyopath*:ti,ab,kw (Word variations have been searched)
#31 MeSH descriptor: [Respiratory Tract Diseases] explode all trees
#32 respirator* near/1 disease*:ti,ab,kw (Word variations have been searched)
#33 asthma*:ti,ab,kw (Word variations have been searched)
#34 respiratory near/1 allerg*:ti,ab,kw (Word variations have been searched)
#35 MeSH descriptor: [Sleep Apnea Syndromes] explode all trees
#36 sleep near/1 apnea:ti,ab,kw (Word variations have been searched)
#37 pulmonary near/1 hypertension:ti,ab,kw (Word variations have been searched)
#38 MeSH descriptor: [Cystic Fibrosis] explode all trees
#39 "cystic fibrosis":ti,ab,kw (Word variations have been searched)
#40 "Broncho-pulmonary dysplasia":ti,ab,kw (Word variations have been searched)
#41 "Bronchopulmonary dysplasia" or "Broncho pulmonary dysplasia":ti,ab,kw (Word variations have been searched)
#42 MeSH descriptor: [Diabetes Mellitus, Type 1] explode all trees
#43 MeSH descriptor: [Diabetes Mellitus, Type 2] explode all trees
#44 "diabetes mellitus" or diabet*:ti,ab,kw (Word variations have been searched)
#45 MeSH descriptor: [Leukemia] explode all trees
#46 MeSH descriptor: [Lymphoma] explode all trees
#47 MeSH descriptor: [Neuroblastoma] explode all trees
#48 MeSH descriptor: [Wilms Tumor] explode all trees
#49 Leukemia or Lymphoma or Neuroblastoma or "Wilms' tumors":ti,ab,kw (Word variations have been searched)
#50 MeSH descriptor: [Central Nervous System Neoplasms] explode all trees
#51 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40 or #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50
#52 #5 and #15 and #20 and #51

C. SportDiscus: 2000 – 1st March 2015

S56 S6 AND S21 AND S25 AND S52 Limiters - Published Date: 20000101-20151231; Peer Reviewed; Language: English; Publication Type: Academic Journal
S55 S6 AND S21 AND S25 AND S52 Limiters - Published Date: 20000101-20151231; Language: English
S54 S6 AND S21 AND S25 AND S52 Limiters - Published Date: 20000101-20151231
S53 S6 AND S21 AND S25 AND S52
S52 S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43 OR S44 OR S45 OR S46 OR S47 OR S48 OR S49 OR S50 OR
S51 DE "CANCER"
S50 DE "LEUKEMIA"
S49 AB Leukemia or Lymphoma or Neuroblastoma or "Wilms' tumor"
S48 AB diabetes mellitus
S47 DE "DIABETES in children" OR DE "DIABETES in youth"
S46 AB "pulmonary hypertension"
S45 AB "sleep apnea" or "cystic fibrosis" or "Broncho-pulmonary dysplasia" or "Bronchopulmonary dysplasia" or "Broncho pulmonary dysplasia"
S44 DE "CYSTIC fibrosis"
S43 DE "SLEEP apnea syndromes in children"
S42 AB "chronic lung disease"
S41 AB wheez*
S40 AB asthma*
S39 AB respiratory N1 (disease* or allerg*)
S38 DE "ASTHMA in children"
S37 DE "RESPIRATORY diseases" OR DE "RESPIRATORY allergy" OR DE "RESPIRATORY obstructions"
S36 DE "CARDIOMYOPATHIES"
S35 AB high N1 (blood pressure)
S34 AB hypertension
S33 DE "HYPERTENSION"
S32 AB "Atrial Septal Defect" or "Coarctation of the Aorta" or "Complete Atrioventricular Canal defect" or "Ventricular Septal Defect" or "Tetralogy of Fallot"
S31 AB "congenital heart disease"
S30 DE "AORTIC coarctation"
S29 DE "CONGENITAL heart disease" OR DE "HYPOPLASTIC left heart syndrome" OR DE "TETRALOGY of Fallot"
S28 AB overweight or obes*
S27 DE "OBESITY in children"
S26 DE "OVERWEIGHT children" OR DE "OVERWEIGHT teenagers"
S25 S22 OR S23 OR S24
S24 AB activity N1 monitor*
S23 AB acceleromet* or actigraph
S22 DE "ACCELEROMETERS"
S21 S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20
S20 AB (computer or PC) N1 time
S19 AB (TV or television) N1 time
S18 AB screen N1 time
S17 AB sitting N1 time
S16 AB sedentary N1 time

S15 AB sedentary behavi?r*
S14 DE "SEDENTARY lifestyles"
S13 DE "SEDENTARY behavior in children"
S12 AB active N2 (living or lifestyle)
S11 AB exercis* or sport*
S10 AB physical* activ*
S9 DE "SPORTS"
S8 DE "EXERCISE" OR DE "ABDOMINAL exercises" OR DE "AEROBIC exercises" OR DE "ANAEROBIC exercises" OR DE "AQUATIC exercises" OR DE "ARM exercises" OR DE "BACK exercises" OR DE "BREATHING exercises" OR DE "BREEMA" OR DE "BUTTOCKS exercises" OR DE "CALISTHENICS" OR DE "CHAIR exercises" OR DE "CHEST exercises" OR DE "CIRCUIT training" OR DE "COMPOUND exercises" OR DE "DO-in" OR DE "EXERCISE -- Immunological aspects" OR DE "EXERCISE adherence" OR DE "EXERCISE for children" OR DE "EXERCISE for girls" OR DE "EXERCISE for men" OR DE "EXERCISE for middle-aged persons" OR DE "EXERCISE for older people" OR DE "EXERCISE for people with disabilities" OR DE "EXERCISE for women" OR DE "EXERCISE for youth" OR DE "EXERCISE therapy" OR DE "EXERCISE video games" OR DE "FACIAL exercises" OR DE "FALUN gong exercises" OR DE "FOOT exercises" OR DE "GYMNASTICS" OR DE "HAND exercises" OR DE "HATHA yoga" OR DE "HIP exercises" OR DE "ISOKINETIC exercise" OR DE "ISOLATION exercises" OR DE "ISOMETRIC exercise" OR DE "ISOTONIC exercise" OR DE "KNEE exercises" OR DE "LEG exercises" OR DE "LIANGONG" OR DE "METABOLIC equivalent" OR DE "MULAN quan" OR DE "MUSCLE strength" OR DE "PILATES method" OR DE "PLYOMETRICS" OR DE "QI gong" OR DE "REDUCING exercises" OR DE "RUNNING" OR DE "RUNNING -- Social aspects" OR DE "SCHOOLS -- Exercises & recreations" OR DE "SEXUAL exercises" OR DE "SHOULDER exercises" OR DE "STRENGTH training" OR DE "STRESS management exercises" OR DE "STRETCHING exercises" OR DE "TAI chi" OR DE "TREADMILL exercise" OR DE "WHEELCHAIR workouts" OR DE "YOGA"
S7 DE "PHYSICAL activity
S6 S1 OR S2 OR S3 OR S4 OR S5
S5 AB young N1 (people or person)
S4 AB child* or adolesc* or teen* or youth or girl* or boy*
S3 DE "YOUTH"
S2 DE "TEENAGERS"
S1 DE "CHILDREN"

D. CINAHL Plus:

S47 S4 AND S12 AND S16 AND S44 Limiters - Publication Year: 2000-2015; Peer Reviewed; Language: English
S46 S4 AND S12 AND S16 AND S44 Limiters - Publication Year: 2000-2015
S45 S4 AND S12 AND S16 AND S44
S44 S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40 OR S41 OR S42 OR S43
S43 (MH "Central Nervous System Neoplasms
S42 (MH "Wilms' Tumor+")

S41(MH "Neuroblastoma+")
S40 (MH "Lymphoma+")
S39 (MH "Leukemia+")
S38 AB Leukemia orLymphoma or Neuroblastoma or "Wilms' tumor"
S37 AB diabetes
S36 (MM "Diabetes Mellitus, Type 1") OR (MM "Diabetes Mellitus, Type 2")
S35 AB cystic fibrosis
S34 (MM "Cystic Fibrosis")
S33 AB respiratory N1 (allerg* or hypersensitivity)
S32 AB "Bronchopulmonary Dysplasia" or "Broncho pulmonary Dysplasia" or "Broncho-pulmonary Dysplasia"
S31 AB sleep apnea
S30 AB asthma* or wheez*
S29 AB "Chronic Respiratory disease" or "Chronic lung disease"
S28 (MM "Bronchopulmonary Dysplasia")
S27 (MH "Sleep Apnea Syndromes+")
S26 (MH "Pulmonary Disease, Chronic Obstructive+") OR (MM "Asthma") OR (MH "Respiratory Hypersensitivity+")
S25 AB high N1 (blood pressure)
S24 AB Hypertension
S23 (MH "Hypertension+")
S22 AB "Cardiomyopathy"
S21 (MH "Myocardial Diseases+")
S20 AB "Congenital Heart Disease" or "Atrial Septal Defect" or "Coarctation of the Aorta" or "Complete Atrioventricular Canal defect" or "Ventricular Septal Defect" or "Tetralogy of Fallot"
S19 (MH "Heart Defects, Congenital
S18 AB overweight or obes*
S17 (MM "Pediatric Obesity")
S16 S13 OR S14 OR S15
S15 AB activity N1 monitor*
S14 AB acceleromet* or actigraph*
S13 (MM "Accelerometers")
S12 S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11
S11 AB (screen or TV or television or PC or computer) N1 time
S10 AB (sedentary or sitting) N1 time
S9 AB sedentary behavio?r*
S8 AB active N1 (living or lifestyle)
S7 AB (physical* activ*) or exercis* or sport*
S6 (MM "Life Style, Sedentary")
S5 (MM "Exercise") OR (MM "Physical Activity") OR (MM "Sports")
S4 S1 OR S2 OR S3
S3 AB young N1 (people or person)
S2 AB child* or adolesc* or youth or teen* or boy* or girl*
S1 (MM "Adolescence") OR (MM "Child").

Than we update the search till March 2017 for those systematic reviews for children with chronic disease.

Inclusion, Exclusion Criteria of Systematic Literature Reviews

Table 1: Inclusion and exclusion criteria for selection of studies

Inclusion criteria	Exclusions criteria
Participants aged ≤ 19 years	Participants aged >19.
Children and adolescent with common chronic diseases: cardiovascular diseases, chronic respiratory diseases diabetes and malignancy. Chronic diseases defined as medical conditions lasting at least 6 months, diagnosed by a doctor or by using generally accepted objective criteria.	Children and adolescents with acute diseases or conditions (e.g. post-surgery) that may have impacted their PA levels. Participants who had any limitation to their PA e.g. orthopaedic injury.
MVPA and/ SB measured by accelerometer methods for at least 6 h/day for three consecutive days or more.	- Studies that used subjective methods of MVPA and SB measurement (child report, parent, or carer proxy report). - Studies that used objective and direct observation methods apart from accelerometers (e.g. heart rate monitors, pedometers). - Studies which measured MVPA or SB for less than 6 hours per day. - Studies that collected PA data over two days or less. - Studies that focused only on specific periods of the day (e.g. school activity only or outdoor activity only).
Articles published in English from 2000. Published in peer-reviewed journals.	Articles published before 2000. Review papers without original data, studies using previously reported data.
Human studies	Animal studies.

MVPA: Moderate-to-Vigorous Intensity Physical Activity; PA: physical activity; SB: sedentary behaviour.

Quality Assessment Criteria of Systematic Literature Reviews

Table 2: Study Quality Assessment Criteria

Criterion	Definition	Mark Allocation
Sample recruitment	Sample: How were they recruited e.g. poster. Time: When was the study conducted Place: Where did the recruitment take place	1 point for listing 3 criteria
Sample description of the sample (number, age, gender)	Number of participants recruited Mean age of participants. % Gender male and female	1 point for listing all 3 criteria
Attrition	Number of participants recruited and the number actually measured	1 point for listing both criteria
Data collection and reduction	Type of device; epoch; no of days of active commuting specified as minimum; duration of monitoring time; monitor placement; data reduction decisions	1 point for listing 3 criteria.
MVPA definition given.	MVPA defined and accelerometer cut-off or other method given	1 point for listing both criteria
Results	Adequate description of numbers actually analysed, with summary MVPA data	1 point for listing both criteria

MVPA: Moderate-to-Vigorous Intensity Physical Activity.

APPENDIX II

Invitation letter

Title of study:

Objective measurement of physical activity, sedentary behaviours, and sleep duration and timing in children with chronic diseases compared to healthy children.

Dear Parent/guardian, **12/07/2016**

We are part of a team of researchers based at the University of Glasgow looking at the relationship between sleep, physical activity and sitting in children with chronic illnesses. We want to see if there is a difference between different illnesses, and between healthy children.

We are interested in this because there is evidence that, physical activity is associated with a reduced risk for several diseases and improved overall quality of life while inactivity and sleep deprivation are linked with many unfavourable health outcomes. Therefore, we need to understand how the behaviors interact on a continuum from sleep (no/low movement) to vigorous-intensity physical activity (high movement). We can measure these behaviours by using a small activity monitor, about the size of a matchbox but a third as thick. This monitor can detect whether a young child is sitting, standing or sleeping.

We would like to invite your child to take part in our study. The study does not require any additional appointments or visits.

I have enclosed an information sheet and participation form. If you are interested in taking part in the study after reading the information leaflet, please complete the participation form and return it in enclosed stamped addressed envelope. We will contact you by phone and arrange a meeting to discuss the study in detail and sign a consent form.

Yours sincerely

Dr. Rabha Sulyman,
MD Student

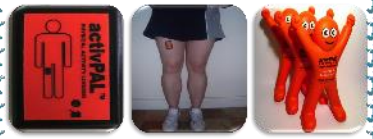
Dr. James Paton,
Reader in Paediatric Respiratory Medicine

Child Information Sheets

Children 3-5 years

Child Information Sheet
(To be read to child)

We would like you to help us. We want to look at how often you run about, sit about and sleep.
To do this you need wear our little box (like a tiny phone) on your leg. We would like you to wear it all the time for a week.



If you wear this box you will help us to do our study.
When you wear the box on your leg, you can do all things you normally do.

Try and keep the little box on all the time. But remember the box is not waterproof so you do need to take it off when you have a bath, a shower or go swimming.

If you need to take it off at any other time please tell the person who looks after you or your teacher.

Thank you

Physical activity, Sedentary and Sleep in children with Chronic Diseases
Children information sheet version 2
19/04/2016

Children 6-10 years

Information Sheet for the Child
6-10 years old

Can you help us?
We are looking at the relationship between sleeping, being active and running around and sitting in children with different illnesses such as diabetes and heart disease.

We want to see if there is a difference between children with these illnesses and healthy children in how they sleep and how active they are. We would like you to help us.

What will I have to do?
You will need to wear one of our small monitors (like a little box) on your leg. You have to wear it fro at least 5-7days. The monitor is worn all the time except when you are having a bath or shower or going swimming.

We also need to check your height and weight.

When the monitor is on.
You can do all things you normally do. But remember it is not waterproof so you do need to take it off when you have a bath, a shower or go swimming.

Physical activity, Sedentary and Sleep in children with Chronic Diseases
Children information sheet version 2.1
19/07/2016

Consent Forms

Parent consent form

University of Glasgow
NHS Greater Glasgow and Clyde

Parent Consent Form

Title of study: Objective measurement of physical activity, sedentary behaviours, and sleep duration and timing in children with chronic diseases compared to healthy children.

To be completed by parent/guardian:

Child's name _____ Date of Birth _____
Address _____
Post Code _____ Tel No _____
Parent's Workhome Tel No _____
Emergency Contact Name _____ Tel No _____

Please initial box

1. I confirm that I have read and understand the information sheet dated 12th of July 2016 (Version 2.1) for the above study and have had the opportunity to ask questions. ☐
2. I understand that all medical information about my child is STRICTLY CONFIDENTIAL ☐
3. I understand that my child's participation is voluntary and that we are free to withdraw at any time, without giving any reason, without my/their legal rights being affected. ☐
4. I understand that my child's information may be looked at by representatives of the study sponsor, NHS Greater Glasgow and Clyde, for audit purposes. ☐
5. I agree for my child to take part in the above study. ☐

Signatures:

Parent(s) name (block letters) _____
Signature(s) _____
Date _____

Name of person taking consent (If not the researcher) _____
Signature _____
Date _____

Researcher's name (block letters) _____
Signature _____
Date _____

Thankyou for your time and co-operation
Copy for participant/parent and copy for researcher

Physical activity, Sedentary and Sleep in children with Chronic Diseases
Parents consent form version 2.1
12/07/2016

Children assent form

University of Glasgow
NHS Greater Glasgow and Clyde

ASSENT FORM FOR THE CHILD 6-10 Years Old

Title of study:
Objective measurement of physical activity, sedentary behaviour, and sleep duration and timing in children with chronic diseases compared to healthy children.

To be completed by the child if able. Please circle your answers:

- Have you read (or had read to you) about this project? Yes/No
- Has somebody else explained this project to you? Yes/No
- Do you understand what this project is about? Yes/No
- Have you asked all the questions you want? Yes/No
- Have you had your questions answered in a way that you understand? Yes/No
- Do you understand that it's OK to stop taking part at any time? Yes/No
- Are you happy to take part? Yes/No

Signatures: If you do want to take part, you can sign your name below

Child name (block letters) _____
Signature (if applicable) _____
Date _____

Name of person taking consent (If not the researcher) _____
Signature _____
Date _____

Researcher's name (block letters) _____
Signature _____
Date _____

THANK YOU FOR YOUR TIME AND CO-OPERATION
Copy for participant/parent, copy for researcher.

Physical activity, Sedentary and Sleep in children with Chronic Diseases. Assent Form for participants aged 6-10 years. Version 2
19/04/2016

ActivPAL-activity Diary

ActivPAL-activity Diary

Device Number **Date:**

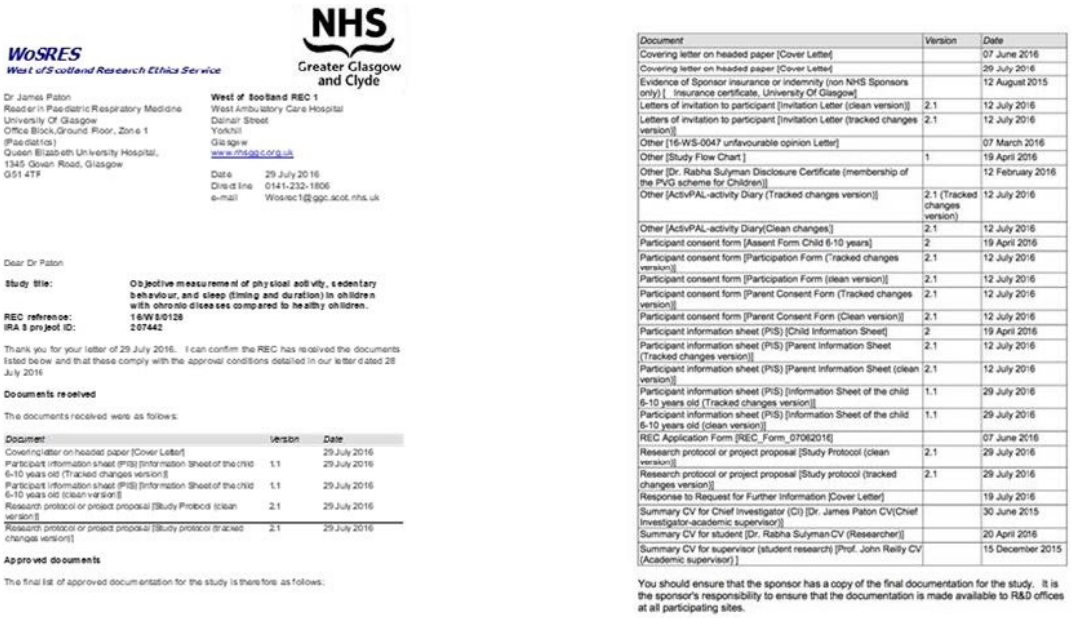
Study ID:

Date, time and reason when device removed or not worn

Day	Time removed	Time replaced	Reason for removing

Return date ..... **Time.....**

Ethical Approval



WoSRES
West of Scotland Research Ethics Service

NHS
Greater Glasgow and Clyde

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West Ambulatory Care Hospital
Dalnair Street
Yorkhill
Glasgow
www.nhsggc.org.uk

Date 29 July 2016
Direct line 0141-232-1806
e-mail Wosrec1@ggc.scot.nhs.uk

Dear Dr Paton

Study title: Objective measurement of physical activity, sedentary behaviour, and sleep (timing and duration) in children with chronic diseases compared to healthy children.
REC reference: 16/WS/0126
IRAS project ID: 207442

Thank you for your letter of 29 July 2016. I can confirm the REC has received the documents listed below and that these comply with the approval conditions detailed in our letter dated 28 July 2016

Documents received

The documents received were as follows:

Document	Version	Date
Covering letter on headed paper [Cover Letter]		29 July 2016
Participant information sheet (PIS) [Information Sheet of the child 6-10 years old (Tracked changes version)]	1.1	29 July 2016
Participant information sheet (PIS) [Information Sheet of the child 6-10 years old (clean version)]	1.1	29 July 2016
Research protocol or project proposal [Study Protocol (clean version)]	2.1	29 July 2016
Research protocol or project proposal [Study protocol (tracked changes version)]	2.1	29 July 2016

Approved documents

The final list of approved documentation for the study is therefore as follows:

Document	Version	Date
Covering letter on headed paper [Cover Letter]		07 June 2016
Covering letter on headed paper [Cover Letter]		29 July 2016
Evidence of Sponsor insurance or indemnity (non NHS Sponsors only) [Insurance certificate, University Of Glasgow]		12 August 2015
Letters of invitation to participant [Invitation Letter (clean version)]	2.1	12 July 2016
Letters of invitation to participant [Invitation Letter (tracked changes version)]	2.1	12 July 2016
Other [16-WS-0047 unfavourable opinion Letter]		07 March 2016
Other [Study Flow Chart]	1	19 April 2016
Other [Dr. Rabha Sulyman Disclosure Certificate (membership of the PVG scheme for Children)]		12 February 2016
Other [ActivPAL-activity Diary (Tracked changes version)]	2.1 (Tracked changes version)	12 July 2016
Other [ActivPAL-activity Diary(Clean changes)]	2.1	12 July 2016
Participant consent form [Assent Form Child 6-10 years]	2	19 April 2016
Participant consent form [Participation Form (Tracked changes version)]	2.1	12 July 2016
Participant consent form [Participation Form (clean version)]	2.1	12 July 2016
Participant consent form [Parent Consent Form (Tracked changes version)]	2.1	12 July 2016
Participant consent form [Parent Consent Form (Clean version)]	2.1	12 July 2016
Participant information sheet (PIS) [Child Information Sheet]	2	19 April 2016
Participant information sheet (PIS) [Parent Information Sheet (Tracked changes version)]	2.1	12 July 2016
Participant information sheet (PIS) [Parent Information Sheet (clean version)]	2.1	12 July 2016
Participant information sheet (PIS) [Information Sheet of the child 6-10 years old (Tracked changes version)]	1.1	29 July 2016
Participant information sheet (PIS) [Information Sheet of the child 6-10 years old (clean version)]	1.1	29 July 2016
REC Application Form [REC_Form_07062016]		07 June 2016
Research protocol or project proposal [Study Protocol (clean version)]	2.1	29 July 2016
Research protocol or project proposal [Study protocol (tracked changes version)]	2.1	29 July 2016
Response to Request for Further Information [Cover Letter]		19 July 2016
Summary CV for Chief Investigator (CI) [Dr. James Paton CV(Chief Investigator-academic supervisor)]		30 June 2015
Summary CV for student [Dr. Rabha Sulyman CV (Researcher)]		20 April 2016
Summary CV for supervisor (student research) [Prof. John Reilly CV (Academic supervisor)]		15 December 2015

You should ensure that the sponsor has a copy of the final documentation for the study. It is the sponsor's responsibility to ensure that the documentation is made available to R&D offices at all participating sites.

16/WS/0126 **Please quote this number on all correspondence**

Yours sincerely

Sophie Bagnall
Assistant Coordinator

Copy to: *Ms Emma-Jane Gault, University of Glasgow/NHS Greater Glasgow and Clyde*
Dr Maureen Travers, NHS Greater Glasgow and Clyde

APPENDIX III

Comparison of activity levels between Libyan and other healthy children -who age and sex matched

Table 1, presented the comparison of activity levels between Libyan and other healthy children

There is a problem comparing Libyan with healthy Scottish children because of difficulties matching age and sex between Libyan healthy and other healthy control children. This because I usually we matched the children with chronic disease and healthy children. Therefore Table 1 in Appendix III, shows a sub group (six of Libyan healthy vs six of other healthy children) where age and sex could be matched. There were there was no significant difference in their activity levels (paired t-test p= 0.53).

Measuring of MVPA in children with chronic disease and healthy peers

Appendix III in the table 2 shown the preliminary analyses of time spent in MVPA measured by using cut-point ≥1418 counts per 15s as suggested by the Janssen et al for all 4 patient groups and all four control groups. Also presented the total number and % of children with chronic disease and healthy peers who were meeting the MVPA recommendation. Our result shown that, time spent in MVPA was lower in children with chronic disease compared to healthy peers, 78% (n=62) in children with chronic disease and 95% (n=76) in healthy children meeting the MVPA recommendation despite the fact the step count was lower than current guideline recommendations. Unfortunately, this discrepancy between their MVPA level and number of steps/day suggests that this cut point is not a secure basis on which to proceed.

Table 1: Comparison of activity levels between 6 of Libyan and 6 of other healthy children -who age, and sex matched

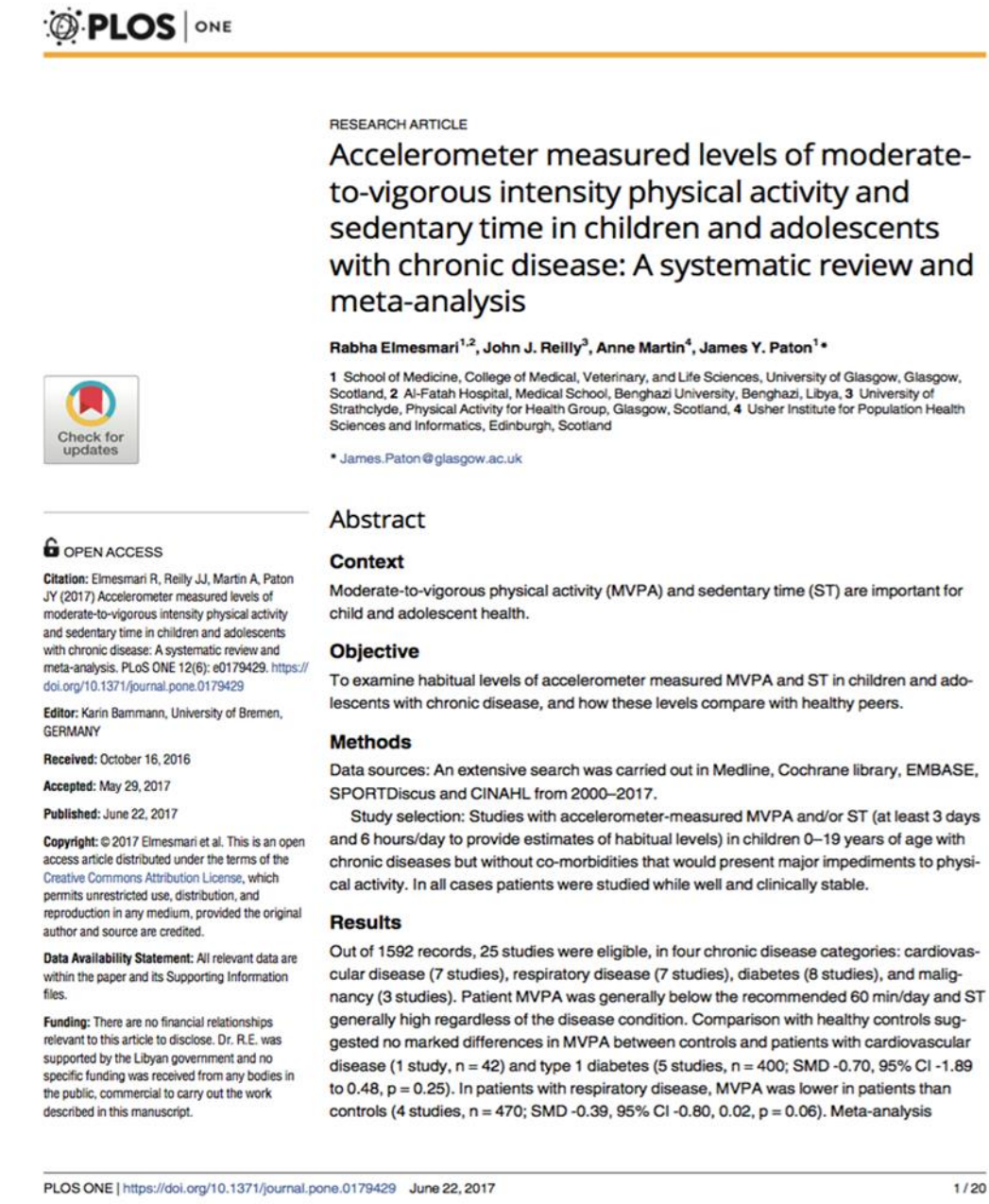
Participants	Gender	age	No. of Monitoring days	Monitoring Tim minutes	Non-Wear Time minutes	Time spent sitting minutes	Time spent standing minutes	Time spent in PA minutes	No steps per 24h	Time spent in sleep minutes
Healthy 15*	F	9.3	7	869.1	11.1	582.6	165.7	120.8	9020.0	564.2
Healthy 23	F	9.5	7	862.1	14.9	577.3	172.1	112.7	9625.7	565.8
Healthy 20*	M	7.2	7	792.7	0.0	470.0	184.3	138.4	10858.9	603.5
Healthy 27	M	7.8	6	781.7	7.7	471.9	176.3	137.2	10160.7	612.1
Healthy 24*	F	4.4	5	836.8	0.0	489.3	209.9	137.3	11095.0	603.2
Healthy 31	F	4.2	6	848.2	0.0	470.8	246.2	131.2	9818.3	591.8
Healthy 43*	M	9.7	7	893.8	0.0	519.2	262.6	114.4	9174.5	535.0
Healthy 48	M	9.9	**8**	913.6	0.0	534.4	254.5	134.7	10168.5	526.1
Healthy 43*	M	6.5	8	868.6	0.0	490.6	265.8	137.9	9436.3	571.4
Healthy 48	M	6.5	8	842.1	10.3	476.2	250.7	147.3	14074.0	587.5
Healthy 51*	F	7.9	6	808.3	14.1	422.7	224. 8	161.2	11662.67	617.6
Healthy 10	F	7.6	7	812.1	0	400.7	237.8	173.6	12711.6	611.2

Table 2: Time spent in MVPA by using cut-point ≥1418 counts per 15s as suggested by the Janssen et al for all 4 patient groups and all four control groups

Variables	**CD (n= 80)**	**HC (n= 80)**	**T1DM (n= 20)**	**HC (n= 20)**	**JIA (n= 20)**	**HC (n= 20)**	**CHD (n= 20)**	**HC (n= 20)**	**CF (n= 20)**	**HC (n= 20)**
Time spent in MVPA based on steeping time h	1.6(0.6)	2.1(0.5)	1.5 (0.7)	1.8 (0.4)	1.9 (0.4)	2.2 (0.4)	1.6 (0.8)	2.1 (0.5)	1.5 (0.5)	2.1 (0.5)
No. of participants *NOT* meeting MVPA recommendation	62 (78%)	76 (95%)	15 (75%)	19 (95%)	18 (90%)	20 (100%)	14 (70%)	18 (90%)	15 (75%)	19 (95%)

Author Bibliography

1. Elmesmari R, Reilly JJ, Martin A, Paton JY. Accelerometer measured levels of moderate-to-vigorous intensity physical activity and sedentary time in children and adolescents with chronic disease: A systematic review and meta-analysis. PLoS One. 2017;12(6):e0179429.



PLOS ONE

RESEARCH ARTICLE

Accelerometer measured levels of moderate-to-vigorous intensity physical activity and sedentary time in children and adolescents with chronic disease: A systematic review and meta-analysis

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Abstract

Context

Moderate-to-vigorous physical activity (MVPA) and sedentary time (ST) are important for child and adolescent health.

Objective

To examine habitual levels of accelerometer measured MVPA and ST in children and adolescents with chronic disease, and how these levels compare with healthy peers.

Methods

Data sources: An extensive search was carried out in Medline, Cochrane library, EMBASE, SPORTDiscus and CINAHL from 2000–2017.

Study selection: Studies with accelerometer-measured MVPA and/or ST (at least 3 days and 6 hours/day to provide estimates of habitual levels) in children 0–19 years of age with chronic diseases but without co-morbidities that would present major impediments to physical activity. In all cases patients were studied while well and clinically stable.

Results

Out of 1592 records, 25 studies were eligible, in four chronic disease categories: cardiovascular disease (7 studies), respiratory disease (7 studies), diabetes (8 studies), and malignancy (3 studies). Patient MVPA was generally below the recommended 60 min/day and ST generally high regardless of the disease condition. Comparison with healthy controls suggested no marked differences in MVPA between controls and patients with cardiovascular disease (1 study, n = 42) and type 1 diabetes (5 studies, n = 400; SMD -0.70, 95% CI -1.89 to 0.48, p = 0.25). In patients with respiratory disease, MVPA was lower in patients than controls (4 studies, n = 470; SMD -0.39, 95% CI -0.80, 0.02, p = 0.06). Meta-analysis

2. Elmesmari R, Martin A, Reilly JJ, Paton JY. Comparison of accelerometer measured levels of physical activity and sedentary time between obese and non-obese children and adolescents: a systematic review. BMC Pediatr. 2018;18(1):106.

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BMC Pediatrics

RESEARCH ARTICLE Open Access

Comparison of accelerometer measured levels of physical activity and sedentary time between obese and non-obese children and adolescents: a systematic review

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Abstract

Background: Obesity has been hypothesized to be associated with reduced moderate-to-vigorous physical activity (MVPA) and increased sedentary time (ST). It is important to assess whether, and the extent to which, levels of MVPA and ST are suboptimal among children and adolescents with obesity. The primary objective of this study was to examine accelerometer-measured time spent in MVPA and ST of children and adolescents with obesity, compared with MVPA recommendations, and with non-obese peers.

Methods: An extensive search was carried out in Medline, Cochrane library, EMBASE, SPORTDiscus, and CINAHL, from 2000 to 2015. Study selection and appraisal: studies with accelerometer-measured MVPA and/or ST (at least 3 days and 6 h/day) in free-living obese children and adolescents (0 to 19 years) were included. Study quality was assessed formally. Meta-analyses were planned for all outcomes but were precluded due to the high levels of heterogeneity across studies. Therefore, narrative syntheses were employed for all the outcomes.

Results: Out of 1503 records, 26 studies were eligible ($n = 14,739$ participants; $n = 3523$ with obesity); 6/26 studies involved children aged 0 to 9 years and 18/26 involved adolescents aged 10.1 to19 years. In the participants with obesity, the time spent in MVPA was consistently below the recommended 60 min/day and ST was generally high regardless of the participant's age and gender. Comparison with controls suggested that the time spent in MVPA was significantly lower in children and adolescents with obesity, though differences were relatively small. Levels of MVPA in the obese and non-obese were consistently below recommendations. There were no marked differences in ST between obese and non-obese peers.

Conclusions: MVPA in children and adolescents with obesity tends to be well below international recommendations. Substantial effort is likely to be required to achieve the recommended levels of MVPA among obese individuals in obesity treatment interventions.
This systematic review has been registered on PROSPERO (International Database of Prospective Register Systematic Reviews; registration number CRD42015026882).

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3. Elmesmari R, Reilly JJ, Paton JY. Objectively measured 24-hour movement behaviors in children with chronic disease: A case-control study. Manuscript in review in PLoS One 2019.

Objectively measured 24-hour movement behaviors in children with chronic disease: A case-control study

Short running title: Movement behaviors in children with chronic disease

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