

DISSERTATION FROM THE
NORWEGIAN SCHOOL OF
SPORT SCIENCES
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Turid Skrede

Prospective associations between sedentary time, physical activity and cardiometabolic health in children

The Active Smarter Kids Study

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SUMMARY

Background: A large proportion of children and adolescents are not sufficiently active according to PA recommendations. Cross-sectional studies find low PA levels to be associated with excessive body weight and poor cardiometabolic health in apparently healthy children, but sedentary time is also suggested as a risk factor for these outcomes.

Main aim: To systematically review and examine the prospective associations between objectively measured sedentary time and intensity-specific PA with cardiometabolic health indicators and adiposity in youth.

Materials and methods: First, a systematic review and meta-analysis were performed to assess the knowledge gaps in the current literature. Three original studies used data from the Active Smarter Kids (ASK) Study, a cluster-randomised school-based PA intervention, conducted in 2014-15 amongst 1180 children aged 10 years old at baseline, in Western Norway. At baseline and follow-up the following health-related variables were assessed; PA were measured by accelerometry (GT3X/GT3X+), and an intermittent running test (the Andersen-test) estimated VO_{2peak} and were used as a measure of CRF. Cardiometabolic outcomes were anthropometry (body mass index (BMI), waist circumference (WC) and sum of four skinfolds), blood samples (low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose and insulin), and blood pressure. The meta-analysis for MVPA and clustering of cardiometabolic risk factors were conducted using random effects models with unstandardized regression coefficients and 95% confidence intervals. Statistical analyses of ASK Study data were performed by linear mixed modelling with schools as random intercept to account for clustering within data, and adjustments by age, sex, socio-economic status, puberty, and baseline value of the outcome.

Results: Based on the systematic review, we found no evidence for a prospective association between sedentary time and cardiometabolic risk factors in youth, while the evidence for a prospective association between MVPA and *clustering* of cardiometabolic risk factors is consistent and inverse, supported by our meta-analysis (**Study I**). These observations also corroborated with results based on ASK Study data (**Study II**). Moreover, CRF is a moderator in the prospective association between PA and the clustered cardiometabolic risk; the association between MVPA and clustered cardiometabolic risk was stronger in children with low CRF, and no associations appeared present in their high fit peers (**Study III**). In bi-directional analyses, time spent sedentary do not predict any adiposity measures, while MVPA and VPA predicts lower skinfolds (**Study IV**). On the contrary, baseline BMI, WC and skinfolds predicts more time spent sedentary, and less PA, MVPA and VPA but mainly in boys.

Conclusion: Apparently, as long as youth spend sufficient time in MVPA, being sedentary causes little harm to cardiometabolic health and do not predict adiposity. Spending time in MVPA might be especially important for children with low CRF. On the contrary, as adiposity predicts higher sedentary time and less PA over a short time period, highlights the crucial role of PA prevention before excess adiposity are established.

Keywords: physical activity, sedentary time, cardiometabolic health, prospective associations, adiposity, children, cardiorespiratory fitness, clustering, bi-directional, moderate and vigorous intensity

SAMANDRAG

Bakgrunn: Mange barn og unge oppfyller ikkje tilrådd dagleg dose med fysisk aktivitet (60 minutt moderat-til-høg fysisk aktivitet). Tverrsnittundersøkingar viser at eit lågt aktivitetsnivå er assosiert med overvekt, men også assosiert med ugunstig metabolsk helse hjå tilsynelatande friske barn. Samstundes er det indikasjonar for at sedat tid er ein risikofaktor for overvekt og metabolsk helse.

Mål: Gjennomføre ei systematisk kunnskapsoppdatering og undersøke samanhangen ved objektivt måla sedat tid og ulike intensitetar av fysisk aktivitet med metabolske risikofaktorar hjå barn og unge basert på prospektive analyser.

Materiale og metode: Først gjennomførte vi ei systematisk kunnskapsoppdatering for å finne kunnskapshøl og vurdere evidensgrunnlaget innanfor dette forskingsfeltet. Dei tre andre studiane er basert på datamateriale frå Active Smarter Kids (ASK) Study. ASK var ein klynge-randomisert skulebasert fysisk aktivitet intervensjon som vart gjennomført i 2014-15 hjå 1180 barn frå 5.klasse i Sogn og Fjordane. Før og etter intervensjon vart det samla inn data på ei mengde helserelaterte variablar. Fysisk aktivitet vart måla med akselerometer (GT3X/GT3X+), medan VO_{2peak} vart estimert frå Andersen-testen som eit mål på fysisk form. Metabolske helsevariablar kroppsmasseindeks (KMI), midjemål, skinfoldmålingar, fastande blodprøver (kolesterol, triglyserid, glukose og insulin), og blodtrykk. Meta-analysen for ein prospektiv samanheng mellom moderat-til-høg fysisk aktivitet og opphoping av metabolske Risikofaktorar vart gjennomført med ein 'random effects' modell med ustandardiserte regresjonskoeffisientar og 95% konfidensintervall. Statistiske analyser av ASK data vart gjennomført med lineær mix modell justert for skulenivå for å ta høgde at data kunne klynge seg. Alle analyser vart justert for alder, kjønn, sosioøkonomisk status, pubertet.

Hovudresultat: Basert på den systematiske kunnskapsoppdateringa er det er særst få indikasjonar for ein prospektiv samanheng mellom sedat tid og metabolske risikofaktorar, medan samanhangen mellom moderat-til-høg fysisk aktivitet og opphoping av metabolske risikofaktorar er negativ og konsistent (**Artikkel I**). Desse observasjonane vert stetta av meta-analysen og samsvarar med resultatane frå ASK data i **Artikkel II**, men assosiasjonane avheng truleg av midjemål. Fysisk form er ein moderator i den prospektive samanhangen mellom fysisk aktivitet og metabolske risikofaktorar. Hjå barn med låg fysisk form er det ein sterkare samanheng mellom moderat-til-høg fysisk aktivitet og opphoping av metabolske risikofaktorar, med ikkje hjå barn med høg fysisk form (**Artikkel III**). Vi finn ikkje indikasjonar på at sedat tid predikerar høgare nivå av KMI, midjemål eller skinfold (**Artikkel IV**). I motsetnad predikerar KMI og midjemål meir sedat tid og mindre fysisk aktivitet – desse samanhengane er hovudsak berre hjå gutar.

Konklusjon: Så lenge barn og unge er tilstrekkeleg fysisk aktive i moderat-til-høg intensitet, spelar total sedat tid lita rolle for metabolsk helse – noko som er ekstra viktig for barn med låg fysisk form. Sedat tid påverkar heller ikkje BMI, midjemål eller skinfeld. I motsetnad predikerar høgare BMI, midjemål og skinfeld meir sedat tid, og lågare nivå av total fysisk aktivitet, samt moderat-til-høg fysisk aktivitet.

Nøkkelord: fysisk aktivitet, sedat tid, stillesitjande tid, metabolsk helse, blodprøver, overvekt, midjemål, barn, unge, moderat, høg, intensitet, prospektive analyser

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Turid Skrede,

Sogndal, July 2018

LIST OF STUDIES

The thesis is based on the following original research studies, which are referred to in the text by their Roman numerals:

- I. Skrede, T., Steene-Johannessen, J., Anderssen, S.A., Resaland, G.K., & Ekelund, U. The prospective association between objectively measured sedentary time, moderate-to-vigorous physical activity and cardiometabolic risk factors in youth: a systematic review and meta-analysis. (Revised and resubmitted July 2018 to *Obesity Reviews*)
- II. Skrede, T., Stavnsbo, M., Aadland, E., Aadland, K. N., Anderssen, S. A., Resaland, G. K., & Ekelund, U. (2017). Moderate-to-vigorous physical activity, but not sedentary time, predicts changes in cardiometabolic risk factors in 10-y-old children: the Active Smarter Kids Study. *Am J Clin Nutr*, 105(6), 1391-1398. Doi: 10.3945/ajcn.116.150540
- III. Skrede, T., Aadland, E., Andersen, L.B., Stavnsbo, M., Anderssen, S.A., Resaland, G.K., & Ekelund, U. (2018). Does cardiorespiratory fitness moderate the prospective association between physical activity and cardiometabolic risk factors in children? *Int J Obes*, 42(5), 1029-1038. Doi: 10.1038/s41366-018-0108-z.
- IV. Skrede, T., Aadland, E., Anderssen, S.A., Resaland, G.K., & Ekelund U. (2018). Bi-directional prospective associations between objectively measured sedentary time, physical activity and adiposity in 10-year-old children. (Submitted)

ABBREVIATIONS

ASK Study	Active Smarter Kids Study
BMI	body mass index
CI	confidence interval
cpm	counts per minute
CRF	cardiorespiratory fitness
DBP	diastolic blood pressure
HDL	high-density lipoprotein cholesterol
HOMA-IR	homeostasis model assessment for insulin resistance
ICC	intra-class correlation
IQR	inter-quartile range
LDL	low-density lipoprotein cholesterol
MET	metabolic equivalent
MetS	the metabolic syndrome
MPA	moderate physical activity
MVPA	moderate-to-vigorous physical activity
PA	physical activity
RCT	randomised controlled trial
SBP	systolic blood pressure
SD	standard deviation
SES	socio-economic status
TC:HDL	total cholesterol/high-density lipoprotein cholesterol ratio
VPA	vigorous physical activity
WC	waist circumference

LIST OF TABLES

Table 1: Example of the complete search strategy	p. 20
Table 2: Criteria List for Assessment of the Methodological Quality of Prospective Studies	p. 37
Table 3: Prospective study characteristics and results sorted by outcome	p. 38
Table 4: Intervention study characteristics and results sorted by outcome	p. 45
Table 5: Quality assessment of the included studies sorted by quality score	p. 47
Table 6: Level of evidence from studies examining associations between objectively measured total sedentary time, MVPA and cardiometabolic outcomes	p. 48
Table 7: Children's characteristics for Study II	p. 49
Table 8: Prospective associations between sedentary time, MPA, VPA and MVPA at baseline and individual cardiometabolic risk factors at follow-up	p. 51
Table 9: Prospective associations between SED, MPA, MVPA and VPA at baseline and clustered cardiometabolic risk at follow-up	p. 52
Table 10: Children's characteristics for Study III	p. 54
Table 11: Prospective associations between sedentary time and PA with individual cardiometabolic risk factors	p. 55
Table 12: Prospective associations between sedentary time and PA with individual cardiometabolic risk factors, adjusted for adiposity	p. 56
Table 13: Prospective associations between sedentary time and PA with clustered cardiometabolic risk factors	p. 57
Table 14: Children's characteristics for Study IV	p. 58
Table 15: Prospective associations between PA at baseline and adiposity at follow-up	p. 59
Table 16: Prospective associations between adiposity at baseline and PA at follow-up	p. 60
Table 17: Prospective associations between baseline MVPA (\geq / $<$ 60 minutes) and adiposity at follow-up	p. 61
Table 18: Prospective associations between normal weight versus overweight/obese at baseline and PA intensities at follow-up	p. 61

LIST OF FIGURES

Figure 1: Flow chart ASK Study: Study II – IV (n = schools [participants])	p. 26
Figure 2: Flow chart systematic literature review	p. 32
Figure 3: Meta-analysis for prospective studies	p. 36
Figure 4: Meta-analysis for intervention studies	p. 36
Figure 5: Clustered cardiometabolic risk at follow-up stratified by baseline quartiles of MVPA	p. 52
Figure 6: Prospective association between quartiles of overall PA and MVPA with clustered cardiometabolic risk, stratified by CRF below and above the sex specific median	p. 57

TABLE OF CONTENT

SUMMARY	
SAMANDRAG	
ACKNOWLEDGEMENTS	
LIST OF STUDIES	
ABBREVIATIONS	
LIST OF TABLES	
LIST OF FIGURES	

INTRODUCTION.....	1
Definitions	2
Physical activity	2
Sedentary behaviour	2
Cardiorespiratory fitness	3
Assessment of physical activity	3
Assessment of cardiorespiratory fitness	4
Traditional cardiometabolic risk factors.....	5
Abdominal obesity.....	5
Insulin resistance.....	5
Hypertension	6
Dyslipidaemia	6
Clustering of cardiometabolic risk factors.....	7
Defining clustering of cardiometabolic risk.....	8
Physical activity and sedentary time in youth.....	9
Sedentary time, physical activity and cardiometabolic health in youth	11
Gaps in the current research.....	15
Research aims and questions	17
MATERIALS AND METHODS	19
Study I: Systematic literature review and meta-analysis	19
Study inclusion criteria and search strategy	19
Study selection	19
Data extraction	19
Assessment of methodological quality	20
Level of scientific evidence.....	21
Study II–IV: The Active Smarter Kids Study	21
Dose and intensity.....	21
Physical activity	23

Cardiorespiratory fitness.....	23
Anthropometry.....	23
Blood pressure.....	24
Blood samples	24
Covariates.....	25
Statistics	27
SUMMARY OF RESULTS	31
Study I.....	31
Studies included	31
Sample characteristics.....	31
Adiposity.....	33
Blood pressure.....	33
Biochemical variables	34
Study II.....	49
Study III.....	53
Study IV.....	57
GENERAL DISCUSSION	63
Study I and II: Is there a prospective association between sedentary time, MVPA and cardiometabolic risk?	63
Study III: Does CRF moderate the prospective association between physical activity and cardiometabolic risk?	67
Study IV: Is the prospective association between sedentary time, physical activity and adiposity bi-directional?.....	69
Methodological considerations.....	71
Study I.....	71
Study II–IV.....	72
Physical activity measured by accelerometry	73
Clustering of cardiometabolic risk factors.....	75
Implications	76
Future research	77
CONCLUSIONS.....	79
REFERENCES.....	81
STUDY I–IV	
APPENDIX I–II	

INTRODUCTION

Overweight and obesity levels in children and adolescents have increased continuously worldwide during the last decades (2). International estimates suggest more than 60 million children will be overweight or obese by 2020, and an even higher number will be at risk of excess body weight (3). Overweight and obesity rates parallel the emergence of adverse cardiometabolic health observed in youth worldwide (4-6), as children with overweight or obesity often have a poor cardiometabolic risk profile (7, 8). The causes of childhood obesity are a complex mix of social, cultural, and behavioural factors (9). Among these factors, physical activity (PA) are acknowledged as a preventive strategy for excess body weight (10), but PA is also inversely associated with other cardiometabolic risk factors such as blood pressure (BP), insulin, and lipids (11-13).

Children achieving 60 minutes of moderate-to-vigorous PA (MVPA) daily have a healthier cardiometabolic risk profile than their less active peers (14). It is therefore worrying that the majority of children and adolescents are not sufficiently active (15, 16), while time spent sedentary increase (17, 18). Sedentary time is considered a risk factor for children's health as sedentary pursuits like TV consumption are adversely associated with cardiometabolic health (19). However, TV consumption is likely to be mediated or confounded by context specific behaviours such as unhealthy snacking (20) and do not reflect total accumulation of sedentary time (21). On the opposite, objectively measured sedentary time do not replicate similar observations as those measured by self-report, especially when time spent in MVPA is taken into account (22, 23). Hence, it is unknown whether time spent sedentary truly is a risk factor for children's health.

Physical activity has favourable influences on children's overall health (24), but many aspects of the potential effect of PA remain unanswered. The evidence for a relationship between PA and health in children is mainly based on overall PA, and it is unclear which aspects of PA are the most beneficial. Moreover, the majority of PA studies are cross-sectional, which preclude inference about temporality and indication of causality. For example, PA interventions have a modest effect on excessive body weight in children and do not produce the effects one could expect from cross-sectional studies (25). On the contrary, a growing number of studies find adiposity to predict sedentary time and PA, and not vice versa (23, 26-28). This contradicts the traditional view – fatness might be a determinant for PA, and physical inactivity could be the result of fatness rather than its cause (28).

Definitions

Inconsistent use of terminology has impacted the field of sedentary behaviour and PA research (29). An overview of terminology is needed as there are many different concepts that are not always synonymous or interchangeable.

Physical activity

Physical activity is defined as any bodily movement resulting from contractions of skeletal muscle that result in an increase in energy expenditure above resting levels (30). Despite the straightforward definition, PA is multidimensional and complex behaviour that is difficult to assess accurately (31). The total amount of PA is based on frequency (number of bouts), duration (bout length), intensity (i.e. energy expenditure), mode (type of behaviour), and domain (the context or reason for being physically active). The terms 'physically inactive' and 'physically active' are often used, which refer to whether a person is performing sufficient amounts of MVPA according to public PA recommendations (32).

Sedentary behaviour

Sedentary behaviour was until recently often applied to describing the behaviour of physically inactive persons and those who engaged in large amounts of sitting, or even sedentary control groups. A consensus of the term sedentary was needed to prevent confusion within articles and journals (32). In 2012, the Sedentary Behaviour Research Network suggested that the formal definition of sedentary behaviour should be 'any waking behaviour characterised by an energy expenditure of ≤ 1.5 metabolic equivalents (METs) while in a sitting, reclining, or lying posture' (32). The definition acknowledges the importance of posture, but also of energy expenditure when defining sedentary pursuits. The Sedentary Behaviour Research Network definition was widely accepted across disciplines, but further refinement of a variety of related and emergent terms was needed (i.e. stationary behaviour, standing, sedentary pattern) (33). For example, there have been discussions as to whether standing is sedentary behaviour, as it induces more muscular activity than sitting or lying. Moreover, sitting and watching TV requires 1.41 METs while sitting and playing Nintendo Wii requires 2.06 METs. However, the current threshold seems reasonable although some sitting-based activities may be classified as non-sedentary (34), and an updated definition from 2017 concluded the threshold of ≤ 1.5 METs to be appropriate in both children and adults (33). Regardless, the most important aspect of a common definition is the confirmation that sedentary behaviour is not defined as failure to attain recommended levels of PA (17).

Cardiorespiratory fitness

Cardiorespiratory fitness (CRF) is one of three components of physical fitness and relates to the ability of the circulatory and respiratory systems to supply fuel during sustained PA and to eliminate fatigue products (30). The two other components of physical fitness are muscular strength and mobility. Different terms are applied to describe CRF, including aerobic fitness, endurance, and aerobic capacity, and these terms are often used interchangeably. Within public health, CRF is the most important component of physical fitness due to its direct and independent association with morbidity and premature mortality in adults (35-37), but CRF is also an independent predictor of children's cardiometabolic health (7, 38, 39).

Assessment of physical activity

Several measurement methods have been applied to quantify energy expenditure and PA behaviour. The methods of measuring free-living PA or related energy expenditures can be divided into two categories: 1) subjective methods such as self-report measures, including questionnaires, logs, diaries, and recalls; and 2) objective methods, such as doubly labelled water (DLW), pedometers, posture measures, heart rate monitoring, and accelerometers (31).

The gold standard method for assessing energy expenditure over a short period (1–4 weeks) in free-living individuals is the DLW method (40). Briefly, the method is based on the exponential disappearance from the body of the stable isotopes ^2H and ^{18}O after a single dose of water labelled with both isotopes (41). The ^2H is lost as water and the ^{18}O as both water and CO_2 . After correction for isotopic fractionation, the excess disappearance rate of ^{18}O relative to ^2H is a measure of the CO_2 production rate (42). The rate can be converted to an estimate of total energy expenditure by using a known or estimated respiratory quotient and the classical principle of indirect calorimetry (43). The usefulness of DLW is limited in terms of the complicated test procedure and high costs. More importantly, DLW measures exclusively total energy expenditure and do not provide information about the intensity, frequency, or duration of PA (31). Therefore, DLW is usually used as a validation criterion for other PA measurement methods.

In the history of PA epidemiology, the evidence for a relationship between PA and health is generally based on subjective measurement methods of PA behaviour (44). Within subjective measurement methods (i.e. self-report), self-administered questionnaires, proxy reports and diaries are most commonly used. Self-reported measurements for PA are low cost and feasible in large populations, but has limitations in all age groups, as they are prone to recall bias, which includes over- and underestimation of both PA and sedentary time (45). The main barrier for valid and reliable self-reported PA in children is their highly intermittent pattern in moderate and vigorous PA (VPA), which

is difficult to quantify correctly and affects estimates of intensity, duration, and frequency at the same time. Indeed, self-report measures have advantages as they provide important information for domain and context of PA (i.e. household or domestic, transportation or leisure time), and can differentiate between sedentary pursuits such as viewing TV, reading a book, or passive transport. This is important information that objective PA measurement methods cannot provide.

Objective PA measurements have largely replaced the use of self-reported PA. There are several different devices available, but accelerometers have been most commonly used in children, and are a reliable and valid tool for free-living PA energy expenditure estimates (46). Accelerometers have methodological advantages that include objective estimates of the different PA intensities, no need for individual calibration and a low burden for respondents. In general, accelerometers are worn during waking hours, but removed while sleeping and water-based activities. The accelerometer measurements are usually assessed over seven consecutive days in order to capture both weekdays and weekends, and each day should comprise a minimum of 8 to 10 hours of wear time to reflect an entire day (47). The two outcomes from accelerometers are: 1) acceleration and 2) estimates of intensity, frequency, and duration of body movement, all collected in real time (45). Accelerometers measure movement (i.e. acceleration) of the body segment to which the monitor is attached. Acceleration is the change in velocity over time ($\text{meter}/\text{sec}^2$), and is assessed from one to three different planes using the amplitude and frequency of acceleration in the accelerometer. However, the acceleration is usually interpreted as 'counts' (48), and dividing the total counts per day into counts per minute (cpm) gives an estimate of PA intensity, depending on which cut points are applied. Counts are an arbitrary unit and based on the specifications of the accelerometer, which cannot be compared between different types of accelerometers (49). During data processing, accelerometer data are collected in a predetermined sampling interval (epoch), which is usually set between 5 and 60 seconds. For children, shorter epochs are recommended due to their variable PA pattern; approximately 96% of activity bouts in children are ≤ 10 seconds (50, 51), and the majority of MVPA occurs in bouts of ≤ 5 seconds (52). The brief activity intervals illustrate the transitory nature of PA in children (31), and shorter epochs are more sensitive to capturing shorter bouts of high intensity PA (45).

Assessment of cardiorespiratory fitness

Directly measured maximal oxygen consumption ($\text{VO}_{2\text{max}}$) is the most reliable and valid method to assess CRF (53), and is defined as the highest rate at which individuals can consume oxygen during strenuous, dynamic work involving large muscle groups (30). In children, the term $\text{VO}_{2\text{peak}}$ is commonly used, as they seldom reach the plateau of oxygen consumption observed in adults (54). Those children who plateau do not have higher VO_2 , heart rate or blood accumulations than those

not exhibiting a VO_2 plateau (55, 56). The use of a maximal or peak oxygen consumption test is time consuming and expensive, and therefore not always suitable for large study samples or feasible for test logistics. Less complex tests have been developed by comparing an estimated measure with the criterion measure, and it is possible to estimate $\text{VO}_{2\text{peak}}$ by using maximal or sub-maximal tests (57). In children and adolescents, running tests such as the Cooper test (58), the 20 meter shuttle run test (59), and the Andersen test (60) are frequently used, but $\text{VO}_{2\text{peak}}$ may also be estimated by ergometer cycling (61). Results from these field-based performance tests have acceptable reliability and validity to estimate $\text{VO}_{2\text{peak}}$ (57, 60, 62, 63), and they are appropriate and feasible methods of assessing children's CRF in real life settings.

Traditional cardiometabolic risk factors

Abdominal obesity

Abdominal obesity is excessive fat distributed in the abdominal area and located within and around internal organs. It is also referred to as central obesity, intra-abdominal fat, visceral fat, adipose tissue or central adiposity. Abdominal obesity were regarded as a passive energy reserve, but is now established as a complex organ comprising a wide range of cell types with diverse functions for energy storage, metabolic regulation, endocrine and immune system (64). Fat cells (i.e. adipocytes) synthesize and secrete pro-inflammatory $\text{TNF-}\alpha$ (65) and leptin which regulates appetite and energy balance (66). Both $\text{TNF-}\alpha$ and leptin also affects insulin and glucose metabolism, with increased levels among those with high BMI (64). Moreover, adipose tissue secretes hormones (i.e. adipokines) and growth factors that increases low-grade inflammation, but also impair the regulation of biological functions such as insulin sensitivity, lipid metabolism, and BP levels (67, 68).

Insulin resistance

Insulin is a peptide hormone required for glucose uptake in muscle and fat, inhibits hepatic glucose production and is the primary regulator of blood glucose within normal concentrations (68). On the opposite, insulin resistance is characterised as 'an impaired ability of plasma insulin at usual concentrations to adequately promote peripheral glucose disposal, suppress hepatic glucose, and inhibit very low-density lipoprotein (VLDL) output' (69). Disturbances in insulin levels also enhances lipid storage in adipocytes by stimulating triglyceride synthesis and inhibiting its breakdown (70). Insulin resistance may occur in multiple organs involving skeletal muscles, liver, adipose tissue, and the heart (71). Insulin resistance is the most common cardiometabolic alteration to obesity, which represents an important link between obesity and cardiometabolic complications (10, 72), and is therefore suggested as a main component of cardiometabolic risk factors clustering (10, 73, 74).

The specific reasons why insulin resistance manifests in some individuals, but not others, are yet to be fully understood (70). There is a genetic influence on the development of insulin resistance (10), but the risk is also dependent on external factors, such as excessive adiposity (75, 76), diet (77), and insufficient PA levels (78). Not all individuals with overweight and obesity are insulin resistant, but the greater the degree of excess adiposity and body fat, the more likely an individual is to be insulin resistant (79, 80).

Hypertension

Hypertension is defined as an elevated BP on the blood vessel walls established over longer periods of time ($BP = \text{cardiac output} \times \text{peripheral resistance}$), and results from increased activation of the autonomic nervous system and renin-angiotensin-aldosterone system in the kidneys. Hypertension is the most important independent modifiable risk factor for cardiovascular disease (81). Hypertension increases the workload on the heart due to thickening of the arterial wall, and can cause ventricular hypertrophy, further affecting the workload and risk of myocardial infarction and heart failure in adults (81, 82). Hypertension is a critical risk factor in the atherosclerosis process because of its degenerating effects on blood vessel elasticity, increased peripheral resistance, and mechanical stress. A close relationship between insulin resistance and hypertension has also been established (83), as approximately half of all cases of essential hypertension also have insulin resistance (84). Hypertension in children is not common, but adolescents may have essential hypertension (85). Childhood obesity is a risk factor for hypertension, but also affected by race and ethnicity, low birth weight, and low-grade inflammation (86).

Dyslipidaemia

Dyslipidaemia is an abnormal and unfavourable lipid and lipoprotein profile. The typical risk profile is increased VLDL, triglycerides, total cholesterol, and low-density lipoprotein (LDL) and decreased concentrations of high-density lipoprotein (HDL) (87). The total level of cholesterol is affected by diet, but the body itself produces the majority of cholesterol. Both the liver and the intestines synthesise HDL, LDL, and VLDL. The LDL is the major transporter of cholesterol within the blood, and delivers fat molecules to cells. In excessive amounts, LDL can drive the progression of atherosclerosis if they become oxidised within the arterial wall and start the atherosclerotic process. Unlike the other cholesterol lipoproteins, the physiological functions of HDL benefit the cardiovascular system. The HDL have a protective effect related to their role in reverse cholesterol transport in blood stream, but does also have anti-inflammatory, anti-oxidative, anti-thrombotic, and anti-apoptotic properties (88, 89). Cholesterols and lipids are connected to water-soluble lipoproteins in order to be transported in the blood stream. These lipoproteins also play a role in the regulation of plasma lipid and lipoprotein transport (90). Over the last decade, evidence has accumulated that a smaller

component of the lipoprotein (apolipoproteins) may improve the prediction of cardiometabolic risk (91). Thus, cardiometabolic risk may be more dependent on the variation in concentrations of apolipoproteins (B and A-I), than the absolute level of HDL, LDL, and VLDL (91, 92).

Triglycerides constitute the majority of body lipids, and are simply referred to as 'fat'. Triglycerides have not always been regarded as a cardiometabolic risk factor (93, 94) due to high within-person variability when compared to serum cholesterol (95). However, high triglyceride levels might reflect insulin resistance (95, 96) and have unfavourable influence on LDL, VLDL and HDL composition and metabolism (90).

Clustering of cardiometabolic risk factors

Clustering of cardiometabolic risk factors is a condition identified by several risk factors being slightly elevated at the same time, but not above thresholds where they are normally treated, as they would be in adult populations. When the aforementioned cardiometabolic risk factors cluster, it is likely that they share common factors that affect all or some of them simultaneously (38, 97). The suggested underlying factors include poor diet, physical inactivity, low CRF and genetics, or more likely a combination of these (38).

Among the cardiometabolic risk factors, excessive body weight/adiposity and insulin resistance are key features for clustering (98). Children and adolescents with overweight and obesity often score worse on cardiometabolic risk factors (8), and are therefore 'at risk' of clustering (8, 99). Increasing weight in children with obesity is associated with a decrease in insulin sensitivity, while weight loss are followed by insulin sensitivity improvement (100). But insulin sensitivity may also improve independent of changes in body composition (101), possibly through changes in PA levels or CRF (101, 102). However, children with clustering of cardiometabolic risk factors are not necessarily overweight or obese (103); suggesting that risk also depends on body fat distribution. Indeed, overweight and obesity are predictors of clustering, but children with abdominal obesity are more likely to have clustering of cardiometabolic risk factors than in those with general overweight or obesity (104). Importantly, as some children are lean and insulin resistant, clustering might occur before excess body weight or adiposity is apparent, and weight gain might be the result of insulin resistance as well as the cause (10, 103). Abdominal obesity and impaired insulin action may therefore have unique pathways to clustering of cardiometabolic risk factors, but the specific mechanisms remain unclear (67); however, the strong inter-correlations among the cardiometabolic risk factors makes it difficult to determine which risk factor, if any, plays the dominant role.

Defining clustering of cardiometabolic risk

Clustering of cardiometabolic risk factors is commonly referred to as the metabolic syndrome (MetS) in adult populations. Several definitions of MetS are available, with gender and ethnicity-specific cut points (105). The most commonly used definitions are those proposed by the International Diabetes Federation (IDF), the National Cholesterol Education Program's Adult Treatment Panel III (NCEP), and the World Health Organization (WHO). The definitions agree on which components make up MetS (adiposity measure, fasting glucose/insulin, BP, dyslipidaemia), but apply different clinical criteria. With time, several attempts to define MetS suitable for children and adolescents have been made, but they also use a wide variety of cut-off points for the MetS components with an age-, sex-, and height-specific percentile approach (106-110). Common to the definitions is the requirement of at least three risk factors above absolute thresholds to be diagnosed. In 2006, the IDF proposed a unified definition for children and adolescents with WC as the main component and the presence of two or more other components (105), similar to their adult definition (111). The IDF definition regards a fatness measure as a '*sine qua non*' since both WC and BMI is independently associated with elevated cardiometabolic risk. The IDF suggests using the same cut-off points for risk factors as for adults, except for WC, where children's age and sex-specific percentiles should be used instead of absolute values.

However, definitions based on dichotomisation of the cardiometabolic risk factors in children are problematic. First, the risk factors are weighted differently, but it is unknown which risk factors are the most important. Second, as no hard endpoints exist in children, the thresholds of the individual risk factors are arbitrary chosen – but we do not know when cardiometabolic risk appears within each risk factor. Applying absolute thresholds for children is unfortunate because lipid and insulin concentration, body composition and BP levels change with age and pubertal development (10, 112). The onset of puberty has an impact on fat distribution, and is known to cause a decrease in insulin sensitivity of approximately 30% with a complementary increase in insulin secretion (112). Third, the selection of risk factors excludes potentially important variables (97, 99). For example, fasting glucose level is an indicator of insulin resistance when diagnosing MetS, but fasting glucose is not strongly associated with clustered cardiometabolic risk in children (103). Thus, early stages of insulin resistance do not elevate fasting blood glucose, because the resistance is compensated for by a large increase in insulin production (103). Using the homeostasis model assessment for insulin resistance (HOMA-IR) as a marker of insulin resistance instead of fasting blood glucose, healthy youth in the upper quartile for insulin resistance with no signs of cardiometabolic disease had an approximately twenty-five times higher risk of having clustering of cardiometabolic risk factors compared with those in the lowest quartile (103). With these perspectives, the current MetS definitions are not able to

define or identify abnormalities in children and adolescents (97). The shortcomings of the definitions result in potential misclassification, and comparison between studies is difficult. In 2008, between 16% and 36% of European children with obesity had three or more risk factors according to the different MetS definitions. The disparity in prevalence was related to the different cut-off values (99). The highest prevalence was observed according to the definition using the lowest cut-off values for triglycerides and high HDL (113), but the WHO definition that includes fasting insulin identified more children with MetS than did the IDF and NCEP definitions (99).

As clustered cardiometabolic risk is likely a continuum, an alternative approach have been applied by examining z-scores from the cardiometabolic risk factors. The z-score approach may to some extent compensate for the natural day-to-day fluctuations within a cardiometabolic risk factors (12), and a more precise picture of risk is obtained as a child with clustered cardiometabolic risk has a poorer health status than if just one risk factor was elevated (97). Therefore, applying a continuous cardiometabolic risk score include more information of children's cardiometabolic health. When comparing the z-score approach with the current MetS-definitions, there is a major difference between the number of children diagnosed with MetS and the number of children in whom clustering actually occurs. A study reported that > 6% of children had clustering of at least four cardiometabolic risk factors (i.e. risk factors were not independently distributed), compared to less than 1% according to the IDF definition (97).

Physical activity and sedentary time in youth

In 2012, an exclusive issue on PA published in the Lancet reported international estimates showing that PA levels among adolescents were much lower than recommended: approximately 80% of 13 to 15 year olds do not achieve 60 minutes of MVPA daily (114). Three years later, a study from the International Children's Accelerometry Database (ICAD) examined objectively measured sedentary time and PA in ≈27,600 children and adolescents from ten countries (15), and were the first study to use standard methodology in analysing raw acceleration of PA data, allowing for a consistent picture of PA to be obtained. The ICAD study reported PA to be consistently lower in girls than in boys, PA was lower in those with overweight or obesity, and PA decreased each year after age 5 (4.2% each year), with a corresponding increase in time spent sedentary. However, there were substantial differences in PA between countries observed for both sexes, including in the proportion of children and adolescents meeting PA recommendations. For example, among 5 to 17 year olds from the ICAD as a whole, only 9.0% of boys and 1.9% of girls met the PA recommendations, while 13% of Norwegian boys did. These estimates were in strict agreement with the WHO PA recommendations (60 minutes of MVPA on every valid day measured) and the proportion of children meeting the recommendations were higher when a more liberal interpretations were applied (the percentage of

valid days where ≥ 60 minutes of MVPA were accumulated) (15). Nevertheless, all of the countries studied were alike in showing differences in PA by sex, age, and weight status (15). One of first studies to examine time spent sedentary by objective measures was performed in a large sample of US children (6 to 19 years) from the NHANES 2003–2004. Overall, children spent approximately 55% of waking hours in sedentary behaviours. More specifically, boys increased their time spent sedentary from 6.0 hours per day at age 6 to 11 years, to 7.9 hours per day at age 16 to 19 years. Girls in same age groups spent 6.1 and 8.1 hours per day, respectively, being sedentary. Similar trends have been observed in UK children where boys and girls at age 10 spend 7.5 and 7.7 hours per day, respectively, in sedentary behaviours (115).

Due to societal changes over the past few decades, there is a belief that PA levels in children have declined. However, data on long-term changes in PA levels in European (116) and American youth (117) provide no clear evidence of declining PA from the 1980s to the 2000s, but these studies have relied on self-report measures of PA and it is therefore difficult to discern whether PA levels have changed (118). The first systematic review of longitudinal changes in PA throughout adolescence (10 to 19 years) found a mean decline of 7% per year (119). Notably, only a handful of studies included objective measurements of PA, with the majority of studies from high-income countries, and few studies obtaining more than two measurements of PA. Since Dumith et al. (119), there has been an increase in longitudinal studies assessing sedentary time and PA by accelerometry. Regarding longitudinal changes in sedentary time, a British cohort (ALSPAC) reported that boys and girls at age 12 were on average sedentary for 6.9 and 7.3 hours per day, but increased to 7.8 and 8.3 hours per day at age 14 (120). At age 16, time spent sedentary had further increased to 8.5 and 8.8 hours per day in boys and girls respectively (120). More recent figures from UK, reported that > 40 minutes of daily PA are replaced by sedentary time from age 10 to 14, and MVPA was reduced by approximately 13 minutes per day (121). There is only one study examining longitudinal change in sedentary time and PA in Norwegian children and adolescents (122); girls and boys spent 55% and 53% respectively of their waking hours sedentary at age 9. By age 15, this had increased to 73% and 70% of waking time in girls and boys, respectively. The longitudinal changes also showed that overall PA, time spent in light PA and MVPA declined. In contrast, time spent sedentary increased by > 2 hours per day in both girls and boys (122). Increasing sedentary time is also apparent from childhood to adolescence (15 to 20 minutes daily per year) based on data from Sweden and Estonia, and the magnitude of the change observed in sedentary time was three to six times larger than the change observed in MVPA (123). However, there were no substantial change from adolescence to young adulthood (123). Thus, increases in sedentary time from childhood to adolescence might level off after adolescence (123, 124), possibly suggesting a maximum time youth can devote to being sedentary (125).

Not all agree with the generally accepted finding with a marked decline in MVPA during adolescence, and that the decline is more marked in girls than in boys. Since the review by Dumith et al. (119), several longitudinal studies have not supported these assumptions (120, 121, 124, 126). The Iowa Bone Development Study has seven accelerometer-measured time points for PA in children between 5 and 19 years of age, and observe that MVPA declines across childhood and adolescence in both sexes; thus, PA declines do not develop at or during adolescence (127). The decrease in PA may also be positively associated with its baseline level (128), although a possible effect of regression-to-the-mean phenomenon could be present, meaning that those with high levels of baseline PA can potentially experience a large decrease in PA levels compared with those starting with lower PA levels. The declines in MVPA, where they occur, might be greatest in those groups with highest baseline MVPA, and so are likely to be greater in boys than in girls (129). For example, Corder et al. (121) found that children with overweight and obesity had higher sedentary time, but normal weight children increased their sedentary time more than the overweight and obese group over four years. Importantly, and without exception, higher values of baseline PA are predictive of greater declines (124). Reilly (16) found it more likely that MVPA declines and sedentary time increases, not at the onset of or during adolescence, but throughout childhood and especially as children start school. The specific causes related to declining PA levels with increasing age are not known (119). It is reasonable to believe that societal changes in some specific contexts, such active versus passive transportation, organised sports, leisure time activities, and access to technology (130, 131) have affected the timing and magnitude of PA decline in recent years (16). Nonetheless, an undisputable fact is that the extent of PA decline, and especially MVPA, along with increases in sedentary time potentially put these young populations at a greater risk of poor cardiometabolic health and excessive adiposity (23, 121, 132).

Sedentary time, physical activity and cardiometabolic health in youth

The association between PA and cardiometabolic health in children has been extensively examined over the last two decades. One of the first reviews examining the association between PA and cardiometabolic health concluded that MVPA or 'continued' PA were needed to have a favourable effect on adiposity, lipids and BP in children (133). However, the necessary dose of PA to prevent or treat MetS was unknown, but suggested that regulation of overweight through PA could have beneficial effects (133). The review by Strong et al. (133) supported the already established PA recommendations (60 minutes MVPA daily), but the majority of the evidence was derived from studies using self-reported PA. In 2010, the publication by Strong et al. (133) was updated with a more specific approach regarding dose, type, and intensity of PA, and including whether the effects of PA vary with sex or age (24). The overall conclusions were that children and youth should

accumulate at least 60 minutes of MVPA, but benefits could be achieved from 30 minutes MVPA daily, aerobic activities should make up the majority of PA, and PA should preferably be performed at the higher end of the PA intensity spectrum for optimal health benefits. Whether PA recommendations should be performed on a daily basis or as an average over time were still unknown (24), and their conclusions were limited by including all forms of PA assessments and only studies that reported their findings in a dichotomous manner (24). Poitras et al. (134, 162) addressed the methodological limitations from Strong et al. (133) and Janssen and LeBlanc (24, 200) in a systematic review. They concluded that higher intensity PA in general showed larger effect sizes and were more beneficial for children's cardiometabolic risk factors, CRF, and adiposity. Moreover, all patterns of PA were favourably associated with adiposity and cardiometabolic risk factors. Similar observations were recently reported in a large study comprising ≈30,000 children and adolescents with objective measurements of PA (135). Accumulated time at higher intensity PA was the main determinant of variation in cardiometabolic risk factors, and did not depend on bout length. The greater magnitude of associations was consistently observed with higher intensities (135). Thus, there is no minimum consecutive duration that must be reached to achieve benefits (134, 135), and substantial data indicates that health benefits will occur in most children and youth who participate in at least 60 minutes of MVPA daily (24, 133, 134).

Despite the evidence of an inverse relationship between PA (11), and especially MVPA (23), with cardiometabolic health, the consistent age-related decline in PA levels concurrent with increasing overweight and obesity rates has led to the suggestion that sedentary time is a behavioural risk factor for poor cardiometabolic health in youth. Cross-sectional studies examining the relationship of sedentary time based on extrapolation of self-reported TV and screen exposure find positive associations with adiposity and cardiometabolic risk factors (19, 136, 137). Consequently, several countries have included guidelines for reducing sedentary time in PA recommendations (138). However, there are a number of limiting factors arising from self-reported sedentary time by TV and screen consumption. First, TV consumption captures only a small fraction of total sitting time and measures only one context-specific behaviour. For example, one study found that parent-reported screen time was equivalent to only a third of children's total sedentary time assessed via accelerometry in a sample of children (139). Second, the link between TV consumption and cardiometabolic risk factors are likely confounded or mediated by diet (140, 141), as snacking while watching TV is highly prevalent (20). Third, the role of confounding by socio-economic status (SES) is particularly important when assessing sedentary time by TV consumption (138); low SES is associated with high TV use in adults (142), and children are affected by their parents' TV use (143). Moreover, children's body weight is associated with SES (144), suggesting that TV consumption, body weight,

and SES are interconnected. The relationship between sedentary time and health is therefore unlikely explained by TV consumption or screen use alone (141).

It is also hypothesised that the adverse health consequences of sedentary time are independent of MVPA, but studies examining adverse associations between sedentary time and health do not always report whether the results are adjusted for time spent in PA or MVPA. When sedentary time is measured objectively, there is little evidence of an association with cardiometabolic health in children (18, 145), especially when accounting for time spent in MVPA (146, 147). Higher intensity PA are independently associated with adiposity (148), SBP, triglycerides, and HDL (23, 149). Ekelund et al. (23) did observe an association between sedentary time and insulin levels, but were attenuated towards null when adjusted for MVPA. These cross-sectional studies indicate that MVPA may be more important than total sedentary time in relation to cardiometabolic risk in youth (148). Taken together, it appears that the conclusions and direction of association between sedentary time with cardiometabolic health in children highly depends on measurement methods performed.

A strong predictor of cardiometabolic health in children is CRF (38, 39, 150), as low CRF in childhood may increase risk of later cardiometabolic disease (151) and myocardial infarction in adult life (152). Thus, some argues that a high CRF is more important than being physically active. However, PA is difficult to measure in children due to its variable nature, while CRF is a stable trait over time and can be measured precisely at the individual level (153). Moreover, CRF and PA appear to be independently associated with cardiometabolic risk in children, possibly affecting cardiometabolic risk through different pathways (39). PA shows independent associations with cardiometabolic risk factors (39), while the association between CRF and cardiometabolic risk is mediated by adiposity (39), partly due to the computation of CRF and correlation with body weight (38, 39). However, CRF also results from genetic composition (154), suggesting that some individuals may be predisposed to higher CRF. Therefore, associations between PA and cardiometabolic risk factors might be differently pronounced in those with low and high CRF. Two studies have examined such an influence of CRF on this relationship (155, 156), with stronger associations between PA and cardiometabolic risk (155) and abdominal adiposity (156) observed in those with lower CRF, but similar moderating effects by CRF have not been examined in prospective studies.

Prospective and cross-sectional studies examining sedentary time, PA, and health sometimes draw conflicting conclusions. This can be exemplified by that sedentary time and PA levels, as well as health indicators (especially adiposity), remain relatively stable in children (117, 157, 158). In this case, sedentary time, PA and health indicators can be associated in cross-sectional analyses, but not when examined prospectively. For example, Griffiths et al. (159) found cross-sectional associations between overall PA and sedentary time with adiposity; however, only MVPA remained associated

with adiposity in longitudinal analyses. Cross-sectional studies cannot determine the direction of associations, which is especially apparent between PA and body composition. Low levels of PA are considered a modifiable risk factor for childhood overweight and obesity, and the leading concept is that the associations between PA and excess body weight and adiposity are a one-way street – that PA has an effect on later body weight and adiposity. However, prospective studies and interventions are not as effective as predicted by cross-sectional studies (160). Meta-analyses find PA interventions have limited effects on body weight (161) and BMI in children (25, 162). Thus, the association between PA and adiposity could be bi-directional: low PA might result in accumulation of excessive body fat, but higher levels of adiposity and body weight may impede PA directly and indirectly (28, 163). A few prospective studies have found that a high percentage body fat at a baseline examination is associated with low levels of PA at a follow-up examination (26-28). Others report that baseline WC appears to predict a higher amount of time spent sedentary, and not the other way around (23). The bi-directional or reverse causation hypothesis may explain why attempts to tackle excessive weight gain in childhood by increasing PA have been largely unsuccessful (25).

Some studies have examined the prospective associations between sedentary time, PA, and clustering of cardiometabolic risk factors in children. Hjorth et al. (164) suggested a prospective association between time spent in MVPA and some individual cardiometabolic risk factors and clustering, but the analyses modelled the association between changes (the follow-up minus the baseline) in exposure (i.e. MVPA) and changes in outcome. This is effectively a cross-sectional analysis, and interpretation of the direction of association is limited. Stamatakis et al. (22) did not observe any prospective association between baseline sedentary time and cardiometabolic risk, whereas time in MVPA was inversely associated with individual cardiometabolic risk factors and clustering. However, blood-based outcomes were measured at follow-up only. Finally, a weak inverse partial correlation between time in MVPA and clustered cardiometabolic risk has been observed in a cohort of British children followed from age 5 to age 8 (165). In this study, the clustered cardiometabolic risk was modelled as the change between baseline and follow-up measurements and correlated with MVPA, which was expressed as the mean of four measurements over the four-year period, which also limited inference of a temporal association.

Gaps in the current research

The present evidence regarding the association between time spent sedentary, PA and cardiometabolic health in young populations is mostly cross-sectional, relies on self-report measures of sedentary time, and few studies distinguish between intensity-specific PA by objective measurements. Despite the strength of objectively measured PA in the prospective studies summarised above, they all appear to have limitations in their analytical approaches assessing the temporal sequence between sedentary time and PA with cardiometabolic health indicators. To address some of the unanswered questions in the current scientific literature, there is a need for prospective studies examining whether sedentary time and intensity-specific PA is prospectively associated with cardiometabolic risk factors and whether the associations between PA and adiposity are bi-directional.

Research aims and questions

The overall aim of this thesis was to investigate the prospective association between sedentary time and different PA intensities with cardiometabolic risk factors and adiposity in children. The specific aims of the four studies were as follows:

I. Systematically review the literature for the prospective association between objectively measured sedentary time, MVPA, and cardiometabolic risk factors in youth.

We hypothesised that objectively measured MVPA was inversely associated with a range of cardiometabolic risk factors, and an adverse association between sedentary time and cardiometabolic risk factors in youth.

II. Examine the prospective association between baseline sedentary time, MVPA, and clustered cardiometabolic risk at follow-up.

We hypothesised that objectively measured MVPA were more strongly associated with cardiometabolic risk factors than total sedentary time from baseline to follow-up.

III. Examine if CRF is a moderator in the prospective association between baseline sedentary time, PA, and cardiometabolic risk factors at follow-up.

We hypothesised that the magnitude of association between PA and cardiometabolic risk differ between children with high and low CRF from baseline to follow-up, and that stronger associations would be found in children with low CRF.

IV. Examine the prospective bi-directional associations between sedentary time, PA, and three different adiposity measures.

We hypothesised that objectively measured sedentary time and different intensities of PA could both predict and be the outcome of three different adiposity measures from baseline to follow-up.

MATERIALS AND METHODS

Study I: Systematic literature review and meta-analysis

Following the PRISMA-P 2015 guidelines (166, 167), five electronic databases (PubMed, Embase, CINAHL, PhysciNFO, and SPORTDiscus) were searched from January 1, 2000 until November 10, 2016. The search was last updated for April 1, 2018, with no additional studies found. The search aimed to identify intervention and prospective observational cohort studies that were both published in peer-reviewed English-language journals and examined the association between objectively measured sedentary time, MVPA and cardiometabolic outcomes in youth. The protocol was published in PROSPERO in November 2016 under registration number CRD42016048860 and adhered to the preferred reporting items of the PRISMA-P checklist (168).

Study inclusion criteria and search strategy

The search included four principal elements, which are described in detail in Table 1.

Population: Children and adolescents aged 6–18 years between baseline and follow-up from populations without any diseases or disabilities except for the MetS, type 2 diabetes, and populations with overweight or obesity.

Exposure: Objectively measured sedentary time and/or MVPA.

Outcomes: Waist circumference (WC), BMI, BP, HDL, TC:HDL, triglyceride, fasting insulin, HOMA-IR; and/or cardiometabolic risk factors reported as a clustered risk score standardised by age and sex.

Study Design: Longitudinal, observational prospective cohort, randomised controlled trials (RCT), and intervention designs. The minimum study length was set to six months, and the number of participants in each study was ≥ 50 .

Study selection

Two independent reviewers reviewed the titles and abstracts of all included studies. A third reviewer contributed to the inclusion of full-text studies. Any disagreements were discussed among all three reviewers, and reasons for exclusions were recorded. The reference lists of included studies from the full-text review were scanned for studies that could meet the inclusion criteria (backward tracking). Finally, a citation search was performed to identify studies that cited the included studies (forward tracking).

Data extraction

The first author performed data extraction after the full-text phase. The following information was extracted: study design, population characteristics (country, sex, age, included/excluded participants, participation rate), measurement of PA including its data reduction (cut points, epoch, non-wear

time, wear time in terms of days or hours, examined cardiometabolic risk factors, covariates included in the analyses, performed statistical analyses, and main results.

Table 1: Example of the complete search strategy

	Keywords
# 1	('cardiovascular disease risk factor' OR 'cardio-metabolic risk factor' OR 'metabolic risk factor' OR 'CVD risk factor' OR 'clustered cardio-metabolic risk' OR 'cluster' OR 'clustering' OR 'composite score' OR 'composite risk score' OR 'z-score' OR 'sum of z-score' OR 'mean of z-score' OR 'metabolic syndrome' OR 'Mets' OR 'pre-diabetes' OR 'metabolic disorders' OR 'metabolic' OR 'insulin' OR 'glucose' OR 'insulin resistance' OR 'HOMA-IR' OR 'HOMA' OR 'high-density cholesterol' OR 'hyperlipidaemia' OR 'dyslipidaemia' OR 'hyperinsulinemia' OR 'hyperglycaemia' OR 'lipoprotein' OR 'HDL' OR 'HDL-cholesterol' OR 'low-density cholesterol' OR 'LDL' OR 'LDL-cholesterol' OR 'triglycerides' OR 'total cholesterol' OR 'waist circumference' OR 'WC' OR 'BMI' OR 'Body Mass Index' OR 'adiposity' OR 'visceral fat' OR 'central obesity' OR 'fat mass' OR 'skinfold' OR 'sum of skinfold')
# 2	('physical activity' OR 'PA' OR 'moderate physical activity' OR 'moderate-to-vigorous physical activity' OR 'MVPA' OR 'vigorous physical activity' OR 'VPA' OR 'sedentary time' OR 'sedentary' OR 'sedated' OR 'inactivity' OR 'physical inactivity' OR 'inactive' OR 'sedentary behaviour' OR 'exercise' OR 'activity' OR 'intensity' OR 'moderate-and-vigorous intensity physical activity' OR 'physical activity energy expenditure' OR 'PAEE')
# 3	('accelerometer' OR 'accelerometry' OR 'objectively measured' OR 'activity monitor' OR 'pedometer' OR 'heart rate monitor' OR 'HR monitoring' OR 'combined sensors' OR 'combined sensing')
# 4	('longitudinal' OR 'prospective' OR 'RCT' OR 'randomized controlled trial' OR 'randomized controlled trial' OR 'cluster-randomized trial' OR 'cluster-randomized controlled trial' OR 'trial' OR 'intervention' OR 'cohort' OR 'observational study')

Assessment of methodological quality

The quality of evidence was assessed by quality criteria adapted from existing tools (157, 169, 170). The methodological quality list contains 13 items categorised in four dimensions: 1) study population and participation, 2) study attrition, 3) data collection, and 4) data analyses. The items distinguish between informativeness (four items) and validity/precision (eight items). The criteria had a 'yes' (+), 'no' (-), or 'unclear' (?) answer format. If the study referred to another publication describing the design or other relevant information about the study, the publication was retrieved. For each study, a total methodological quality score was calculated by counting the number of items scored positively on the validity/precision (V/P) criterion and dividing that number by the total number of V/P criteria. If a study scored at least 0.75 (75%), the study was considered to be of high methodological quality. Studies scoring lower than 0.75 were considered to be of low methodological quality. The quality score did not exclude any studies from the review. One researcher (TS) conducted the quality scoring, which was thereafter re-examined by two of the co-authors (Table 2 and 5).

Level of scientific evidence

Results for each outcome were coded using the approach first employed by Sallis et al. (171) and subsequently applied to observational and prospective studies examining associations with health (146). Results were classified as having 'no evidence' if 0–33% of studies reported a significant association. If 34–59% of studies reported a significant association, or if fewer than five studies reported results for the specific outcome, the result was classified as being 'inconsistent'. If $\geq 60\%$ of studies found a significant association, the result was classified as 'positive/adverse' or 'negative/inverse', depending on the direction of the association, which was defined by significance ($P < 0.05$). The scientific evidence coding was performed only among studies considered of high quality (Table 6).

Study II–IV: The Active Smarter Kids Study

The Active Smarter Kids (ASK) Study was a seven-month cluster-randomised parallel group controlled trial, with random allocation at the school level with a 1:1 ratio (172). All children were aged 10 years (born in 2004) situated in Sogn and Fjordane County, Norway. Inclusion criteria was that schools should have at least seven children in 5th grade, and that children were healthy (with no serious or chronic illnesses) and able to participate in daily PA and physical education (PE). Participants had to be able to complete the tests. Sixty schools, totalling 1,202 children, fulfilled the inclusion criteria and agreed to participate. This represented 86.2% of the population of 10 year olds in the county, and 95.2% of total possible recruitment. Thirty schools for the intervention (I-schools) and 30 schools for the control (C-schools) arm were randomised. The randomisation process was performed by a neutral third party (Centre for Clinical Research, Haukeland University Hospital, Bergen, Norway). After randomisation, three schools (two I-schools and one C-school) from the same municipality declined to participate. In total, 1,145 (97.4%) out of 1,175 children from 57 schools (28 I-schools and 29 C-schools) agreed to participate in the study.

Dose and intensity

In the following, the ASK intervention is described in brief:

- 1) Physical activity educational lessons (3 × 30 minutes each week) during academic lessons in three core subjects (Norwegian, mathematics, and English) were carried out in the school playground.
- 2) Children were given short PA breaks during classroom lessons (5 minutes × 5 days each week).
- 3) Physical activity homework was prepared by teachers (10 minutes daily, 5 × 10 minutes each week).

As a part of the mandatory school curriculum in Norway, all children (I-schools and C-schools) participated in curriculum-prescribed 90 minutes per week of physical education and 45 minutes per

week of PA – in total, 135 minutes per week. Therefore, children from the I-schools performed 300 minutes per week of PA and physical education, while children from the C-schools performed 135 minutes per week of PA and physical education. However, the C-school could carry out planned amount of PA and physical education regardless of participating in the ASK Study. The three PA intervention components were planned to be varied and enjoyable. It was emphasised that the activities should include all children, especially those who were not particularly fit or enthusiastic about PA. Special attention was given to creating an encouraging and motivating atmosphere during lessons in order to support positive feelings and attitudes towards PA. Approximately 25% of daily PA in the intervention was intended to be of vigorous intensity ('children would be sweating and out of breath'). The VPA component was achieved by selecting a variety of high intensity activities such as running, relay, obstacle courses, and other forms of active play. Fifty-nine ASK teachers led the PA component in the I-schools. These ASK teachers are classroom teachers assigned by the school principal to teach 5th grade in the I-schools (independent of the ASK Study). To ensure that teachers were empowered, supported, and qualified to deliver the PA intervention to their students, we conducted three comprehensive instructional seminars (April, June, and September 2014) for the ASK teachers. Further, we provided two regional refresher sessions during the intervention period (December 2014 and February 2015) to encourage teachers to share experiences and solve challenges together with each other and the research team.

Despite the planning of the study, the ASK intervention did not lead to significant differences in children's PA levels or time spent sedentary in I-schools when compared to C-schools (1). There are several possible reasons for this. The high baseline level of MVPA (> 74 minutes daily) in both groups may have resulted in a limited potential to intervene, and ceiling effects may have occurred. The objectively measured PA also suggested that participants in both I-schools and C-schools were on average slightly more active than a population-based national sample of Norwegian 10 year olds (122, 173) and their European and US counterparts (15) and obtained higher CRF level (173). However, PA reports from ASK teachers indicated adherence to the intervention and a clear contrast between the groups. The PA reports by teachers were made for the group as a whole, possibly overestimating the dose and intensity at the individual level as when compared with objective PA measurements. In addition, some of the activities performed by the I-schools (e.g. activities focusing on motor skills as throwing, catching, balance, or muscular strength) are likely underestimated by accelerometers placed on the hip. As no differences in PA levels were found, the whole sample was pooled into one observational cohort study in the current thesis (Study II – IV).

Physical activity

Sedentary time and PA were measured by GT3X/GT3X+ accelerometers (ActiGraph, LLC, Pensacola, Florida, USA). ActiGraph accelerometers are the most frequently used PA device by researchers, accounting for > 50% of published studies (174). All children were fitted with accelerometers at school and instructed to wear the accelerometer on the right hip at all times for seven consecutive days, except during water-based activities and sleeping. Valid monitor wear-time was defined as achieving ≥ 480 minutes daily accumulated between 06:00 AM and 00:00 PM. Continuous bouts of ≥ 20 minutes of zero counts was defined as non-wear time (175). Children recording during ≥ 4 out of 7 days were included in the analyses (46). Outcomes for PA were overall PA (cpm), sedentary time (< 100 cpm), moderate PA (MPA) (> 2296 cpm), and VPA (> 4012 cpm), which were defined according to previously established and validated cut points (176, 177). All accelerometer data were analysed in 10-second epochs and 30 Hz using the KineSoft analytical software (KineSoft version 3.3.80, Loughborough, UK).

Cardiorespiratory fitness

We assessed CRF using the Andersen test (60). The Andersen test is a reliable and valid tool for the determination of CRF (63). Children ran from one line to another that were 20 meters apart in an intermittent pattern of 15 seconds of running and 15 second breaks. They had to place one hand on the floor behind the line at each turn. The test lasts for 10 minutes (in total: 5 minutes of running, 5 minutes of breaks), and distance covered by each child was recorded in meters. The children were instructed to perform their maximum effort, and encouragement were given during the test. One person from the research staff was responsible for registering the number of laps performed for either one or two children.

Anthropometry

Body mass was measured to the nearest 0.1 kg using an electronic scale (SECA 899, SECA GmbH, Hamburg, Germany) with children wearing light clothing. Height was measured to the nearest 0.1 cm with a portable stadiometer (SECA 217, SECA GmbH, Hamburg, Germany). Each child was faced forward, with feet together and shoes removed. Body mass index was calculated using weight in kilograms divided by the square of height in meters (kg/m^2).

Waist circumference was measured using an ergonomic circumference measuring tape (SECA 201, SECA GmbH, Hamburg, Germany). The measure was taken between the lower rib and iliac crest over the umbilicus with the child's abdomen relaxed at the end of a gentle expiration. The child stood with arms hanging slightly away from the body. We collected two measurements from each child. If

the difference between the measurements was > 1 cm, we obtained a third measurement and the mean of the two closest measurements was used for analyses.

Subcutaneous body fat was measured using four skinfold thickness sites (biceps, triceps, subscapular, and suprailiac) on the left side of the body using a Harpenden skinfold caliper (Bull; British Indicators Ltd., West Sussex, England) as described by Lohman (178). The caliper was placed around the skinfold 1 cm below where the skin was held between thumb and forefinger. We collected two measurements at each site in sequence. If the difference between the two measurements was > 2 mm, a third measurement were obtained and the mean of the two closest measurements was used for analyses. Only specifically trained research staff (5-7 persons) collected skinfold measurements at baseline and follow-up. The skinfold staff performed intra- and inter-reliability testing specific to skinfold measurements before baseline testing were initiated.

At both time points, trained research staff following the standardised test procedures performed the measurements and tests at schools/gymnastic halls, but they were not blinded to control/interventions status. Anthropometric measures, pubertal stage, and BP measurements were conducted in a private room at schools/gymnastic halls.

Blood pressure

Blood pressure were measured using the Omron HBP-1300 automated BP monitor (Omron Healthcare, Inc., Vernon Hills, IL, US). The BP monitor is validated according to both AAMI validation protocol and the validation criteria of the international protocol for measuring devices (179, 180). Children rested quietly for 10 minutes in a sitting position before BP measurements. Blood pressure was measured on the upper right arm using an appropriately sized cuff. Four measurements were taken within a 1-minute interval. The mean of the last three measurements was included for analyses.

Blood samples

After an overnight fast, a nurse or phlebotomist collected an intravenous blood sample from each child's antecubital vein between 08:00 and 10:00 AM. Serum was obtained according to a standardised protocol consisting of the following procedure. Blood plasma was collected in 5 ml tubes with gel (Vakurette® Serum Gel with activator, G456073). Tubes were carefully turned upside-down five times and placed vertically for coagulation. After 30 minutes, the sample was centrifuged at 2000 G for 10 minutes. Serum was then visually inspected for residues and centrifugation was repeated if residue was present. The serum tube was kept in refrigerator at 4 °C before 0.5 ml was pipetted into cryo tubes. The cryo tubes were then stored at -80 °C prior to biochemistry analyses. Serum samples were analysed for constituents related to traditional cardiometabolic risk factors,

such as insulin, glucose, and the standard lipid panel (triglyceride, total cholesterol, HDL, and LDL) using standard laboratory methods. The total cholesterol (TC) to HDL (TC: HDL) ratio, which is the most informative cholesterol-related index, was calculated for the analyses (181). The HOMA-IR was calculated by multiplying fasting insulin by fasting glucose and dividing by 22.5 (182). Baseline and follow-up intervention samples were analysed at the same time in one batch at an ISO certified laboratory.

Covariates

Covariates were self-reported by children or parents. Children self-reported their pubertal stage by the Tanner method using a scale of colour images proposed by Carel and Léger (183). Children were given a standardised series of images with an oral explanation by the research staff. The research staff instructed the children to put a checkmark in the box below the picture that best represented their stage of development. Both girls and boys reported pubic hair and genital development, but girls also reported breast development and if they had reached menarche. The test was performed in a private room. Parental SES, weight, and children's birth weight and relevant medical history of their child were reported by parents at baseline.

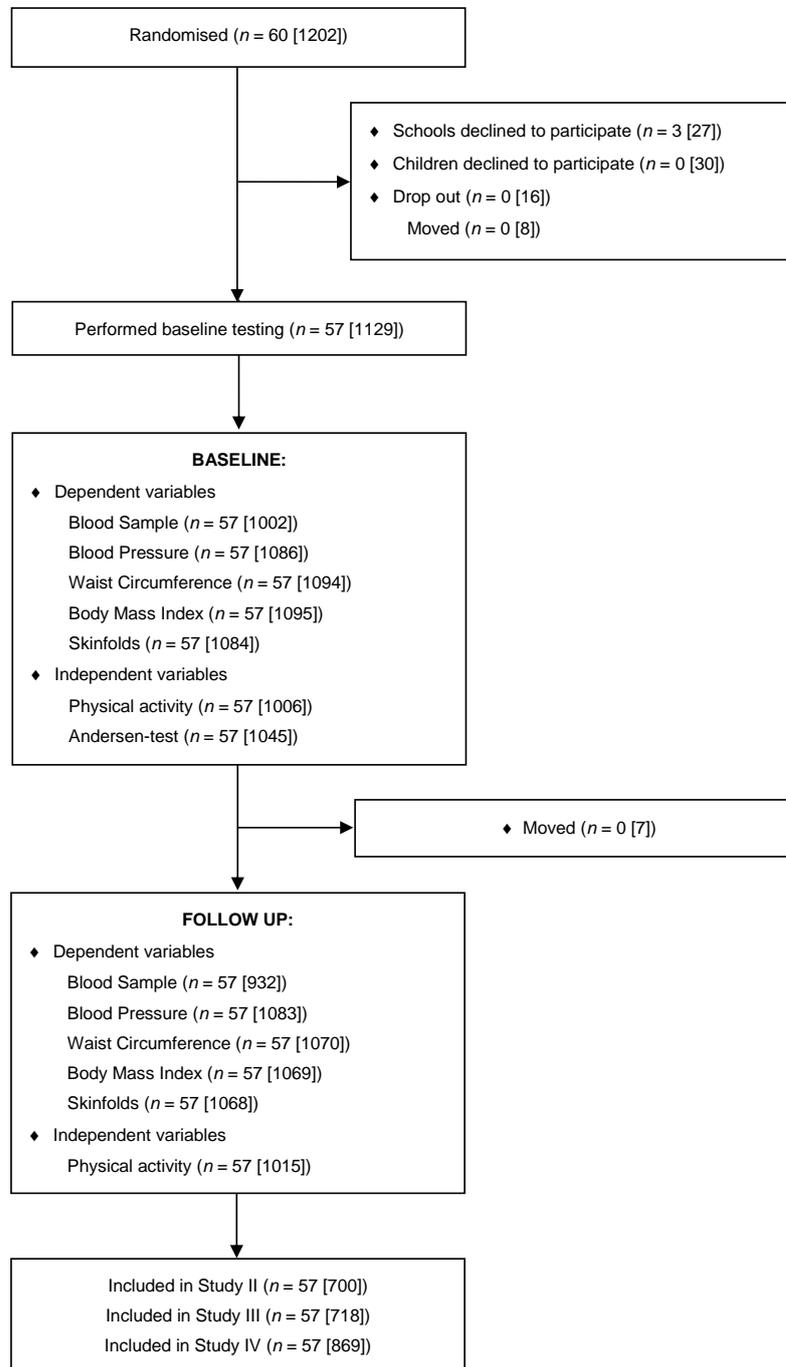


Figure 1: Flow chart for Study II – IV ($n =$ schools [participants]) based on the ASK Study data. For a more detailed flow chart of the ASK Study, please see Resaland et al. (1)

Statistics

Study I

The studies were heterogeneous in their measurements of exposures. Few studies had two measurement points of both sedentary time, PA, and blood-based outcomes, and none of the outcomes were reported in \geq five studies using the same analytical approach with outcomes expressed in the same units. Thus, statistical pooling was not possible for most outcomes, but we aimed to meta-analyse the association between MVPA and clustered cardiometabolic risk from three prospective observational studies (22, 164, 184) and three intervention/follow-up studies (102, 185, 186). The authors of one of the prospective studies was contacted (164) to reanalyse their data in a similar fashion. The meta-analysis was conducted using random effects models with unstandardized regression coefficients and 95% confidence intervals (CI). Analyses were performed in Stata/SE 13.1 for Windows.

Study II – IV

Descriptive characteristics are presented as the mean and standard deviation (SD), median, and interquartile range, or as frequencies (percentages). The effect of time and the prospective associations between exposure and outcome were analysed using linear mixed models, including the random intercept of school to account for the cluster effect. All PA variables except sedentary time were log-transformed to improve the normality of the distributions. However, when both baseline *and* follow-up of a PA or cardiometabolic risk factor variable were applied in a model at the same, they were not log-transformed as the change between baseline and follow-up were normally distributed. All variables were standardised to z-scores for ease of interpretation and regression coefficient are given in SD units. In all models, sedentary time and PA variables were analysed one by one to avoid multi-collinearity. Analyses were performed using the SPSS software, version 24 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp., USA). A *P*-value of < 0.05 was used to indicate statistical significance

Study II and III

A continuous cardiometabolic risk score was calculated by age- and sex-specific z-scores ($z_{\text{SBP}} + z_{\text{WC}} + z_{\text{triglycerides}} + z_{\text{TC:HDL}} + z_{\text{HOMA-IR}} / 5$). Each of these variables was standardised as follows: $z = (\text{value} - \text{mean}) / \text{SD}$. The sum of these five z-scores were also standardised. In addition, a non-obesity cardiometabolic risk score was computed by omitting WC. The summarised score only applies to this study population, but allows measurement of possible associations within our study population. The computed risk scores are continuous variables with a mean of zero by definition, with lower scores

denominating a more favourable profile, and vice versa. The interaction term (*sex × baseline exposure*) were included to test if sex modified the associations. However, there were no sex-specific effects, and all analyses were performed in the total sample.

Study II

First, we modelled the associations between baseline sedentary time, MPA, VPA, and MVPA with individual cardiometabolic risk factors at follow-up adjusted for sex, Tanner stage, SES, monitor wear time, and respective cardiometabolic risk factors at baseline (Model 1). Second, we adjusted the analyses for WC to assess whether the associations were independent of adiposity when WC was not the outcome of interest (Model 2). The associations between subcomponents of PA and clustered cardiometabolic risk at follow-up were modelled, adjusting for cardiometabolic risk at baseline and the covariates described above. Thereafter, WC was excluded from the summarised score, but added as a covariate in the next model to examine whether the prospective associations were independent of adiposity. For illustrative purposes, we categorised the children by quartiles of baseline MVPA and examined differences between these quartiles in clustered cardiometabolic risk in an adjusted model as explained above.

Study III

The statistical analyses were performed in three steps using two models. First, we modelled the prospective associations between baseline sedentary time, VPA, MVPA, and overall PA (cpm) with individual cardiometabolic risk factors at follow-up adjusted for the baseline value of the respective cardiometabolic risk factor, CRF, sex, pubertal stage, SES, monitor wear time, and group allocation (Step 1, Model 1). Thereafter, we examined potential interactions between the different PA exposures (sedentary time, VPA, MVPA, overall PA) and CRF by including the interaction term *CRF × PA exposure* by baseline values in the model (Step 2, Model 1). If a significant interaction ($P < 0.05$) was observed, we stratified the analyses by sex-specific median splits of CRF to explore the difference in magnitude of the prospective association between the exposure variables in low and high CRF groups (Step 3, Model 1). In Model 2, we repeated the three steps in Model 1 with additional adjustment for WC to examine whether the associations were independent of abdominal adiposity. Finally, we repeated the two models using the continuous clustered cardiometabolic risk score.

Study IV

All adiposity and PA variables except sedentary time were log-transformed to improve the normality of the distributions. First, we modelled the prospective association between baseline exposure of

MVPA, VPA, and sedentary time and the three different adiposity measures using a linear mixed model. The models were adjusted for sex, pubertal stage, SES, birth weight, parental weight, and baseline value of the outcome (adiposity). We also tested for interaction by sex (baseline exposure (PA or adiposity) \times sex). If a significant interaction ($P < 0.05$) was observed, the analyses were additionally stratified by sex. Second, we modelled the prospective association between baseline exposures of adiposity (BMI, WC and skinfolds) with MVPA, VPA, and sedentary time adjusted for the same covariates as in the previous model and the baseline value of the outcome (MVPA, VPA, or SED). Last, we dichotomised BMI into normal weight versus overweight/obese according to Cole et al. (187), and MVPA into groups according to the achievement of current recommendations for PA in youth, that is, above or below 60 minutes of daily MVPA. Following this, we examined whether the BMI (normal weight versus overweight/obese) and MVPA (above/below 60 minutes) categories at baseline differed in PA and adiposity outcomes at follow-up, respectively.

SUMMARY OF RESULTS

Study I

Studies included

The initial search identified 5,733 studies (Figure 2). After removal of duplicates, 4,599 studies were retrieved. After title review, 172 studies were assessed for abstract review. Sixty-eight studies met the inclusion criteria and were eligible for full-text screening and data extraction. In this process, eight additional studies were identified from the reference lists, and one study was in press and nominated for inclusion by collaborators. After the full-text phase, 30 studies were included and eligible for evidence synthesis and quality scoring. Twenty-one studies were prospective, seven studies were interventions or trials, and two studies were long-term follow-ups of previous intervention studies.

Sample characteristics

Tables 3 and 4 present study characteristics and results sorted by outcomes. Table 3 gives an overview of the prospective studies. Studies were conducted in North America ($n = 4$), Australia ($n = 1$), and Europe ($n = 16$). In total, the prospective studies comprised 32,036 participants. Study populations ranged from 120 to 6,497 with participants aged 4.9 to 18.0. The median follow-up time was 2.8 years. Table 4 depicts a summary of the seven intervention studies and the two long-term follow-ups of previous interventions. The studies were conducted in North America ($n = 1$), Australia ($n = 1$), Europe ($n = 6$), and South America ($n = 1$). Study populations ranged from 88 to 1,527, with participants aged 6.8 to 14.0 years. The median study follow-up time was 2.0 years. The intervention studies comprised 5,764 participants. Table 2 lists the quality of informativeness and the V/P for all studies. Of the 30 included studies, 21 were categorised as high quality (Table 5).

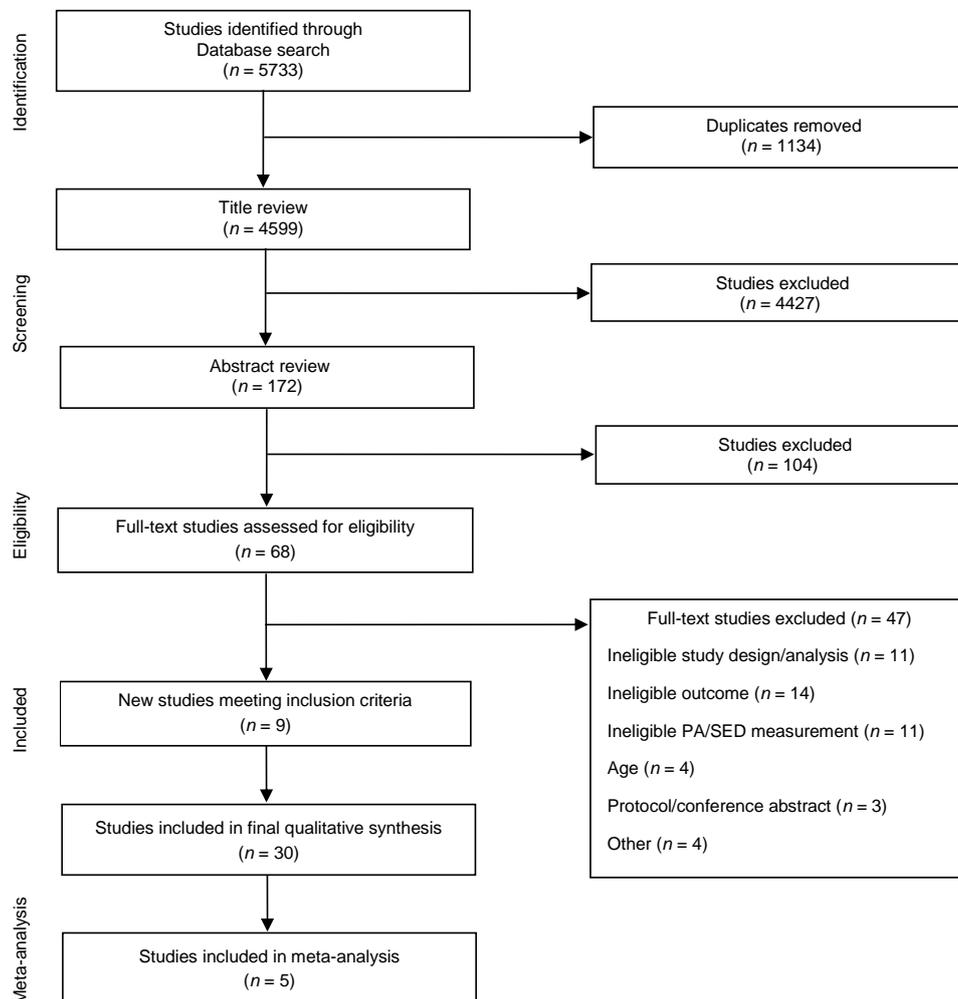


Figure 2: PRISMA flow chart of study selection for the systematic literature review

Adiposity

One observational longitudinal study found that an increased time spent sedentary predicted changes in BMI from age 9 to 15 that were independent of MVPA (188). At the 90th BMI percentile, an additional hour spent sedentary per day was associated with a 0.84 unit increase in BMI. Weaker findings were observed at the 75th and 50th BMI percentiles (188). In general, studies examining the prospective associations between sedentary time and adiposity reported no evidence for any association (23, 159, 164, 184, 189-193). Two studies found that sedentary time predicted lower BMI (22) and WC (8), even after adjustment of MVPA. Activity of at least moderate intensity was inversely associated with BMI (159, 193-195) and WC (8, 196). Similarly, a declining MVPA was associated with increased BMI during two years of follow-up (191). However, differences between boys and girls were present, as an inverse association was evident between vigorous PA and WC in boys only (196). Moreover, boys not meeting the threshold of 20 minutes of vigorous PA at baseline had an increased risk for overweight 2 years later (OR = 4.14) (192). Half of the studies found no significant prospective associations between MVPA at baseline and BMI (165, 197) or WC (23, 164, 165, 184, 189, 194) in models that were ultimately adjusted.

No intervention study reported the *effect* of sedentary time on adiposity. For MVPA, three of seven intervention studies reported a beneficial development in BMI (185, 198) and WC (199) in the intervention group. By the end of a non-randomised intervention, Gorely et al. (198) observed that children in the intervention schools performed 20 minutes more MVPA per day, which was associated with a lower increase in BMI than was observed in the control group (0.4 versus 0.9 BMI units per year of age). In the KISS study, lower BMI at follow-up was observed in the intervention group (185). However, the favourable changes in BMI that were reported by Gorely et al. (198) and Kriemler et al. (185) were not sustained at 1.5 and three-year follow-ups respectively (186, 200). Two intervention studies and two cluster RCTs found no effect for MVPA on BMI (102, 201-203). Notably, these intervention studies did not induce significant differences in MVPA between intervention and control groups, except for Donnelly et al. (202). However, objective measurement of PA was only assessed in a sub-sample ($n = 167$). As summarised in Table 6, there was no evidence for a prospective association between total sedentary time and adiposity. The evidence for a prospective association between MVPA and adiposity was inconsistent.

Blood pressure

Three studies found no associations between baseline sedentary time and BP at follow-up (22, 164, 184), but one study reported an independent and beneficial association between both sedentary time and MVPA with follow-up SBP (8). Stamatakis et al. (22) observed an inverse association between MVPA and SBP, but that association was attenuated by adjustment of important covariates

and baseline value of SBP, which corresponded with the four other studies reporting no prospective associations (22, 164, 184, 204). However, some studies observed inverse associations in boys; Carson et al. (196) reported a dose-response association across quartiles of baseline vigorous PA (Q1: 1.3 minutes per day versus Q4: 8.0 minutes per day) with follow-up SBP. The EarlyBird cohort found that number of minutes spent ≥ 3 METs were associated with lower mean arterial BP (MAP) in boys from ages 5 to 8 (165). From the same cohort, diastolic BP (DBP) were marginally lower in active boys (≥ 50 minutes MVPA per day) when compared with those that were less active throughout adolescence (age 9 to 16) (205). Similarly, one study observed a favourable but non-significant effect on SBP in the intervention group between baseline and post-intervention (102). However, at the four-year follow-up, the intervention boys had a smaller increase in SBP compared with the control boys (102). The remaining intervention studies found no effect of MVPA on SBP or DBP (185, 186, 199). Taken together, there was no evidence for a prospective association between sedentary time and BP, while the evidence appeared inconsistent for MVPA and BP (Table 6).

Biochemical variables

One prospective study found that sedentary time was associated with unfavourable changes in HOMA-IR, but not independent of MVPA (164). Three studies reported no associations between sedentary time and HOMA-IR (8, 22, 184). In contrast, MVPA was associated with lower insulin/HOMA-IR in four studies (8, 22, 164, 184). Moreover, baseline MVPA (≥ 38.7 min per day) had a protective effect on the development of HOMA-IR two years later in a large European cohort (206). In a follow-up from age 9 to 16, children in the more active groups (boys: ≥ 50 minutes MVPA per day, girls: ≥ 35 minutes MVPA per day) attenuated the mid-adolescent peak in HOMA-IR compared to the less active group, independent of body fat percentage and pubertal status (205). However, at age 16 there were no differences between the activity groups (205). Similarly, an Estonian study ($n = 120$) found no association between MVPA and HOMA-IR in boys (207). One intervention study observed an effect of MVPA on HOMA-IR in boys in the intervention group, but the effect did not persist to long-term follow-up (102). Seabra et al. (199) did not observe any effect of MVPA on HOMA-IR.

One study reported an inverse association between sedentary time and HDL, independent of MVPA (164), with no relationship observed between sedentary time and HDL in three studies (8, 22, 184). Three of six studies concluded that MVPA was prospectively associated with higher HDL/TC:HDL levels (8, 22, 164). Similarly, time spent in MVPA predicted lower triglyceride levels during 6 to 9 months of follow-up (8, 164, 184). However, associations between MVPA and HDL that were independent of sedentary time were found in only one of these studies, but not for triglycerides (164). Conversely, the largest observational prospective study did not observe any association between MVPA and triglycerides (22). Two studies from the EarlyBird cohort found that triglyceride

levels in more active girls (above median) were lower than in less active girls between age 5 and 8 (165); this effect also persisted throughout adolescence (205). Physical activity intervention effects on HDL and triglycerides were reported by Kriemler et al. (185), while Bugge et al. (102) and Seabra et al. (199) did not observe any intervention effect on HDL/TC:HDL or triglycerides.

Sedentary time was unrelated to clustered cardiometabolic risk in prospective observational studies (22, 184), even when accounting for MVPA, sleep, and adiposity (164). In contrast, one study observed an unexpected beneficial association between sedentary time and clustered cardiometabolic risk, independent of MVPA (8). However, all studies examining MVPA and clustered cardiometabolic risk found inverse associations (8, 22, 164, 165, 184), suggesting that those with higher levels of MVPA had a favourable cardiometabolic risk profile. Few intervention studies were identified that examined the effect of MVPA on clustered cardiometabolic risk. Kriemler et al. (185) observed an effect of MVPA on the clustered cardiometabolic risk in the intervention group between baseline and follow-up. However, the effect was no longer evident at later follow-up (186). Bugge et al. (102) found no effects of MVPA on clustered cardiometabolic risk at post-intervention or at long-term follow-up. The meta-analyses that examined the relationship between baseline MVPA and clustered cardiometabolic risk at follow-up pooled data of 5,489 participants from five independent samples. The pooled effect for MVPA was small but significant for both prospective (ES -0.014 [95% CI, $-0.024, -0.004$]) (Figure 3) and intervention studies (ES -0.137 [95% CI, $-0.237, -0.037$]) (Figure 4).

In summary, there was no evidence for a prospective association between sedentary time, individual biochemical risk factors, or clustered cardiometabolic risk. The evidence for an association between MVPA and the individual biochemical risk factors was inconsistent. However, a consistent and inverse prospective association was evident for MVPA and *clustered* cardiometabolic risk (Table 6, Figure 3 and Figure 4).

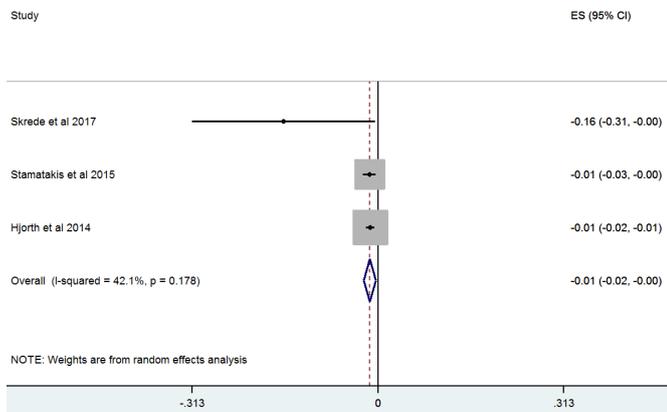


Figure 3: Forest plot for baseline MVPA and clustered cardiometabolic risk at follow-up from prospective studies. Estimates are adjusted for baseline value of the outcome

Please note: Stamatakis et al. (22) adjusted for baseline BMI when clustered cardiometabolic risk was regressed as outcome.

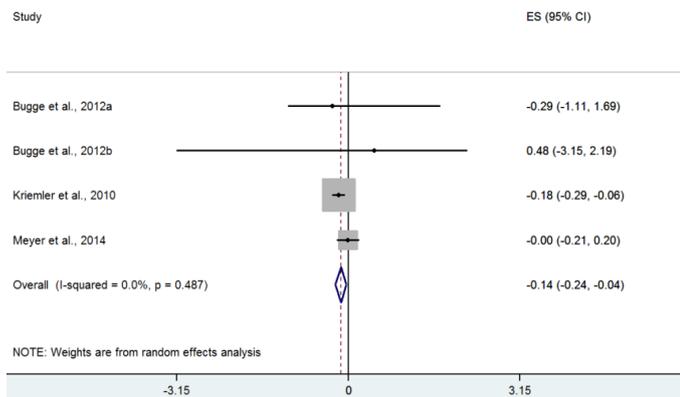


Figure 4: Forest plot for MVPA and clustered cardiometabolic risk by intervention studies. Estimates are based on the difference between intervention and control group at follow-up

Please note: Bugge et al. (2012a) is baseline to post-intervention, and Bugge et al. (2012b) is baseline to long-term follow up, but reported in the same publication (102).

Table 2: Criteria List for Assessment of the Methodological Quality of Prospective Studies based on Chinapaw et al. (169), Singh et al. (157), and Tooth et al. (170)

Criteria (rating of criteria: + = yes, - = no, ? = not or insufficiently described)	I, V/P*	% of studies scoring +
Study population and participation (baseline): The study sample represents the population of interest on key characteristics:		
1 Adequate† description of sampling frame, recruitment methods, period of recruitment, and place of recruitment (setting and geographical location)‡	I	63.3
2 Participation rate at baseline at least 80%, or if the non-response was not selective (show that baseline study sample does not significantly differ from population of eligible subjects)	V	23.3
3 Adequate description of baseline study sample (i.e. individuals entering the study) for key characteristics (number of participants, age, sex, sedentary time, PA, and health outcome)‡	I	90.0
Study attrition: Loss to follow-up is not associated with key characteristics (i.e. the study data adequately represent the sample):		
4 Provision of the exact number of participants at each follow-up measurement	I	90.0
5 Provision of exact information on follow-up duration	I	96.7
6 Response at short-term follow-up (up to 12 months) was at least 80% of the number of participants at baseline and response at long term follow-up was at least 70% of the number of participants at baseline	V	50.0
7 Not selective non-response during follow-up measurement(s)§	V/P	63.3
Data collection:		
8 Adequate measurement of PA‡	V	100
9 PA was assessed at a time point prior to the measurement of the health outcome	V	100
10 Adequate measurement of the health outcome: objective measurement of the health outcome done and not by self-report	V	100
Data analyses:		
11 The statistical model used was appropriate¶	V/P	50.0
12 The number of cases was at least 10 times the number of the independent variables	V/P	96.7
13 Presentation of point estimates and measures of variability (confidence interval or standard error)	I	96.7

*I = criterion on informativeness, V/P = criterion on validity/precision.

†Adequate = sufficient information to be able to repeat the study.

‡+/- is given only if adequate information is given on all items.

§+/- is given only if non-selective dropout on key characteristics (age, sex, sedentary behaviour, health outcomes) is reported in the text or tables.

¶+/- is given only if a multivariate regression model was used adjusting the baseline value of the outcome/RCT-design

#+/- is given only if at least three of the following points were mentioned; type of instrument, description of monitor placement, number of days worn, length of epoch, number of hour day⁻¹ worn, and number of minutes monitored, data reduction methods described.

Table 3. Prospective study characteristics and results sorted by outcome

Author	Country	N	Baseline Age	Study Length	Exposure	Outcome	PA Device	PA Data Reduction	Statistical Model and Covariates	Results
Basterfield et al., 2012	UK	403	Age 7.4	24 months	SED, MVPA	BMI (z-score)	GT1M	SED < 1100 cpm MVPA > 3200 cpm Epoch: --- Non wear: manually deleting Wear time/day: 6 h Valid days: 3	Model: Multiple linear model. Exposure were %change in MVPA and SED, changes in adiposity Covariates: Sex, SES, FMI at baseline	Declining MVPA was associated with increased BMI z-score in boys but not girls ($\beta \times 10^3$ -34.8, 95% CI, -61.8, -7.8, $P = 0.012$) Avoiding reductions in MVPA may reduce excessive fat gain. No associations for SED and later BMI (+/-)
Lätt et al., 2015	EE	136	Age 11.9 (σ^2)	2 years	SED, MVPA, VPA	BMI	GT1M	SED: < 100 cpm MPA > 2000 cpm VPA > 4000 cpm Epoch: 15 sec Non wear: 10 min Wear time/day: 8 h Valid days: 3	Model: Thresholds for PA were calculated by ROC and AUC curves. Logistic regression were used to calculate OR's overweight and obese at baseline and follow-up, based on PA thresholds at baseline and follow-up Covariates: Age and puberty	Boys not meeting thresholds of 5 and 20 min VPA/day at baseline had an increased risk of being overweight (OR = 4.1, 95% CI, 1.4, 11.6, and OR = 4.14, 95% CI, 1.4, 12.7, respectively), and obese (OR = 6.5, 95% CI, 2.1, 21.7, and OR = 8.8, 95% CI, 1.1, 68.5, respectively) two years later. No associations for SED (+/-)
Griffiths et al., 2016	UK	6497	Age 7	4 years	SED, MVPA	BMI	GT1M	SED < 100 cpm MVPA \geq 2240 cpm Epoch: 15 sec Non wear: 20 min Wear time/day: 10 h Valid days: 2	Model: Linear regression models with baseline values of adiposity, SED and MVPA as covariate Covariates: Weekend, season, age, puberty, ethnicity, maternal BMI, maternal SES, maternal age at birth of cohort member, # cars, annual income, lone parenthood status country, urban/rural indicators, baseline value of the outcome	MVPA at age 11 were inversely associated with BMI at age 7. In boys, but not girls, BMI at age 11 were on average 2.5% (95% CI, 0.9, 4.2) lower for each 20 min increase in MVPA/day at age 7 No association for SED and later adiposity (+/-) 7-year-old children who are more physically active are less likely to be obese at that age and at age 11 years

Stevens et al., 2007	US	984	Age 11.9 (♀)	2 years	MVPA	BMI	7164	SED < 100 cpm MVPA > 4.6 METs Epoch: 30 sec Non wear: 20 min Wear time/day: 80% of different time blocks of day Valid days: 1	SED < 100 cpm Epoch: 30 sec Non wear: -- Wear time/day: 6 h Valid days: 1	Model: Mixed-model linear regression with BMI and body fat% modelled as continuous variables on the mean and deviation scores for PA Covariates: Height, intervention assignment	No associations between MVPA and BMI over 2-year follow-up (-)
Treuth et al., 2009	US	984	Age 11.9 (♀)	2 years	SED	BMI	7164	SED < 100 cpm Epoch: 30 sec Non wear: -- Wear time/day: 6 h Valid days: 1	Model: Mixed models with 1) the mean and 2) the deviation from each girl's SED were used to predict change in BMI in a repeated measures structure Covariates: Age, ethnicity, field centre/school	Changes in SED over time were not associated with changes in BMI. The estimates were in the expected direction, but not significant (-)	
Trinh et al., 2013	AUS	182	Age 7.3	3 years	SED, MVPA	BMI (z-score)	Actial (multiaxial)	SED < 100 cpm MVPA ≥ 900 cpm Epoch: 60 sec Non wear: 20 min Wear time/day: 10 h Valid days: 5	Model: Linear regression with the initial level of PA or change in PA used to predict change in BMI Covariates: Initial PA, intervention status, sex, age, SES, maternal BMI, maternal education	Every 10% change in time spent in MVPA, predicted -0.24 (95% CI, -0.43, -0.05) in BMI z-score. No associations for SED (P = 0.39) (+)	
Riddoch et al., 2009	UK	4150	Age 12	2 years	MVPA	BMI	N/A	MVPA > 3600 cpm Epoch:-- Non wear: 10 min Wear time/day: 10 h Valid days: 3	Model: Multilevel modelling with baseline adjustment of the outcome. The adjusted regression coefficient for the association between MVPA at age 12 and fatness at age 14 was calculated from random effects associated with MVPA and fatness Covariates: age, puberty, maternal education, occupation, pre-pregnancy BMI, smoking, total PA(cpm)	A 15 min increase in MVPA/day at age 12 were associated with -2.9% and -2.2% for BMI in boys and girls, respectively, at age 14 The changes in BMI with incremental changes in MVPA were -0.4% and -0.7% in boys and girls (+)	
Ekelund et al., 2012	ICAD ^b	6413	Age 6-18	2.1 years	MVPA SED	WC	ICAD	SED < 100 cpm MVPA > 3000 cpm	Model: Linear regression model	Neither time in MVPA or SED predicted WC, but WC	

Knowles et al., 2013	UK	427	Age 6.5	2 years	MVPA	BP	ActiHeart	Epoch: 60 sec Non wear: 60 min Wear time/day: 8 h Valid days: 1 MVPA \approx 2000 cpm Epoch: 30 sec Non-wear: -- Wear time/day: -- Valid days: --	Covariates: Age, sex, monitor wear time, follow-up time and the baseline value of the outcome variable Model: Multiple linear regression with baseline adjustment of the outcome Covariates: Age, sex, ethnicity, change in age/height, height at baseline, school, baseline BP, group allocation, duration of PA, measurement, baseline BMI z-score	predicted higher SED (β 0.40, 95% CI, 0.19, 0.61) (-) Every 15 min MVPA/day at baseline were not associated with SBP (β -0.11, 95% CI, -0.63, 0.41, $P = 0.68$) or DBP (β -0.18, 95% CI, -0.65, 0.29, $P = 0.45$) at follow-up (-)
Peplies et al., 2016	Europe ^a	3348	Age 6.4 ^b	2 years	MVPA	HOMA-IR	GT1M	SED < 100 cpm MPA > 2296 cpm VPA > 4012 cpm Epoch: 60 sec Non wear: 20 min Wear time/day: 8 h Valid days: 3	Model: Multivariate mixed logistic models using age- and sex-specific z-score for HOMA-IR Covariates: Audio-visual media time, sex, age, SES, MVPA	MVPA has a protective effect for HOMA-IR in the two upper MVPA quartiles (\geq 38.7 min MVPA/day), but not a clear trend. MVPA reduces the risk of developing IR, also for children with normal weight at baseline which indicates that the effect of missing PA is not just mediated by obesity. Longitudinal reduction of HOMA-IR was accompanied with a parallel BMI decline (+)
Metcalfe et al., 2015	UK	300	Age 8.9	7 years	MVPA	HOMA-IR, MAP, SBP, DBP, TG, HDL	7164	MVPA \approx 2500 cpm Non-wear: 17 min Epoch: 60 sec Wear time/day: 9 h Valid days: 4	Model: Multilevel modelling of longitudinal/repeated measure. MVPA level from 9-16 y were averaged and analysed both as a continuous and categorical variable (above/below 50 min MVPA/day in boys, 35 min MVPA/day in girls) Covariates: body fat%, age as a fixed and random effect, then polynomials of increasing order were added	HOMA-IR was lower in the 'active group' at age 12.5, independent of body fat%. For every 15 min MVPA/day, HOMA-IR was 5.5% lower (95% CI, -9.5, -1.3, $P = 0.01$) at age 12.5. However, no difference in HOMA-IR between activity groups at age 16 'More active' girls: 9.7% lower TG ($P = 0.05$), independent of puberty and body fat%. 'More active' boys: 1.20 mmHg lower

Lätt et al., 2016	EE	120	Age 11.9 (σ)	2 years	MVPA	TG, HOMA-IR, TC:HDL	GT1M	MVA > 2000 cpm VPA > 4000 cpm Non-wear: 10 min Epoch: 60 sec Wear time/day: 10 h Valid days: 3	one by one as the age-related trends were not linear Model: Logistic regression model with follow-up outcomes regressed on change in MVPA Covariates: Puberty	DBP. No associations for HDL or SBP (+/-) MVPA do predict changes in either TG, HOMA-IR or TC:HDL (-)
Metcalf et al., 2008	UK	307	Age 4.9	3 years	MVPA	HOMA-IR, TG, TC:HDL, MAP, BMI, and CMRisk	MTI/CSA	MVPA ≈ 2500 cpm (≥ 3 METs) Epoch: 60 sec Non wear: -- Wear time/day: 9 h Valid days: min. 20 days over four assessments	Model: Multiple linear regression (MLR) to find partial correlation between MVPA and changes in outcome. ANCOVA to compare changes in outcome according to activity group (high/low) Linear mixed models (LMM) to test if trends in BMI and CMRisk over four time points differed by more or less active children Covariates: Age at baseline, years/time to follow-up, SES, PA adjusted for season and sensitivity of each accelerometer, respective baseline value	MLR: No associations between ≥3 METs for BMI or WC. Small to moderate inverse partial correlations between minutes spent >3 METs and changes in: TG (girls only: $r = -0.26$, $P = 0.02$) CMRisk (girls only: $r = -0.23$, $P = 0.03$) MAP (boys only: $r = -0.22$, $P = 0.02$) ANCOVA: Active girls (>45 min MVPA/day) had more beneficial change in TG. Change in CMRisk in favour to the active group in both sex, but significant for boys only LMM: CMRisk above/below median activity diverged, and was linear over time (0.08 z-scores/year, $P=0.001$) Notably, only 11% of girls and 42% of boys met recommended PA level (≥3 METs)
Skrede et al., 2017	NOR	700	Age 10	7 months	SED, MPA, VPA, MVPA	WC, SBP, TG, TC:HDL, HOMA-IR, CMRisk	GT3X	SED < 100 cpm MPA > 2296 cpm VPA > 4012 cpm Epoch: 10 sec	Model: Linear mixed model with baseline adjustment of the outcome at follow-up Covariates: Sex, school, SES, puberty, monitor wear time,	MVPA associated with lower TG ($\beta -0.090$, 95% CI, -0.165 , -0.015) and HOMA-IR ($\beta -0.075$, 95% CI, -0.139 , -0.010). PA level (≥3 METs) (+/-)

van Sluijs et al., 2016	UK	367	Age 9.8	4 years	SED, MPA, VPA	WC	GT1M	SED < 100 cpm MPA > 2000 cpm VPA > 4000 cpm Epoch: 5 sec Non wear: 10 min Wear time/day: 8 h Valid days: ≥ 3	Model: Linear (continuous outcome) or logistic (binary outcome) regression models. Including robust standard errors to account for clustering within schools. Covariates: Age, sex, SES, birth weight, maternal BMI, puberty at follow-up, sleep duration, height, baseline diet, adjusted for baseline value of the outcome	increase in BMI unit, adjusted for MVPA and covariates. Similar findings from the 50 th percentile) (+)
Hjorth et al., 2014	DK	554	Age 10	200 days	SED, MVPA	WC, MAP, HOMA-IR, TG, HDL, CMRisk	GT3X	SED < 100 cpm MPA > 2296 VPA > 4012 Epoch: 60 sec Non wear: 60 min Wear time/day: 10 h Valid days: 4	Model: Linear regression with change in exposure vs change in outcome Covariates: Age, sex, puberty interaction, days of follow-up, baseline value of behaviour movement and outcome risk factor, baseline BMI z-score	Change in MVPA had beneficial influence on HDL (β 0.019, 95% CI, 0.012, 0.026), TG (β -0.02, 95% CI, -0.04, -0.004), and HOMA-IR (β -0.07, 95% CI, -0.11, -0.003) but not for WC. Associations for MVPA with HOMA-IR and HDL were independent of SED. Change in SED reduced HDL (β -0.006, 95% CI, -0.009, -0.004), independent of MVPA. Low MVPA and short sleep at baseline associated with increased CMRisk at follow-up, independent of SED (β -0.12, 95% CI, -0.22, -0.01), but attenuated by FMI. SED not associated with CMRisk ($P = 0.39$) or adiposity (+/-)
Stamatakis et al., 2015	UK	2963 / 4369	Age 11.5	4 years	SED, MVPA	BMI, WC, SBP, DBP, TG, HDL, Insulin, CMRisk	7164/GT1M	SED < 200 cpm MVPA > 3600 cpm Epoch: 60 sec Non wear: 10 min	Model: Multiple linear regression with baseline adjustment of the outcome at follow-up	In fully adjusted models, MVPA was beneficially associated with insulin (β -0.024, 95% CI, -0.036, -0.013), HDL (β 0.006, 95% CI, 0.001, 0.011) and

Chinapaw et al., 2018	DK	460	Age 9.4	10 months	SED, MVPA	TG, TC:HDL, HOMA-IR, SBP, WC, CMRisk	GT3X	Wear time/day: 10 h Valid days: 3	Covariates: Age, sex, monitor wear time, time between PA measurement and cardiometabolic risk factor, paternal social class, birth weight, maternal BMI, puberty, energy intake, baseline adjustment of outcome (baseline BMI for blood variables), SED adjusted for MVPA, but MVPA not adjusted for SED	CMRisk (β -0.014, 95% CI, -0.025, -0.004) Baseline SED at age 11 was not independently deleteriously associated with cardiometabolic markers at age 15, except for BMI (β -0.004, 95% CI, -0.007, -0.001). However, in a nonimputed data set, there were no associations between SED and BMI (+/-)
								SED < 100 cpm MVPA > 2296 cpm Epoch: 2 sec Non wear: 60 min Wear time/day: 8 h Valid days: 6	Model: Multilevel linear mixed models with school and class as random effects Covariates: age, sex, parental education, puberty and school (i.e. intervention or control), mutual adjustment for MVPA and SED. Outcome not adjusted for baseline value	In fully adjusted models, higher mean (T1+T2) MVPA levels were significantly associated with lower WC (β -18.4, 95% CI, -23.8, -13.0), SBP (β -5.6, 95% CI, -10.8, -0.5), HOMA-IR (β -10.2, 95% CI, -16.2, -4.2) and CMRisk (β -9.4, 95% CI, -13.0, -5.9), independent of SED Higher mean SED (T1+T2) were associated with lower WC (β -5.8, 95% CI, -7.6, -3.9), and CMRisk (β -2.1, 95% CI, -3.4, -0.9), independent of MVPA. Change in SED were associated with lower SBP (β -2.2, 95% CI, -4.0, -0.3) (+/-)

^a 85% of participants were 6 to 9 years

^b Belgium, Cyprus, Estonia, Greece, Germany, Hungary, Italy, Spain and Sweden

^c ICAD: the International Children's Accelerometry Database: UK, Switzerland, Denmark, Estonia, Scotland, US, Norway, Brazil, Portugal

-- No information given

- Or + indicates the whether the is an association (+), no association (-) or mixed findings (+/-)

Table 4: Intervention study characteristics and results sorted by outcome

Author	Country	N	Baseline Age	Study Length	Exposure	Outcome	PA Device	PA Data Reduction	Statistical Model and Covariates	Results
Andrade et al., 2014	EC	226* / 1378	Age 12.8	28 months	MVPA	BMI (z-score)	GT-256 /GT1M	SED < 100 cpm MPA ≥ 760 cpm Epoch:-- Non-wear: -- Wear time/day: 9 h Valid days: 3	Model: ITT by linear mixed regression model Covariates: Baseline BMI z-score, sex, SES, knowledge of PA recommendations	Intervention did not lead to favourable changes in BMI z-score (-0.004, 95% CI, -0.09, 0.08). 95.0% of intervention children and 93.6% of control children met ≥60 min MVPA/day at baseline (-) *Only n = 226 wore accelerometer, n = 134 valid measurements
Donnelly et al., 2009	US	167** / 1527	Age 7-9	3 years	MVPA	BMI	7164	MVPA ≥ 4 METs Epoch: -- Non-wear: -- Wear time/day: -- Valid days: 4 d	Model: Adjusted t-test Covariates: --	Intervention children had 27% higher MVPA ($P < 0.001$), but did not reduce BMI (-) **Only n =167 wore accelerometer (n = 77 intervention, n = 90 control)
Lubans et al., 2012	AUS	357	Age 13.2 (♀)	1 year	MVPA	BMI	7164/GT1M /GT3X	MVPA = 2000 cpm Epoch: -- Non-wear: -- Wear time/day: 10 h Valid days: 4	Model: ITT by linear mixed regression model Covariates: Adjusted for clustered nature of the data	No intervention effect of MVPA on BMI (-0.19, 95% CI, -0.70, 0.33), but changes in favour of intervention group (+)
Gorely et al., 2009	UK	589	Age 8.8	10 months	MVPA	BMI, WC	GT1M + pedometer	MVPA = 2500 cpm Epoch: 5 sec Non-wear: 20 min Wear time/day: 9 h Valid days: 4	Model: ITT by multilevel-modelling (ML-win) Covariates: --	Intervention group had significant lower increase in BMI (intervention 0.4 vs control 0.9 BMI units) per year of age and WC (intervention 1.8 cm vs control 2.8 cm) per year of age (+)
Gorely et al., 2011 ^a	UK	421	Age 7-11	18-20 months	MVPA	BMI, WC	GT1M	MVPA = 2500 cpm Epoch: 5 sec Non-wear: 20 min Wear time/day: 9 h Valid days: 4	Model: ITT by multilevel-modelling (ML-win) Covariates: --	The beneficial effects on BMI reported by Gorely et al. (2009) were not sustained (-)

Seabra et al., 2016	PT	88	Age 10.5 (σ)	6 months	MVPA	BMI (z-score), WC, SBP, DBP, HOMA-IR, TG, HDL	GT3X	SED < 100 cpm MPA ≥ 2296 cpm VPA > 4012 cpm Epoch: --- Non-wear: --- Wear time/day: --- Valid days: ---	Model: one way ANOVA, chi-square tests, and calculated effect size Covariates: ---	From baseline to follow-up, the interventions groups decreased BMI z-score, WC TG, and HDL. The interventions groups decreased WC (-5.0 and -5.3 cm) compared to the control group (-0.2 cm) (+)
Bugge et al., 2012	DK	441-613	Age	3 & 4 years (7 years)	MVPA	BMI, WC, SBP, TG, HOMA-IR, CMRisk	7164 /GT1M	SED < 100 cpm MVPA > 1500 cpm Epoch: 10 sec Non-wear: 10 min Wear time/day: 8 h Valid days: 3	Model: General linear model Covariates: Sex, puberty, baseline level of outcome, school as cluster variable	Intervention boys had smaller increase in HOMA-IR from baseline to post-intervention (3 years) compared with control boys (P = 0.004). From baseline to follow-up (7 years) group boys had a smaller increase in SBP compared with control boys (P = 0.010) (+/-)
Kriemler et al., 2010	CH	502	Age 7 & 11	9 months	MVPA	BMI, WC, SBP, DBP, HDL, TG, CMRisk	MTI/CSA 7164	MVPA > 2000 cpm Epoch: 60 sec Non-wear: 15 min Wear time/day: 12 h Valid days: >2	Model: ITT by mixed linear model Covariates: group, sex, and grade as fixed factors; school class as a random effect; and the respective baseline z-score as a covariate	I-children decreased BMI: -0.12 (95% CI, -0.19, -0.04) TG: -0.10 (95% CI, -0.18, -0.01) CMRisk: -0.18 (95% CI, -0.29, -0.06) HDL: 0.27 (95% CI, 0.09, 0.44) (+)
Meyer et al., 2014 ^b	CH	289	Age 10 & 14	3 years	MVPA	BMI, WC, SBP, DBP, HDL, TG, CMRisk	MTI/CSA 7164	MVPA > 2000 cpm Epoch: 60 sec Non-wear: 15 min Wear time/day: 12 h Valid days: 3	Model: Multilevel linear models with z-scores at follow-up as dependent variables Covariates: Group, gender and grade as fixed factors, BMI z-score and change in puberty, the respective baseline z-score as covariate. Original school class were used as random effect	Beneficial effects on BMI, TG or CMRisk reported by Kriemler et al. (2010) were not sustained (-)

-- No information given

- Or + indicates the whether the is an association (+), no association (-) or mixed findings (+/-)

Table 5: Quality assessment of the included studies sorted by quality score (based on criteria as listed in Table 2)

	1	2*	3	4	5	6*	7*	8*	9*	10*	11*	12*	13	Score (%)
Prospective studies														
Basterfield et al., 2012	+	+	+	+	+	+	+	+	+	+	-	+	+	88
Fisher et al., 2011	+	-	+	+	+	+	+	+	+	+	+	+	+	88
Skrede et al., 2017	+	-	+	+	+	+	+	+	+	+	+	+	+	88
Stevens et al., 2007	+	+	+	+	+	+	+	+	+	+	-	+	+	88
Treuth et al., 2009	+	+	+	+	+	+	+	+	+	+	-	+	+	88
van Sluijs et al., 2016	+	-	+	?	+	+	+	+	+	+	+	+	+	88
Carson et al., 2014	+	-	+	+	+	-	+	+	+	+	+	+	+	75
Chinapaw et al., 2018	+	+	+	+	+	-	+	+	+	+	-	+	+	75
Griffiths et al., 2016	+	-	+	+	+	+	-	+	+	+	+	+	+	75
Knowles et al., 2013	+	-	+	+	?	-	+	+	+	+	+	+	+	75
Metcaif et al., 2008	+	-	?	+	+	+	+	+	+	+	-	+	+	75
Metcaif et al., 2015	+	?	+	+	+	+	+	+	+	+	-	+	+	75
Stamatakis et al., 2015	+	+	?	+	+	-	?	+	+	+	+	+	+	75
Hjorth et al., 2014	+	+	+	+	+	-	-	+	+	+	-	+	+	63
Mitchell et al., 2013	+	-	+	+	+	-	?	+	+	+	-	+	+	63
Peplies et al., 2016	?	-	+	+	+	+	?	+	+	+	-	+	+	63
Riddoch et al., 2009	+	-	+	+	+	-	+	+	+	+	-	+	+	63
Trinh et al., 2013	+	-	+	+	+	-	-	+	+	+	-	+	+	63
Lätt et al., 2015	-	?	+	+	+	-	-	+	+	+	-	+	+	50
Lätt et al., 2016	+	?	+	+	+	-	?	+	+	+	-	?	+	50
Ekelund et al., 2012	+	n/a	+	n/a	+	n/a	n/a	+	+	+	+	+	+	n/a
Intervention studies														
Bugge et al., 2012	+	-	+	+	+	+	+	+	+	+	+	+	+	88
Lubans et al., 2012	+	?	+	+	+	+	+	+	+	+	+	+	+	88
Seabra et al., 2016	+	-	+	+	+	+	+	+	+	+	+	+	+	88
Andrade et al., 2014	+	+	+	+	+	-	?	+	+	+	+	+	+	75
Gorely et al., 2009	?	?	+	+	+	+	+	+	+	+	?	+	+	75
Gorely et al., 2011	-	?	+	+	+	+	+	+	+	+	?	+	+	75
Kriemler et al., 2010	+	-	+	+	+	-	+	+	+	+	+	+	+	75
Meyer et al., 2014	+	-	+	+	+	-	+	+	+	+	+	+	+	75
Donnelly et al., 2009	?	-	-	-	+	-	?	+	+	+	+	+	-	63

*validity/precision criteria, + = publication met the quality criterion at issue; - = publication did not meet the quality criterion; ? = quality criterion was insufficiently described; score % = methodological quality score calculated by counting the number of V/P criteria that were met, divided by total the amount of V/P criteria.

Table 6: Level of evidence from studies examining associations between objectively measured total sedentary time, MVPA and cardiometabolic outcomes. Level of evidence coding were performed amongst studies with high quality only and based on ultimately adjusted analyses

Outcome	Beneficially associations with SED	Not associated with SED	n/N for outcome (%)	Level of evidence
BMI	Obs.: Stamatakis ^a	Obs.: Treuth, Griffiths ^a , Basterfield ^b	1/4 (25%)	No evidence
WC	Obs.: Chinapaw ^b	Obs.: Skrede ^a , Stamatakis ^a , van Sluijs ^a	1/4 (25%)	No evidence
Insulin/HOMA-IR	n/a	Obs.: Skrede ^a , Stamatakis ^b , Chinapaw ^b	0/3 (0%)	No evidence
TG	n/a	Obs.: Skrede ^a , Stamatakis ^b , Chinapaw ^b	0/3 (0%)	No evidence
HDL/TC:HDL	n/a	Obs.: Skrede ^a , Stamatakis ^b , Chinapaw ^b	0/3 (0%)	No evidence
Blood Pressure (MAP, SBP, DBP)	Obs.: Chinapaw ^b	Obs.: Skrede ^a , Stamatakis ^b	1/3 (33%)	No evidence
CMRisk	Obs.: Chinapaw ^b	Obs.: Skrede ^a , Stamatakis ^b	1/3 (33%)	No evidence
Outcome	Beneficially associations with MVPA	Not associated with MVPA	n/N for outcome (%)	Level of evidence
BMI	Obs.: Stamatakis ^a , Carson ^a , Griffiths ^a (σ), Fisher ^a , Basterfield ^b (σ) Int.: Kriemler ^c , Gorely ^d (2009)	Obs.: Metcalf ^b (2008), Stevens ^b , Int.: Meyer ^e , Bugge ^d , Gorely ^e (2011), Lubans ^c , Seabra ^d , Andrade ^d	7/15 (43%)	Inconsistent
WC	Obs.: Stamatakis ^a , Chinapaw ^b Int.: Bugge ^d , Gorely ^d (2009), Seabra ^d	Obs.: Fisher ^a , Skrede ^a , Metcalf ^a (2008), van Sluijs ^a Int.: Meyer ^e , Bugge ^d , Gorely ^e (2011)	5/12 (41%)	Inconsistent
Insulin/HOMA-IR	Obs.: Skrede ^a , Stamatakis, Chinapaw ^b Int.: Bugge ^d (σ) (baseline to post-intervention)	Obs.: Metcalf ^b (2008), Metcalf ^b (2015), Int.: Seabra ^d , Bugge (long-term)	4/8 (50%)	Inconsistent
TG	Obs.: Skrede ^a , Metcalf ^b (♀) (2015), Metcalf ^a (♀) (2008), Int.: Kriemler ^c	Obs.: Stamatakis Int.: Meyer ^e , Bugge ^d , Seabra ^d	4/8 (50%)	Inconsistent
HDL/TC:HDL	Obs.: Stamatakis ^b Int.: Kriemler ^c	Obs.: Skrede ^a , Metcalf ^b (2015), Metcalf ^a (2008) Int.: Meyer ^e , Seabra ^d	2/7 (29%)	Inconsistent
Blood Pressure (MAP, SBP, DBP)	Obs.: Metcalf ^b (σ) (2008), Carson ^a (σ), Chinapaw ^b , Metcalf ^b (σ) (2015) Int.: Bugge ^d (σ)	Obs.: Knowles ^a , Skrede ^a , Stamatakis ^b Int.: Kriemler ^c , Meyer ^e , Seabra ^d	5/11 (45%)	Inconsistent
CMRisk	Obs.: Skrede ^a , Stamatakis, Chinapaw ^b , Metcalf ^a (2008) Int.: Kriemler ^c	Int.: Bugge ^d , Meyer ^e	5/7 (71%)	Negative/inverse

^a Prospective study with adjustment for baseline value of the outcome, ^b Prospective study not adjusting for baseline values of the outcome ^c Randomised controlled trial, ^d Non-randomised controlled interventions, ^e Long-term follow-ups, Obs. = observational prospective studies, Int. = intervention studies

Results/associations are coded using the approach first employed by Sallis et al. (171) and subsequently applied to observational studies examining associations with health outcomes. The result was classified as 'no evidence (0)' if 0–33% of studies reported a significant association. If 34–59% of studies reported a significant association, or if fewer than five studies reported on the outcome, the result was classified as being inconsistent. If ≥ 60% of studies found a significant association, the result was classified as positive/adverse or negative/inverse.

Study II

Baseline and follow-up characteristics are presented in Table 7. Of 1,129 participants, $n = 700$ children (49.1% boys) were included in the analyses. Those who were excluded between baseline and follow-up ($n = 395$) from the analysis were shorter in height ($P = 0.009$), but no differences in body weight ($P = 0.330$), WC ($P = 0.824$) or SBP ($P = 0.817$) at baseline between those included and those excluded.

Table 7: Children's characteristics for Study II presented as mean (SD), median (IQR), and/or distributions/frequencies (%)

	Baseline $n = 700$	Follow-up $n = 700$	Correlation Baseline to Follow-up	Change Score Baseline to Follow-up	P-value Change Score
Age (y)	10.2 (0.3)	--	--	--	--
Boys / Girls (%)	49.1 / 50.9	--	--	--	--
Height (cm)	143.1 (6.7)	147.0 (7.0)	0.98	3.9 (1.3)	< 0.001
Weight (kg) ¹	35.6 (31.6, 41.4)	37.9 (33.6, 43.8)	0.98	2.4 (1.7)	< 0.001
Tanner			0.46		< 0.001
Stage 1 (n / %)	206 / 24.9	91 / 13.0		-115	
Stage 2 (n / %)	413 / 59.0	446 / 63.7		+33	
Stage ≥ 3 (n / %)	75 / 10.7	162 / 23.1		+87	
Missing (n / %)	6 / 0.9	1 / 0.1		-5	
SES (%)					
Low	44.3	--	--	--	--
Middle	26.9	--	--	--	--
High	23.5	--	--	--	--
Missing	5.3	--	--	--	--
BMI ¹	17.3 (15.9, 19.5)	17.5 (16.3, 19.6)	0.96	0.13 (0.8)	0.369
Normal (%)	78.4	81.2	--	--	--
Overweight (%)	17.7	15.2	--	--	--
Obese (%)	3.9	3.6	--	--	--
WC (cm) ¹	60.5 (56.8, 66.5)	61.3 (58.0, 66.5)	0.93	1.1 (2.8)	0.004
SBP (mmHg)	105.4 (8.3)	104.7 (8.1)	0.53	-0.6 (8.0)	0.133
TG (mmol/L) ¹	0.69 (0.54, 0.89)	0.66 (0.54, 0.85)	0.43	-0.04 (0.36)	0.012
TC:HDL (mmol/L) ¹	2.77 (2.41, 3.25)	2.67 (2.36, 3.12)	0.83	-0.10 (0.40)	0.002
HOMA-IR ¹	1.78 (1.25, 2.47)	1.89 (1.26, 2.63)	0.63	0.3 (6.7)	0.374
Monitor wear time (min/day)	783.2 (49.9)	786.2 (50.5)	0.33	3.0 (58.0)	0.247
Overall PA (counts/min) ¹	706 (554, 883)	606 (484, 740)	0.36	-123 (285)	< 0.001
SED (min/day) ¹	467.0 (428, 503)	496 (458, 530)	0.54	27.1 (53.3)	< 0.001
MPA (min/day) ¹	44.4 (31.5, 48.2)	39.1 (31.5, 48.2)	0.53	-4.7 (12.0)	< 0.001
VPA (min/day) ¹	29.8 (20.5, 48.5)	25.6 (18.0, 35.5)	0.53	-4.6 (14.7)	< 0.001
MVPA (min/day) ¹	74.6 (58.7, 93.6)	65.9 (51.4, 82.1)	0.56	-9.2 (23.2)	< 0.001

Change from baseline to follow up are analysed using linear mixed model with school as random intercept.

¹ Presented as median (interquartile ranges)

Abbreviations: BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance; MPA, moderate physical activity MVPA; moderate-to-vigorous physical activity; SBP, systolic blood pressure; SED, sedentary; SES, socio-economic status; TC:HDL, the ratio of total cholesterol and high density lipoprotein cholesterol; TG, triglycerides; VPA, vigorous physical activity; WC, waist circumference

P-value in bold is statistic significant to the level of $P < 0.05$.

At baseline, 78.4% of the children were categorised as having normal BMI. On average, children recorded 6.3 (mean 783.2 minutes per day) and 6.4 (mean 786.2 minutes per day) days of valid PA measurements at baseline and follow-up, respectively. MPA and VPA decreased by 4.7 (95% CI; 3.4, 6.0) minutes per day and 4.6 (95% CI; 3.5, 5.7) minutes per day respectively, while MVPA decreased by 9.2 (95% CI; 7.5, 10.9) minutes per day between baseline and follow-up (all $P < 0.001$). Sedentary time increased by 27.1 (95% CI; 31.1, 23.2) minutes per day ($P < 0.001$). A statistically significant increase was observed for WC ($P = 0.004$), while triglycerides ($P = 0.012$) and TC:HDL ($P = 0.002$) decreased. HOMA-IR and SBP did not change over time ($P > 0.133$).

Table 8 shows the prospective associations between sedentary time, PA and individual cardiometabolic risk factors from the adjusted analyses. Sedentary time showed no significant associations with any of the cardiometabolic risk factors at follow-up ($P > 0.052$). MPA was significantly and inversely associated with triglycerides ($\beta = -0.086$ [-0.160, -0.013], $P = 0.021$) and HOMA-IR ($\beta = -0.070$ [-0.132, -0.008], $P = 0.027$) at follow-up and remained significant after adjustment for WC. Prospective associations between MVPA and individual cardiometabolic risk factors were similar as for MPA, although attenuated for HOMA-IR following adjustment for WC. VPA was associated with triglycerides at follow-up, but this association was attenuated ($P = 0.052$) when adjusting for WC.

Table 8: Prospective associations between sedentary time, MPA, VPA and MVPA at baseline and individual cardiometabolic risk factors at follow-up

	Model 1 ¹ n = 700		Model 2 ² n = 700	
	SED	P-value	SED	P-value
WC	-0.016 (-0.049, 0.017)	0.342	---	---
SBP	-0.015 (-0.097, 0.068)	0.731	-0.024 (-0.107, 0.059)	0.570
TG	0.083 (-0.001, 0.168)	0.052	0.061 (-0.022, 0.143)	0.150
TC:HDL-c	-0.008 (-0.061, 0.045)	0.757	-0.015 (-0.068, 0.038)	0.571
HOMA-IR	0.013 (-0.059, 0.085)	0.722	-0.001 (-0.070, 0.070)	0.989
	MPA	P-value	MPA	P-value
WC	0.011 (-0.018, 0.040)	0.456	---	---
SBP	-0.006 (-0.067, 0.079)	0.870	0.016 (-0.058, 0.090)	0.669
TG	-0.107 (-0.182, -0.033)	0.005	-0.086 (-0.160, -0.013)	0.021
TC:HDL	-0.005 (-0.052, 0.042)	0.821	0.001 (-0.046, 0.047)	0.993
HOMA-IR	-0.083 (-0.147, -0.020)	0.010	-0.070 (-0.132, -0.008)	0.027
	VPA	P-value	VPA	P-value
WC	-0.001 (-0.031, 0.028)	0.926	---	---
SBP	-0.008 (-0.081, 0.063)	0.816	0.009 (-0.066, 0.084)	0.810
TG	-0.120 (-0.194, -0.046)	< 0.001	-0.073 (-0.148, 0.001)	0.052
TC:HDL-c	-0.030 (-0.077, 0.016)	0.208	-0.019 (-0.069, 0.029)	0.439
HOMA-IR	-0.058 (-0.122, 0.005)	0.075	-0.027 (-0.090, 0.037)	0.413
	MVPA	P-value	MVPA	P-value
WC	0.005 (-0.024, 0.035)	0.725	---	---
SBP	-0.001 (-0.073, 0.073)	0.991	0.014 (-0.60, 0.089)	0.704
TG	-0.127 (-0.202, -0.051)	< 0.001	-0.090 (-0.165, -0.015)	0.019
TC:HDL	-0.019 (-0.066, 0.029)	0.437	-0.001 (-0.057, 0.038)	0.694
HOMA-IR	-0.075 (-0.139, -0.010)	0.022	-0.051 (-0.115, 0.012)	0.113

¹ β coefficients adjusted for sex, monitor wear time, Tanner, SES, and cardiometabolic risk factor at baseline.

² WC is omitted from the clustered cardiometabolic risk and added as covariate.

P-value in bold is statistic significant to the level of $P < 0.05$.

We thereafter examined the prospective association between sedentary time and PA with clustered cardiometabolic risk, adjusting for the same covariates as described above (Table 9). Sedentary time and MPA were not associated with clustered cardiometabolic risk in any of the models. Time spent in VPA (β -0.060 [-0.113, -0.007], $P = 0.028$) and MVPA (β = -0.056 [-0.109, -0.002], $P = 0.043$) was inversely associated with cardiometabolic risk at follow-up. However, when excluding WC from the clustered cardiometabolic risk score and adjusting the analyses for WC, these associations were attenuated.

Table 9: Prospective associations between SED, MPA, MVPA and VPA at baseline and clustered cardiometabolic risk at follow-up

	Model 1 ¹ n = 700		Model 2 ² n = 700	
	Cardiometabolic Risk	P-value	Cardiometabolic Risk	P-value
SED	0.012 (-0.047, 0.072)	0.683	0.001 (-0.066, 0.068)	0.984
MPA	-0.044 (-0.097, 0.008)	0.099	-0.051 (-0.110, 0.008)	0.093
VPA	-0.060 (-0.113, -0.007)	0.028	-0.044 (-0.105, 0.016)	0.152
MVPA	-0.056 (-0.109, -0.002)	0.043	-0.052 (-0.113, 0.008)	0.091

¹ β coefficients adjusted for sex, monitor wear time, Tanner, SES, and cardiometabolic risk factor at baseline.

² WC is omitted from the clustered cardiometabolic risk and added as covariate.

P-value in bold is statistic significant to the level of $P < 0.05$.

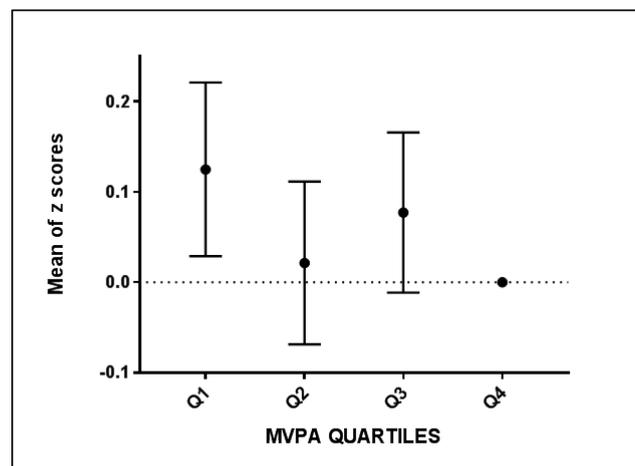


Figure 5: Clustered cardiometabolic risk (z-score) at follow-up stratified by baseline quartiles of MVPA (each quartile consists n = 175). Error bars represent standard error. Median for MVPA quartiles were Q1; 48.3 minutes per day, Q2; 66.6 minutes per day, Q3; 82.2 minutes per day, Q4; 107.7 minutes per day. A significant difference was observed between the first and fourth quartile for clustered cardiometabolic risk.

Study III

Children's characteristics at baseline are presented in Table 10. Of 1,129 participants, $n = 718$ children (50.3% boys) had valid measurements for exposure and outcome at both time points. Excluded children ($n = 411$) were shorter (1.00 cm [95% CI 0.15, 1.8]; $P = 0.021$), but there were no differences in baseline BMI ($P = 0.533$), WC ($P = 0.755$) or SBP ($P = 0.716$) compared to the included children. The majority of the children were normal weight (78.1%), and 3.6% were categorised as obese. At baseline and follow-up, the children had > six days of valid PA measurement and a mean of 784 ± 51 minutes per day of monitor wear time. Boys spent more time in MVPA [15 minutes (95% CI 12, 19); $P < 0.001$] and covered a longer distance during the Andersen test compared to the girls (60 meters [95% CI 46, 75]; $P < 0.001$), but there were no differences in time spent sedentary ($P = 0.691$). Children with high CRF at baseline (above the median split) had more beneficial values in all PA and cardiometabolic measures ($P < 0.05$) except for SBP. There were no differences between groups for pubertal stage and monitor wear time. The sex specific median split by the Andersen test (940 meter for boys, 875 meters for girls) correspond to a peak oxygen uptake of 58.2 ml/kg/minute and 50.8 ml/kg/minute, respectively (62).

Table 10: Children's characteristics for Study III presented for total sample and by the sex specific median split for CRF (n = 718)

	Sample in total at baseline	Sample in total at follow up	Low CRF Below median split baseline	High CRF Above median split baseline
Age (years)	10.2 (0.3)	---	10.2 (0.3)	10.3 (0.3) ^d
Boys / girls (%)	50.3 / 49.7	---	58.6 / 41.4	44.2 / 58.4 ^d
Height (cm)	143.0 (6.7) ^a	147.0 (7.1)	143.3 (6.9)	142.9 (6.6)
Weight (kg)	35.5 (31.6, 41.2) ^b	37.8 (33.6, 43.7)	37.8 (32.4, 45.1)	34.1 (31.1, 28.1) ^d
BMI (kg × m ²)	17.3 (15.9, 19.5)	17.4 (16.1, 19.5)	18.6 (16.3, 21.3)	16.7 (15.5, 18.1) ^d
SES ^c (n & %)				
Low	666 (46.4)	---	187 (61.5)	134 (44.1)
Middle	325 (22.6)	---	48 (15.8)	76(25.0)
High	350 (24.4)	---	40(13.2)	77 (25.3)
Missing	95 (6.6)	---	29 (9.5)	17 (5.6)
Pubertal status (n & %)				
Stage 1	210 (29.4)	---	89 (29.3)	121 (29.2)
Stage 2	428 (59.9)	---	168 (55.3)	260 (62.8)
Stage ≥ 3	77 (10.7)	---	45 (14.8)	32 (7.7)
Missing	3 (0.4)	---	2 (0.7)	1 (0.2)
Clustered risk score	-0.22 (-0.64, 0.45)	-0.21 (-0.70, 0.45)	0.07 (-0.50, 0.94)	-0.38 (-0.74, 0.16) ^d
WC (cm)	60.3 (56.8, 65.5)	61.3 (58.0, 6.5)	63.8 (58.4, 70.9)	59.0 (56.0, 62.3) ^d
SBP (mmHg)	105.4 (8.4)	104.7 (8.1)	105.3 (8.4)	105.5 (8.5)
TG (mmol/L)	0.69 (0.54, 0.88)	0.66 (0.54, 0.85)	0.73 (0.57, 0.97)	0.66 (0.53, 0.54) ^d
TC:HDL (mmol/L)	2.77 (2.42, 3.22)	2.66 (2.35, 3.11)	2.89 (2.52, 3.49)	2.69 (2.37, 3.1) ^d
HOMA-IR	1.77 (1.25, 2.47)	1.89 (1.26, 2.63)	1.92 (1.39, 2.86)	1.67 (1.21, 2.23) ^d
Monitor wear time (min/day)	784.0 (51.1)	784.4 (53.8)	781.3 (51.7)	786.1 (50.6)
SED (min/day)	467.2 (58.0)	492.6 (54.4)	473.0 (61.9)	462.9 (54.6)
VPA (min/day)	30.0 (20.7, 40.6)	25.8 (18.0, 51.9)	24.7 (17.0, 35.0)	32.9 (23.0, 43.0) ^d
MVPA (min/day)	74.7 (59.2, 93.7)	66.4 (51.9, 82.5)	67.6 (53.3, 84.8)	79.2 (63.7, 98.2) ^d
Overall PA (cpm)	710 (560, 880)	611 (487, 742)	652 (515, 809)	747 (583, 906) ^d
Andersen-test (meters)	901 (102)	941 (98)	819 (77)	961 (71) ^d

^a Mean and SD (all such values)

^b Median and IQR (all such values)

^c SES reported by both parents

^d Significant difference between low/high CRF

Abbreviations: CRF, cardiorespiratory fitness; cpm, counts per minute, HOMA-IR, homeostatic model assessment of insulin resistance; MVPA; moderate-to-vigorous physical activity; SBP, systolic blood pressure; SED, sedentary; SES, socio-economic status; TC:HDL, the ratio of total cholesterol and high density lipoprotein cholesterol; TG, triglycerides; VPA, vigorous physical activity; WC, waist circumference

MVPA was associated with lower triglyceride level at follow-up, independent of CRF (β -0.080 [95% CI: $-0.159, -0.001$]; $P = 0.047$) (Table 11), but this association was attenuated by WC (β 0.044 [95% CI: $-0.021, 0.010$] $P = 0.085$) (Table 12). CRF modified the prospective associations between overall PA and time spent in at least moderate PA with HOMA-IR ($P < 0.005$) at follow-up (Table 11) and when adjusted for WC ($P < 0.022$). In children with low CRF, both VPA and MVPA at baseline were significantly associated with lower HOMA-IR (MVPA β -0.153 [95% CI: $-0.245, -0.062$]; $P = 0.002$) at follow-up, also when adjusted for WC (MVPA β -0.133 [95% CI: $-0.223, -0.043$]; $P = 0.004$). CRF did not modify the prospective associations between sedentary time and the other PA variables and cardiometabolic risk factors (Table 11 and 12).

Table 11: Prospective associations between sedentary time and PA with individual cardiometabolic risk factors (model 1) ($n = 718$)

	SED (min/day)	VPA (min/day)	MVPA (min/day)	Overall PA (cpm)
WC				
Overall association	-0.019 (-0.053, 0.015) $P = 0.274$	0.004 (-0.027, 0.035) $P = 0.809$	0.010 (-0.021, 0.042) $P = 0.508$	0.010 (-0.020, 0.040) $P = 0.509$
Interaction (CRF \times PA exposure)	-0.020 (-0.047, 0.008) $P = 0.150$	0.014 (-0.011, 0.039) $P = 0.275$	0.017 (-0.009, 0.042) $P = 0.192$	0.007 (-0.020, 0.032) $P = 0.613$
SBP				
Overall association	-0.018 (-0.101, 0.065) $P = 0.671$	0.010 (-0.064, 0.085) $P = 0.785$	-0.019 (-0.057, 0.094) $P = 0.626$	0.029 (-0.043, 0.100) $P = 0.426$
Interaction (CRF \times PA exposure)	-0.018 (-0.054, 0.082) $P = 0.682$	0.002 (-0.061, 0.064) $P = 0.957$	0.001 (-0.065, 0.063) $P = 0.958$	-0.029 (-0.093, 0.036) $P = 0.384$
TC:HDL				
Overall association	0.019 (-0.045, 0.036) $P = 0.497$	-0.020 (-0.069, 0.029) $P = 0.421$	-0.010 (-0.060, 0.039) $P = 0.687$	-0.003 (-0.051, 0.044) $P = 0.894$
Interaction (CRF \times PA exposure)	-0.032 (-0.076, 0.013) $P = 0.164$	0.028 (-0.012, 0.069) $P = 0.172$	0.022 (-0.020, 0.063) $P = 0.311$	0.033 (-0.010, 0.076) $P = 0.128$
TG				
Overall association	0.045 (-0.042, 0.132) $P = 0.306$	-0.077 (-0.155, 0.001) $P = 0.050$	-0.080 (-0.159, -0.001) $P = 0.047$	-0.061 (-0.136, 0.014) $P = 0.112$
Interaction (CRF \times PA exposure)	-0.065 (-0.135, 0.005) $P = 0.069$	0.061 (-0.003, 0.125) $P = 0.063$	0.057 (-0.009, 0.123) $P = 0.091$	0.071 (0.004, 0.137) $P = 0.037$
Low CRF	n/a	n/a	n/a	-0.130 (-0.235, -0.026) $P = 0.015$
High CRF	n/a	n/a	n/a	-0.003 (-0.098, 0.099) $P = 0.995$
HOMA-IR				
Overall association	0.009 (-0.066, 0.084) $P = 0.807$	-0.020 (-0.098, 0.038) $P = 0.389$	-0.048 (-0.117, 0.020) $P = 0.165$	0.002 (-0.068, 0.063) $P = 0.941$
Interaction (CRF \times PA exposure)	-0.035 (-0.095, 0.025) $P = 0.254$	0.081 (0.026, 0.136) $P = 0.004$	0.088 (0.032, 0.145) $P = 0.002$	0.081 (0.024, 0.138) $P = 0.005$
Low CRF	n/a	-0.130 (-0.220, -0.040) $P = 0.005$	-0.153 (-0.245, -0.062) $P = 0.002$	-0.085 (-0.175, 0.005) $P = 0.065$
High CRF	n/a	0.031 (-0.099, 0.037) $P = 0.377$	0.022 (-0.057, 0.123) $P = 0.474$	0.067 (-0.019, 0.152) $P = 0.129$

All values are standardised β coefficients (95 % CIs) adjusted for sex, group allocation, pubertal status (Tanner), SES, monitor wear time, respective baseline cardiometabolic risk factor, and Andersen-test at baseline. Individual cardiometabolic risk factors are analysed as z-scores (not log transformed).
P-value in bold is statistic significant to the level of $P < 0.05$.

Table 12: Prospective associations between sedentary time and PA with individual cardiometabolic risk factors, adjusted for adiposity (model 2) (n = 718)

	SED (min/day)	VPA (min/day)	MVPA (min/day)	Overall PA (cpm)
	SBP			
Overall association	0.021 (-0.106, 0.062) P = 0.606	-0.018 (-0.057, 0.093) P = 0.634	-0.024 (-0.052, 0.200) P = 0.537	-0.032 (-0.040, 0.103) P = 0.383
Interaction (CRF × PA exposure)	0.014 (-0.054, 0.083) P = 0.682	-0.005 (-0.068, 0.057) P = 0.865	-0.007 (-0.071, 0.057) P = 0.826	-0.034 (-0.100, 0.030) P = 0.293
	TC:HDL			
Overall association	0.023 (-0.075, 0.028) P = 0.428	-0.013 (-0.062, 0.037) P = 0.621	-0.005 (-0.055, 0.046) P = 0.854	-0.003 (-0.050, 0.044) P = 0.889
Interaction (CRF × PA exposure)	-0.028 (-0.072, 0.017) P = 0.224	0.022 (-0.018, 0.064) P = 0.276	0.017 (-0.026, 0.059) P = 0.433	0.028 (-0.014, 0.070) P = 0.192
	TG			
Overall association	0.040 (-0.044, 0.125) P = 0.347	-0.056 (-0.132, 0.020) P = 0.146	-0.068 (-0.146, 0.009) P = 0.085	-0.054 (-0.126, 0.019) P = 0.147
Interaction (CRF × PA exposure)	-0.054 (-0.122, 0.014) P = 0.121	0.046 (-0.017, 0.109) P = 0.155	0.044 (-0.021, 0.110) P = 0.183	0.057 (-0.008, 0.122) P = 0.085
	HOMA-IR			
Overall association	0.005 (-0.167, 0.030) P = 0.886	-0.017 (-0.084, 0.050) P = 0.618	-0.042 (-0.110, 0.025) P = 0.218	0.001 (-0.066, 0.063) P = 0.964
Interaction (CRF × PA exposure)	-0.020 (-0.079, 0.040) P = 0.520	0.064 (0.010, 0.119) P = 0.020	0.074 (0.018, 0.130) P = 0.009	0.066 (0.009, 0.119) P = 0.022
Low CRF	n/a	-0.098 (-0.187, -0.009) P = 0.031	-0.133 (-0.223, -0.043) P = 0.004	-0.071 (-0.160, 0.017) P = 0.117
High CRF	n/a	0.054 (-0.035, 0.143) P = 0.233	0.032 (-0.056, 0.121) P = 0.466	0.057 (-0.026, 0.141) P = 0.180

All values are standardised β coefficients (95% CIs), adjusted for sex, group allocation, pubertal status (Tanner), SES, monitor wear time, respective baseline cardiometabolic risk factor, baseline Andersen-test and waist circumference as a measure of adiposity. Individual cardiometabolic risk factors are analysed as z-scores (not log transformed). P-value in bold is statistic significant to the level of $P < 0.05$.

CRF modified the associations between time spent in VPA, MVPA and overall PA with the clustered cardiometabolic risk score ($P < 0.039$) (Table 13). In less fit children, we observed a significant association between baseline VPA and clustered cardiometabolic risk score at follow-up ($\beta -0.099$ [95% CI: $-0.171, -0.025$]; $P = 0.009$). A similar association was observed for MVPA ($\beta -0.094$ [95% CI: $-0.169, -0.019$]; $P = 0.014$), but not for overall PA. However, neither sedentary time nor any of the PA variables were associated with the non-obesity clustered cardiometabolic risk scores at follow-up when adjusted for WC.

Table 13: Prospective associations between sedentary time and PA with clustered cardiometabolic risk factors (model 1 and 2) (n = 718)

	SED (min/day)	VPA (min/day)	MVPA (min/day)	Overall PA (cpm)
MODEL 1^a				
Clustered cardiometabolic risk				
Overall association	-0.007 (0.068, 0.055) P = 0.830	-0.026 (-0.081, 0.030) P = 0.364	-0.021 (-0.077, 0.035) P = 0.453	-0.002 (-0.051, 0.056) P = 0.931
Interaction (CRF × PA exposure)	-0.047 (-0.096, 0.002) P = 0.058	0.055 (0.010, 0.100) P = 0.017	0.054 (0.008, 0.100) P = 0.023	0.049 (0.002, 0.096) P = 0.039
Low CRF	N/A	-0.099 (-0.171, -0.025) P = 0.009	-0.094 (-0.169, -0.019) P = 0.014	-0.042 (-0.116, 0.032) P = 0.268
High CRF	N/A	0.040 (-0.033, 0.115) P = 0.280	0.040 (-0.034, 0.112) P = 0.289	0.043 (-0.027, 0.112) P = 0.232
MODEL 2^b				
Clustered non-obesity cardiometabolic risk				
Overall association	-0.011 (-0.081, 0.059) P = 0.761	-0.024 (-0.087, 0.040) P = 0.463	0.031 (-0.095, 0.032) P = 0.333	-0.001 (-0.068, 0.054) P = 0.820
Interaction (CRF × PA exposure)	-0.033 (-0.089, 0.023) P = 0.246	0.047 (-0.005, 0.098) P = 0.077	0.047 (-0.005, 0.100) P = 0.079	0.042 (-0.011, 0.096) P = 0.118

All values are standardised β coefficients (95 % CIs),

^a Adjusted for sex, group allocation, pubertal status (Tanner), SES, monitor wear time, baseline clustered cardiometabolic risk score, and Andersen-test.

^b Adjusted as model 1, but WC omitted from the cardiometabolic risk score and added as covariate.

P-value in bold is statistic significant to the level of $P < 0.05$.

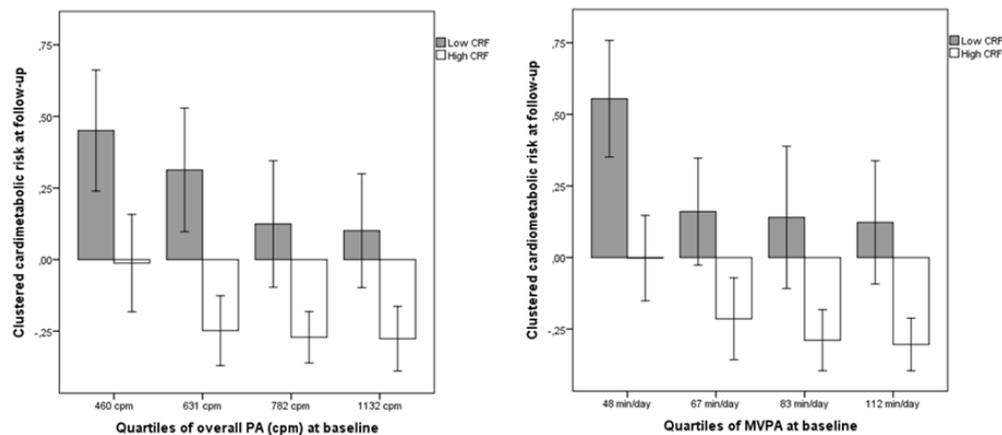


Figure 6: Illustrates the prospective association between high and low CRF with clustered cardiometabolic risk at follow-up adjusted for all covariates, based on quartiles of overall PA and MVPA at baseline.

Study IV

Children's characteristics at baseline are presented in Table 14. Of 1,129 participants, $n = 869$ children provided valid measurements for PA and adiposity at both time points. Excluded children ($n = 253$) did not differ in any of the adiposity measures at baseline ($P \geq 0.280$), but baseline overall PA (cpm) were lower ($P = 0.030$). At baseline, the majority of the children were normal weight (77.4%), while 18.6% were categorised as overweight and 3.9% were obese.

Table 14: Children's characteristics for Study IV at baseline and follow-up ($n = 869$)

	Baseline Autumn 2014	Follow-up Spring 2015	Change baseline to follow-up
Age (years)	10.2 (0.3)	--	--
Boys / girls (%)	48.9 / 51.1	--	--
Height (cm)	142.9 (6.8) ^a	146.9 (7.1)	< 0.001
Body weight (kg)	35.3 (31.6, 41.0) ^b	37.8 (33.7, 43.6)	< 0.001
Children's birth weight (g)	3591 (623)	--	--
Mother's body weight (kg)	70.0 (12.0)	--	--
Father's body weight (kg)	86.8 (12.4)	--	--
SES (%)			
Low	22.9 / 44.6	--	--
Middle	41.2 / 32.2	--	--
High	31.4 / 19.3	--	--
Missing	4.5 / 8.1	--	--
Pubertal status (%)			< 0.001
Stage 1	29.2	13.3	--
Stage 2	59.4	63.2	--
Stage ≥ 3	10.4	33.1	--
Missing	0.9	0.3	--
BMI ($\text{kg} \times \text{m}^2$)	17.3 (15.9, 19.4)	17.5 (16.1, 19.6)	0.231
Normal weight (%)	77.4	79.1	--
Overweight (%)	18.6	17.2	--
Obese (%)	3.9	3.7	--
WC (cm)	60.3 (56.8, 65.5)	61.3 (58.0, 66.5)	0.001
Skinfold (mm)	41.8 (29.9, 63.0)	41.8 (30.5, 60.0)	0.333
Monitor wear time (min/day)	782.0 (50.8)	785.8 (50.5)	0.133
SED (min/day)	467.2 (58.3)	494.5 (53.1)	< 0.001
MVPA (min/day)	74.2 (58.6, 92.4)	65.0 (50.2, 81.7)	< 0.001
VPA (min/day)	29.1 (20.5, 39.1)	25.1 (17.3, 34.4)	< 0.001
Overall PA (cpm)	695 (556, 875)	593 (480, 733)	< 0.001

^a Mean and SD (all such values)

^b Median and interquartile range (all such values)

^c Mother reporting (n)

^d Father reporting (n)

Abbreviations: BMI; body mass index, cpm; counts per minute, MVPA; moderate-to-vigorous physical activity, SED; sedentary time, SES; socio-economic status, VPA; vigorous physical activity, WC; waist circumference
P-value in bold is statistic significant to the level of $P < 0.05$.

Neither overall PA nor time spent sedentary predicted lower BMI or WC at follow-up ($P \geq 0.080$) (Table 15), but time spent in MVPA and VPA at baseline predicted lower skinfolds at follow-up ($P < 0.022$). There were an interaction by sex for MVPA ($P = 0.017$), but were borderline significant for VPA ($P = 0.069$). However, both MVPA and VPA predicted lower skinfolds at follow-up in boys (MVPA $\beta -0.066$ [95% CI $-0.105, -0.027$] $P = 0.001$), but not in girls ($\beta 0.003$ [95% CI $-0.041, 0.048$] $P = 0.889$).

Table 15: Prospective associations between PA at baseline and adiposity at follow-up

		Outcome at follow-up		
		BMI	WC	S4SF
Exposure at baseline	Overall PA (cpm)	0.019 (-0.002, 0.040) $P = 0.080$	0.009 (-0.019, 0.036) $P = 0.536$	-0.022 (-0.051, 0.008) $P = 0.153$
	<i>cpm</i> × sex	$P = 0.916$	$P = 0.686$	$P = 0.369$
	SED	-0.016 (-0.040, 0.008) $P = 0.191$	-0.007 (-0.038, 0.024) $P = 0.649$	0.010 (-0.024, 0.045) $P = 0.552$
	<i>SED</i> × sex	$P = 0.938$	$P = 0.977$	$P = 0.990$
	MVPA	0.009 (-0.013, 0.030) $P = 0.435$	0.003 (-0.025, 0.031) $P = 0.809$	-0.036 (-0.067, -0.005) $P = 0.022$
	<i>MVPA</i> × sex	$P = 0.563$	$P = 0.806$	-0.069 (-0.126, -0.012) $P = 0.017$
	Boys	<i>n/a</i>	<i>n/a</i>	-0.066 (-0.105, -0.027) $P = 0.001$
	Girls	<i>n/a</i>	<i>n/a</i>	0.003 (-0.041, 0.048) $P = 0.889$
	VPA	0.017 (-0.004, 0.039) $P = 0.116$	0.003 (-0.024, 0.032) $P = 0.782$	-0.043 (-0.074, -0.012) $P = 0.006$
	<i>VPA</i> × sex	$P = 0.335$	$P = 0.877$	-0.053 (-0.111, 0.005) $P = 0.069^*$
	Boys	<i>n/a</i>	<i>n/a</i>	-0.064 (-0.105, -0.026) $P = 0.001$
	Girls	<i>n/a</i>	<i>n/a</i>	-0.011 (-0.057, 0.036) $P = 0.643$

The model is adjusted for sex, SES, parental weight, pubertal stage, child's birth weight, monitor wear time, and baseline value of the outcome,
P-value in bold is statistic significant to the level of $P < 0.05$.

On the contrary, all adiposity measures predicted lower overall PA, MVPA, VPA and higher sedentary time at follow-up ($P < 0.043$) (Table 16). We observed significant interactions by sex between all baseline adiposity measures and PA outcomes ($P < 0.048$), but not for sedentary time ($P \geq 0.477$). Baseline BMI and WC predicted lower overall PA, MVPA and VPA in boys ($P < 0.001$), but not in girls ($P \geq 0.112$). When skinfolds was modelled as the exposure, time spent in VPA was lower at follow-up in both girls ($\beta -0.098$ [95% CI $-0.194, -0.002$] $P = 0.045$) and boys ($\beta -0.276$ [95% CI $-0.372, -0.180$] $P < 0.001$).

Table 16: Prospective associations between adiposity at baseline and PA at follow-up

		Outcome at follow-up			
		Overall PA (cpm)	SED	MVPA	VPA
Exposure at baseline	BMI	-0.124 (-0.198, -0.050) P = 0.001	0.088 (0.020, 0.157) P = 0.011	-0.092 (-0.156, -0.028) P = 0.005	-0.136 (-0.205, -0.068) P < 0.001
	BMI × sex	-0.137 (-0.273, -0.001) P = 0.048	P = 0.508	-0.209 (-0.326, -0.093) P < 0.001	-0.140 (-0.263, -0.017) P = 0.025
	Boys	-0.193 (-0.295, -0.092) P < 0.001	n/a	-0.199 (-0.287, -0.112) P < 0.001	-0.208 (-0.301, -0.115) P < 0.001
	Girls	-0.056 (-0.156, -0.043) P = 0.266	n/a	0.010 (-0.076, 0.095) P = 0.822	-0.068 (-0.159, 0.023) P = 0.141
	WC	-0.150 (-0.225, -0.074) P < 0.001	0.072 (0.007, 0.148) P = 0.043	-0.102 (-0.169, -0.036) P = 0.002	-0.151 (-0.220, -0.082) P < 0.001
	WC × sex	-0.139 (-0.277, -0.001) P = 0.048	P = 0.477	-0.207 (-0.326, -0.089) P = 0.001	-0.148 (-0.273, -0.024) P = 0.020
	Boys	-0.221 (-0.324, 0.118) P < 0.001	n/a	-0.209 (-0.298, -0.120) P < 0.001	-0.227 (-0.323, -0.133) P < 0.001
	Girls	-0.081 (-0.183, 0.019) P = 0.112	n/a	-0.002 (-0.089, -0.085) P = 0.969	-0.079 (-0.171, -0.012) P = 0.090
	S4SF	-0.175 (-0.252, -0.098) P < 0.001	0.088 (0.016, 0.160) P = 0.016	-0.120 (-0.189, -0.051) P = 0.001	-0.187 (-0.258, -0.116) P < 0.001
	S4SF × sex	-0.168 (-0.311, -0.024) P = 0.022	P = 0.894	-0.262 (-0.392, -0.133) P < 0.001	-0.178 (-0.307, -0.049) P = 0.007
	Boys	-0.258 (-0.363, -0.154) P < 0.001	n/a	-0.240 (-0.331, -0.149) P < 0.001	-0.276 (-0.372, -0.180) P < 0.001
	Girls	-0.090 (-0.195, -0.015) P = 0.094	n/a	-0.019 (-0.110, 0.073) P = 0.689	-0.098 (-0.194, -0.002) P = 0.045

The model is adjusted for sex, SES, parental weight, pubertal stage, child's birth weight, monitor wear time, and baseline value of the outcome.

P-value in bold is statistic significant to the level of $P < 0.05$

Lastly, we examined the bi-directional prospective associations between PA and adiposity by dichotomising the sample into according to PA recommendations (60 minutes MVPA per day) and BMI into normal-weight and overweight/obese at baseline to examine if these groups differed. There were no difference in adiposity at follow up between children categorised as active or inactive at baseline ($P > 0.235$) (Table 17). Children with overweight and obesity had significantly lower follow-up overall PA ($\beta -0.235$ [95% CI $-0.405, -0.065$] $P = 0.007$), MVPA ($\beta -0.199$ [95% CI $-0.347, -0.052$] $P = 0.008$) and VPA ($\beta -0.266$ [95% CI $-0.423, -0.110$] $P = 0.001$) than normal-weight children, while there were difference between groups in relationship with sedentary time at follow-up (Table 18).

Table 17: Prospective associations between baseline MVPA (\geq / $<$ 60 minutes) and adiposity at follow-up

Exposure at baseline	Outcome at follow-up		
	BMI	WC	S4SF
MVPA	Ref.	Ref.	Ref.
< 60 min			
MVPA	0.016 (−0.028, 0.067)	−0.021 (−0.080, 0.037)	−0.039 (−0.105, 0.026)
\geq 60 min	<i>P</i> = 0.467	<i>P</i> = 0.469	<i>P</i> = 0.235

The model is adjusted for sex, SES, pubertal stage, child's birth weight, parental weight, monitor wear time, and baseline value of the outcome.

Table 18: Prospective associations between normal weight versus overweight/obese (BMI) at baseline and PA intensities at follow-up

Exposure at baseline	Outcome at follow-up			
	Overall PA (cpm)	SED	MVPA	VPA
BMI < 25	Ref.	Ref.	Ref.	Ref.
BMI \geq 25	−0.235 (−0.405, −0.065)	0.105 (−0.053, 0.262)	−0.199 (−0.347, −0.052)	−0.266 (−0.423, −0.110)
	<i>P</i> = 0.007	<i>P</i> = 0.192	<i>P</i> = 0.008	<i>P</i> = 0.001

The model is adjusted for sex, SES, pubertal stage, child's birth weight, parental weight, monitor wear time, and baseline value of the outcome.

P-value in bold is statistic significant to the level of $P < 0.05$

GENERAL DISCUSSION

The four studies comprising this thesis provide evidence that higher intensity PA is inversely associated with cardiometabolic risk factors, and especially in those children with low CRF. The interaction between CRF and PA means that the effect of PA is different in the CRF groups. In contrast, time spent sedentary appears to have no detrimental effects on either cardiometabolic risk factors or adiposity. Furthermore, prevention of excessive adiposity in children might be important to maintain PA levels, which highlights the complexity of public health challenges and the need for interventions and PA strategies at early ages.

In the following, discussion of the results from Study I and Study II are merged together. Study III and Study IV will be discussed separately. Lastly, important methodological considerations and implications within the studies and the thesis as a whole are discussed.

Study I and II: Is there a prospective association between sedentary time, MVPA and cardiometabolic risk?

We have summarised the evidence for the prospective relationship between sedentary time, MVPA and cardiometabolic risk factors in youth, and have systematically reviewed 30 studies. First, the evidence for an association between sedentary time and cardiometabolic risk factors is inconsistent, which is in line with the conclusions of previous systematic reviews and meta-analyses (23, 145-147, 169). Second, the evidence for a prospective association between MVPA and individual cardiometabolic risk factors is inconsistent. However, MVPA is consistent and inversely associated with *clustered* cardiometabolic risk score.

We found no evidence for an association between sedentary time and adiposity (BMI and WC), and found inconsistent prospective associations with MVPA. These findings may be explained by the fact that PA, sedentary time (158), and the prevalence of overweight and obesity show moderate tracking (157, 208), which indicates a tendency of individuals to maintain their position within a group or trait over time (209). Moreover, overall PA may not be a strong predictor of adiposity (210), as excessive energy intake is more likely the major driver of overweight and obesity in youth. PA might rather be a moderator influencing the steepness of adiposity increases (211). Some studies suggest that the prospective association between sedentary time, MVPA, and adiposity is more apparent in overweight or obese populations, or in those at risk of overweight or obesity (188, 212). However, Trinh et al. (193) found that long-term reductions in BMI were small even with the largest change in MVPA among children with overweight and obesity. BMI as a fatness indicator in children is widely used as an outcome, but has some important limitations. First, BMI is affected by growth and puberty. Second, BMI incorporates fat and lean body mass, which are likely influenced by PA in

opposite directions. As associations are generally weaker between MVPA and BMI (reduced by a factor of around four), than between MVPA and the fat mass index calculated using dual-energy X-ray absorptiometry (DEXA) measurements of body composition (195), more precise measures of adiposity might produce stronger associations. Importantly, only three of seven intervention studies managed to increase MVPA levels (185, 198, 199), which limits the conclusions of cause and effect between PA and adiposity. Therefore, no change in MVPA (102, 201, 203), high PA levels in control groups (213), a short follow-up (25), and issues with adherence are likely explanations for the conflicting results from interventional studies. Long-term follow-ups showing that beneficial changes in BMI are lost after intervention has ended (186, 200) also imply that changes in PA behaviour are not sustained over time. A reverse causation or bi-directional associations between sedentary time and PA might also explain the inconsistency and adiposity, which will be further discussed in Study IV.

Sedentary time appears unrelated to BP, and the association with MVPA is inconsistent. This does not mean that sedentary time or MVPA is irrelevant for abnormal BP development, but that the associations are likely affected by the continuous increase in BP with age (214). Moreover, the estimated prevalence of hypertension in young populations is uncertain and varies between 1% to 10% (86). However, childhood BP tracks into adulthood (215), and the association between PA and BP may become evident later in life. This would suggest that MVPA at an early age might have a preventive effect (216).

The evidence synthesis concludes that the prospective associations between MVPA and biochemical outcomes were inconsistent. Indeed, we observe that MVPA decreases insulin resistance and enhances lipid concentrations in youth, but the low number of high-quality studies examining each outcome limit our conclusions. Nonetheless, the meta-analysis and evidence synthesis shows a consistent and inverse association between MVPA and *clustering* of cardiometabolic risk. The meta-analysis must be interpreted with caution because of the small number of studies available, and we were not able to differentiate between follow-up durations within studies. However, as the finding is consistent, it is likely that inclusion of additional studies would have strengthened the observed effects. Clustering of cardiometabolic risk is indeed an undesirable condition, and a biological sign of poor cardiometabolic health. The condition depends highly on the occurrence of abdominal adiposity and/or impaired insulin regulation (10, 110), which may in turn affect BP, lipid metabolism, and low-grade inflammation simultaneously (67). It is uncertain how elevated risk in a child is related to later cardiovascular disease (97, 217). Hence, clustering of cardiometabolic risk factors is only of interest if clustering is a stable characteristic (218). However, clustering of cardiometabolic risk factors appears fairly stable throughout the first decades of life (218) and tracks into adulthood (219-221). Clustering

of cardiometabolic risk factors is therefore a meaningful health outcome, and may be an important indicator of future cardiometabolic disease (218).

There was no evidence for an association between sedentary time and individual biochemical outcomes, which corresponds with the conclusions of previous systematic reviews (145, 169) and large-scale studies (22, 23), but it does not mean that there is evidence for no association (222). Shorter lifetime exposure may explain the lack of robust associations between sedentary time, adiposity, and cardiometabolic risk factors (22). Sedentary bouts in children are relatively short (< 20 min) (223) and possibly not extensive enough to have a negative influence on cardiometabolic health. At present, the evidence for prolonged and uninterrupted sedentary bouts' detrimental effect is limited when accounting for MVPA (146, 169), but few prospective studies examining sedentary patterns exist. Other possibilities for the discrepancy include that the associations between sedentary time and cardiometabolic outcomes in the adult studies are not true, or are exaggerated by reverse causality and poor control of dietary confounding, and that the measurements of sedentary time in children contain larger measurement errors than in adults due to greater day-to-day variation (22).

Moreover, a recurring question is whether sedentary time and MVPA are independently associated with cardiometabolic health. Of the prospective studies included, only seven studies mutually adjusted MVPA for sedentary time (8, 22, 164, 188, 189, 194, 196). However, time spent in different PA intensities is co-dependent and difficult to separate statistically (i.e. multi-collinearity). Some even suggest these adjustments could be erroneous, calling for more appropriate analytical methods (224). Replacing 10 minutes of sedentary time with MVPA using isotemporal substitution modelling shows beneficial, but theoretical, associations with WC, SBP, insulin, and triglycerides (225). Similar replacement by light PA does not provide similar associations (225), indicating that change in sedentary time is most beneficial when replaced by higher intensity PA. Hence, the beneficial associations between MVPA and cardiometabolic risk factors are likely independent of time spent sedentary, while associations between sedentary time and cardiometabolic risk are attenuated by MVPA. Therefore, it appears that as long as youth spend a sufficient amount of time in MVPA, the pattern of MVPA (134, 135) and accumulated sedentary time is less important for cardiometabolic health (8, 146).

The main challenge in synthesising the results in the systematic review is that different statistical models are applied. The most common statistical models in prospective studies are the change model and the determinant model (226). The change model consists of the absolute change of outcome associated with the absolute change of exposure. However, this model has been criticised

for using a masked cross-sectional analysis, and bias may arise by not adjusting for baseline values of either exposures or outcomes (226). In the determinant model, a follow-up outcome or change in outcome is regressed on a baseline value, but not all studies adjust for the baseline values of outcome. In the present systematic review, only eight prospective studies applied the determinant model, adjusting for baseline values. We believe that this statistical approach is more appropriate, because the baseline value of the outcome is the strongest confounder in prospective analyses.

Our Study II based on ASK data corroborates with the existing literature; higher intensity PA is inversely associated cardiometabolic risk factors, with no associations observed when sedentary time were modelled as exposure. Baseline PA of at least moderate intensity was inversely associated with HOMA-IR and triglycerides follow-up independent of adiposity and confounding factors, indicating a causal relationship. This is in agreement with previous studies suggesting that most of the variation in the cardiometabolic risk explained by PA seems to be attributed to reductions in fasting insulin and triglycerides (155). Interestingly, the association between VPA and HOMA-IR and triglycerides was attenuated following adjustment for adiposity. This may be explained by low levels of time spent in VPA in children with overweight, with an attenuating effect of adiposity when it is included as a confounder. Hence, the effect of PA might partly be mediated by adiposity (226), implying that the adjustment for WC is overly conservative. However, an ICAD study examining if adiposity mediates the associations between PA and cardiometabolic risk factors found a more beneficial cardiometabolic risk profile among children achieving 60 minutes of MVPA daily, and the associations was mainly explained by the direct effects of PA (14). The specific mechanisms of how PA affects cardiometabolic risk factors are mainly derived from exercise studies in adults. Physical activity of at least moderate intensity influences a range of biological mechanisms, which may acutely affect cardiometabolic risk profiles without influencing adiposity (227). An acute effect of PA is improved insulin action and glucose transport by increased GLUT4-translocation to the cell membrane (228, 229). However, the total GLUT4-translocation does not necessarily differ between intensities of PA, although this has been hypothesised (230). Exercise at approximately 40% and 80% VO_{2peak} , with total work equal increased GLUT4 mRNA and GLUT4 protein in human skeletal muscle to a similar extent, despite differences in exercise intensity and duration (231). Such findings are indicated by other studies where no differences in postprandial glycaemia or insulinaemia were found as a result of exercise intensities between ~55% and 90% of maximal oxygen consumption (232, 233). This means that exercise of an intensity that does not increase aerobic capacity *per se* can have important glycaemia lowering effects, which is highly relevant for our findings. Nonetheless, exercise training remains the most potent stimulus to increase skeletal muscle GLUT4 expression (230). In contrast, triglyceride reductions by PA occur after 18–24 hours, and the effects appear to increase with higher

intensity (234). Muscular activity also increases blood flow and oxygen supply through increased density of capillaries and vasodilatation by nitric oxide, hence improving fat metabolism (235, 236).

Study III: Does CRF moderate the prospective association between physical activity and cardiometabolic risk?

We found a moderation by CRF between overall PA and time spent in at least moderate intensity PA with cardiometabolic outcomes. In children with low CRF (below the median split), both MVPA and VPA predict lower HOMA-IR and clustered cardiometabolic risk. These associations were not observed in high fit children. There were no moderating effects of CRF between sedentary time and cardiometabolic outcomes. The public health impact of such findings are that the beneficial effects of PA are independent of CRF, and children with lower CRF could obtain similar health benefits from PA as those children with high CRF.

We are only aware of one study examining whether CRF modifies the relationship between PA and clustered cardiometabolic risk (155). In line with our findings, a significant interaction between CRF and overall PA was found, suggesting a stronger relationship between PA and clustered cardiometabolic risk in children with low CRF (155). Our observations extend these previous observations (155) by examining intensity-specific PA in a prospective design. Previous studies have shown that the association between PA and cardiometabolic risk appears to be independent of adiposity, while adiposity may mediate the association between CRF and cardiometabolic risk (39, 237). Other studies indicate that adolescents with higher amounts of body fat might benefit most from increased time spent in VPA in relation to HOMA-IR (238). Similarly, we found that overall PA and MVPA could lead to beneficial changes in HOMA-IR independent of adiposity in less fit children. The mechanisms of why PA, especially higher intensity PA, is more strongly associated with cardiometabolic risk in low fit children may be due to the short-term effects of PA. For example, insulin levels are more sensitive to acute changes in PA than adiposity (239), and the main independent pathway between PA and insulin levels is likely due to an effect on muscle tissue (240). Thus, engaging in PA, and especially MVPA, increases muscle contraction and blood flow, which in turn enhances glucose uptake via glucose transporter GLUT4 in the muscles, and thereafter affects insulin levels (230, 241). However, PA may also act by increasing lean body mass and concomitantly reducing body fat indirectly (242).

On the other hand, CRF is based on the ability of the circulatory and respiratory systems to supply fuel during sustained PA, and includes more stable physiological traits (i.e. higher resting energy expenditure, increased capillary density, specific muscle characteristics). The traits included by CRF also benefit cardiometabolic health (39), and may be more pronounced in high fit children. We did

not observe any effect modification of CRF when modelling the prospective association between PA variables and the non-obesity clustered cardiometabolic risk score. This may be explained by lack of power (interaction terms $P < 0.08$) or the confounding effect of abdominal adiposity when WC was modelled as a confounder rather than included in the clustered cardiometabolic risk. Indeed, abdominal adiposity is a strong determinant of cardiometabolic risk in healthy children (243), and public health interventions should aim at both increasing PA of at least moderate intensity and reducing abdominal adiposity (237).

The estimated VO_{2peak} was high compared to similar populations, and the low fit group in our sample might be relatively fit. Previous data suggests that VO_{2peak} is high in Norwegian children (173), and especially children from the region where the present study was conducted (244). In addition, Norwegian children have higher PA levels when compared to other populations (15). There has been suggested CRF cut points associated with cardiometabolic risk in children and adolescents that could have been useful for Study III instead of using the median split (245). However, but these CRF cut points have two important limitations: 1) they do not account for the age-related development of VO_{2peak} , which is a main feature during childhood growth and development, and 2) VO_{2peak} were in most studies estimated from indirect performance measures. When defining the Andersen test results in the present study according to the cut points of 41.8–47.0 mL/kg/minute (boys) and 34.6–39.5 mL/kg/minute (girls) suggested by Ruiz et al. (245), this would correspond to cut points of approximately 530–660 meters in boys and 365–475 meters in girls. In our sample, only eight boys were then classified ‘at risk’ (ran shorter than 660 meters), and none of the girls were classified ‘at risk’ (ran shorter than 475 meters). The suggested CRF standards might be population specific, and therefore not appropriate to use in our sample. However, despite the high CRF levels in Study III, it is unlikely this influences the validity of our findings and the main conclusions.

The relationship between CRF and PA is not linear, and a ceiling effect might be present for the high fit children. There are also considerable individual differences in the response to regular PA, at least in terms of risk factor changes, even when all individuals of an exercising group are exposed to the same volume of PA adjusted for their own tolerance levels (246). These aspects, rather than genetic predisposition, could partly explain the effect modification by CRF. Although the heritability for CRF is $> 50\%$ (154), CRF is also a surrogate measure of PA levels during the last three to six months, and high intensity PA is needed to increase CRF (246). In contrast, children’s habitual PA shows a weak correlation with CRF (39). Some PA interventions in healthy children successfully manage to increase CRF and subsequently affect favourable changes in cardiometabolic outcomes (185, 244). Therefore, the favourable effects on cardiometabolic risk might be explained by an increase in daily high-intensity PA, rather than higher CRF *per se*, or a combination of both.

Repeated measures of PA by accelerometers in the same individuals suggest substantial intra-individual variability with an intra-class correlation coefficient (ICC) of about 0.5, which indicates that there is substantial instability in PA over time (247). The low ICC for PA affects the direction of associations between exposures and outcomes measures. The different degree of measurement error is problematic, and attenuates the true relationship between the exposure and the outcome(s) (248). When the more imprecise variable is modelled as the outcome, the magnitude of effect is estimated accurately, but with wider CIs. In contrast, when the more imprecise variable is modelled as the exposure it tends to attenuate the regression coefficient (248). Our analyses and results will suffer from regression dilution bias as CRF or adiposity that takes months or years to change is a more stable trait compared to PA, which prone to acute changes within hours and days. In contrast to the ICC of PA, CRF measured by the Andersen test has an ICC of 0.84 (63). It is therefore not surprising that many studies have suggested that CRF is more strongly associated with cardiometabolic health outcomes (153). However, due to regression dilution bias, the associations for PA are probably stronger than those observed; it is therefore difficult to judge the true relative importance of PA over CRF (155), as the association between PA and cardiometabolic health are likely underestimated.

Study IV: Is the prospective association between sedentary time, physical activity and adiposity bi-directional?

During seven months follow-up, either time spent sedentary or any PA exposure predicted lower BMI or WC, but baseline MVPA and VPA predicted lower skinfolds in boys. All measures of adiposity at baseline (BMI, WC and skinfolds) predicted lower overall PA, MVPA, and VPA in boys. The association between baseline skinfolds and lower VPA at follow-up were also observed in girls. All baseline adiposity measures predicted higher sedentary time at follow-up in both sex.

These findings corroborate with the previous studies examining bi-directional associations between PA, sedentary time and adiposity. Kwon et al. (249) and Metcalf et al. (28) measured adiposity as body fat (%) using DEXA in children aged 5 to 11, and found that adiposity levels may be a determinant of lower PA levels, but not vice versa. Metcalf et al. (28) also examined associations using BMI and WC as exposure variables, but the associations were weaker and non-significant using BMI and WC. However, an ICAD meta-analysis found that MVPA and sedentary time were not associated with WC at follow-up, but a higher WC at baseline predicted higher amounts of sedentary time at two years follow-up (23). Lastly, a higher fat mass index at baseline was associated with lower PA and higher sedentary time in a sample of Danish 10 year olds during six months follow-up (26). These studies imply that PA and sedentary time does not predict change in adiposity – but rather

supports the hypothesis that the association between PA, sedentary time, and weight gain could be in the opposite direction.

However, it is difficult to directly compare results from previous studies due to differences in follow-up duration (months versus years) and different anthropometric assessment methods aggravate comparisons. For example, DEXA distinguishes fat mass from lean tissue and provide a measure of total fat mass and body fat percentage. Body mass index does not make the distinction, which is crucial because PA could readily increase lean tissue. Two prospective studies using an isothermal substitution modelling approach found different magnitude of associations between PA and adiposity. There were no prospective associations with BMI when substituting sedentary time (10 minutes) with VPA (250), while replacing sedentary time (30 minutes) with an equal amount of time in MVPA were associated with a favourable body composition by DEXA in children (251). Moreover, improvements in skinfold have been observed in school-based PA interventions, without similar reductions in BMI (252). Thus, the lack of distinction between fat mass and lean body mass in the present study could explain why the observed associations between PA and BMI were weaker than those between PA and skinfolds (28), likely due to different degree of measurement precision of adiposity.

In contrast to previous studies, the present study observe interactions by sex. These findings could be explained by that obese boys are less active than non-obese boys (253). Moreover, PA is found to be progressively lower across the weight spectrum in boys (254), while PA was consistently low across all weight categories in girls (254). As boys have a higher PA levels than girls (15) a possible effect of regression-to-the-mean phenomenon could be present. Those with high levels of baseline PA can potentially experience a large decrease in PA levels compared with those starting with lower PA levels (124), and so are likely to be greater in boys than in girls (129). However, the possibility of a bi-directional association is plausible. Children with overweight and obesity favour participation in sedentary behaviours (141), and consistently engage in less overall PA and MVPA (15, 255). A study using the Mendelian Randomisation (MR) approach to infer causality suggested that increasing adiposity (BMI and fat mass index) led to a reduction in overall PA and MVPA, and increase in sedentary time in 11 year old children, but they were not able to exclude that low PA may also lead to increases in adiposity (256). A recent study with similar MR approach, found that BMI may have a causal influence on sedentary time, but not on total PA or MVPA at age 3 (257).

In a broader perspective, it is suggested that motor skill competence in early childhood is a critically, yet underestimated, causal mechanism partially responsible for physical inactivity (258). Motor skills is an important determinant of PA (259); thus, poorer fundamental movement skills in children with

overweight and obesity compared to their normal-weight counterparts might influence their PA levels negatively (260). Even self-efficacy may influence PA levels; children with obesity is less confident in their ability to overcome barriers to PA, ask parents to provide opportunities for PA, and choose physically active pursuits over sedentary ones (261).

It is a common belief that the secular and longitudinal PA declines with increasing sedentary time largely contributes to childhood overweight and obesity rates. However, our findings do not support this assumption. This does not mean that PA is a useless strategy combating childhood overweight and obesity, but underscores the difference between preventing weight gain and achieve weight loss (163). Indeed, PA is important for various health outcomes beyond adiposity (11, 23, 25), but PA does not solve the complex health issue of weight loss in children. Overweight and obesity is a result long-term energy imbalance (77), but the impact of PA on body weight is also affected by hormones that acutely suppress (or stimulate) food intake, and the integration of these signals influences overall energy balance in a manner that is not yet fully understood (160). As overweight and obesity is established early in life (262), other important determinants and risk factors include birth weight and rapid weight gain during infancy, parental obesity, maternal smoking, breastfeeding, TV-viewing, sleep duration and diet (i.e. sugar consumption) (263, 264). It is difficult to establish a causal association and relative importance between determinants and obesity (263). However, as the rising rates is so severe and sudden, it is likely that environmental factors and not genetics play a greater role. Thus, targeting early life determinants *and* daily PA are cornerstones in the prevention of excessive adiposity in childhood (263, 264).

Methodological considerations

Our findings must be interpreted with the following methodological considerations in mind. First, strengths and limitations specific to the four studies will be presented. Afterwards, methodological considerations regarding accelerometer data, the use of clustered cardiometabolic risk as outcome and implications of our study findings will be discussed.

Study I

The main strength of **Study I** is that the evidence is synthesised from prospective and interventional studies using a comprehensive search strategy with strict inclusion criteria, and differentiated analyses of sedentary time and MVPA. By exclusively including studies with long-term design, biases from cross-sectional studies are removed. Thus, our results are homogenous in both study design and PA measured by accelerometry. To our knowledge, no previous study has examined the association between MVPA and clustered cardiometabolic risk using a meta-analytical approach. However, some limitations need to be mentioned. First, few studies assess health indicators other

than adiposity. Additional studies investigating other cardiometabolic risk factors (e.g. blood samples) as outcomes are warranted. Second, the conclusions should be interpreted keeping the short duration of follow-up in mind, as the median follow-up time for prospective studies was 2.8 years and interventions lasted 2.0 years. In relative terms, these periods represent about 10% to 20% of the lifetime of the majority of participants included in these studies.

Study II–IV

The strengths of **Study II–IV** are the objective measurements of PA and sedentary time, a mean of more than six valid days of PA monitoring at baseline, a cardiometabolic risk profile and anthropometry at two time points. Further, we have adjusted for important confounders such as the baseline value of the outcome, pubertal stage, and parental SES in a relatively large sample of children. The prospective analyses with baseline adjustments of the outcome are robust, and provide inference of temporality between exposures and outcomes. However, the short time frame between baseline and follow-up raises questions as to whether the observations can be linked to meaningful and lasting effects in either direction, especially for study IV. The temporal association between PA and adiposity *before* the baseline measurements is unknown. Hence, the associations between baseline sedentary time, PA and adiposity at follow-up could be evident in studies with longer follow-up (163). On the other hand, seven months is a fair amount of time relative to children at age 10 given the rapid biological changes during growth and maturation. Thus, the ‘short-term’ observations could be stronger in magnitude if the study had longer follow-up, and does provide more temporality than cross-sectional data.

As in all observational research, we cannot exclude the possibility that our observations are explained by residual and unmeasured confounding factors. Physical activity levels are shown to vary between seasons and weather patterns, especially in Norway with distinct season characteristics. Weather and season is shown to be an important determinant for PA in younger populations (265). However, weather is not likely to confound our analyses, as weather and season are not logically related to cardiometabolic outcomes, but may indeed introduce error in PA measurements. We did not include any measure of sleep or diet, which may be both predictors and confounders between PA and cardiometabolic outcomes in youth (266). The lack of dietary records are an important aspect missing, especially in Study IV, as energy imbalance is a main determinant of excess body weight and diet quality is linked to a lower prevalence of MetS in adolescents (267). Thus, lifestyle changes in diet *and* PA are recommended to improve body weight and to lower cardiometabolic risk (267). Lastly, the ASK study was carried out in one rural Norwegian county where the majority of the children are Caucasian, and the generalisation of our results to other populations are limited.

Study II–IV include a high number models and analyses, and could be criticised for multiple comparisons that potentially inflate type I error. We did not account for multiple comparisons in our studies. It is debated how multiple comparisons should be handled, and there are advocates for their advantages as well as critics for their disadvantages (268). There are different approaches to handle multiple comparisons, such as the Neyman-Pearson theory or Bonferroni adjustments. However, the Neyman-Pearson theory mainly aids decision-making in repetitive situations, and does not assess evidence in data sets. The Bonferroni method is concerned with the general null hypothesis, which is rarely of interest. Thus, adjustment by the Bonferroni method decreases type I error but inflates type II error, which is no less false. If adjustments of multiple comparisons were made mandatory, it is argued that ‘...cynical researchers would slice their results like salami, publishing one *P*-value at a time...’ (268). Consequently, it could hamper the possibility of conducting large studies with multiple research aims. The best approach is simply describing the methods, discussing the possible interpretations of each result, and drawing a reasonable conclusion without Bonferroni adjustments (268).

In **Study III**, CRF (VO_{2peak}) was estimated indirectly using the Andersen test. However, one should be aware that predicting VO_{2peak} from any running test is problematic. A bias of up to ± 5 ml/kg/minute was found when predicting VO_{2peak} from the Andersen test (62). Nonetheless, validation studies show that the Andersen test appears to be a good measure of CRF (62, 63, 269). Importantly, when comparing the Andersen test and directly measured VO_{2peak} with indicators of cardiometabolic risk in this age group, the Andersen test shows a stronger association with clustered cardiometabolic risk than directly measured VO_{2peak} (269).

Physical activity measured by accelerometry

Accelerometers are indeed a criterion method for measuring intensity-specific PA. Although accelerometers are objective measurements of PA, accelerometer-based prevalence estimates are largely dependent on the investigators’ subjective choice of intensity cut-off points. There exists some consensus in data reduction of accelerometer data, but still discrepancies. For example, MVPA cut points varied from ≥ 760 cpm (201) to ≥ 4012 cpm (194) in Study I, which result in highly different estimates of time spent in MVPA and likely affect the observed associations with health outcomes. Even small differences in accelerometer reduction criteria can have substantial impact on sample size, PA and sedentary estimates outcomes (270). The choice of data reduction impairs the associations between sedentary time, PA and cardiometabolic outcomes, and complicates comparability between studies. However, the Evenson cut-points (176) applied in our studies are based on the vertical axis and cross-validated (177), and widely used in children and adolescents in recent years, for example in the ICAD (271, 272).

The threshold of 100 cpm is commonly used for sedentary time (272), although 200 cpm (22) and 1100 cpm were also applied (191) in the included studies. Choosing a higher cpm for sedentary time is likely to capture sitting *plus* standing (273). Consequently, a higher cpm may misclassify light PA into the sedentary category and increase collinearity with MVPA (274). Moreover, when examining sedentary time as the exposure, the definition of non-wear time is especially important, which is often defined as between 10 to 60 minutes of consecutive zero counts (possibly allowing one or two minutes exceptions). A long non-wear time increases the risk of assessing sedentary time when in fact the monitor is off (overestimation), but a shorter definition misclassifies 'true' sedentary time as if the monitor were off (underestimation). The non-wear time definitions might also differ in sub-groups of children (270). For example, children and adolescents with overweight or obesity might need a longer time of consecutive zero, since they are less active and have a higher time spent sedentary than can be misclassified as non-wear time (271).

One should keep in mind that accelerometers are developed for assessing acceleration, and not lack of acceleration, which is the outcome of the sedentary 'intensity'. An accelerometer cannot discriminate between sedentary activities and non-sedentary activities if no movement is occurring at the body segment where the monitor is attached, and this is most likely the main disadvantage with using a single accelerometer to capture sedentary activities (275). Hence, accelerometers are not necessarily an appropriate device for quantifying time spent sedentary. Posture measures (i.e. inclinometers) with accelerometers have received attention as a more suitable measurement method for assessing sedentary time more accurately as they can distinguish between different posture allocations (sitting, lying, standing). However, when examining agreement between ActiGraph accelerometers and posture measures (activPAL) for sedentary time the estimates are comparable when applying the 100 cpm cut point (273). Nonetheless, more precise measurement methods of sedentary behaviours are indeed warranted.

Another challenge is how many days of monitoring are needed to reflect an individual's usual or habitual level of PA. Children and adolescents require a higher number of monitoring days than adults. Reliable estimates of PA in adults are achieved with between three and five days of monitoring, while days needed to achieve a reliability of 0.80 in children range from four to nine (46). In the present thesis, the included children have an average of six monitoring days. However, based on data from the ASK study, we have previously observed that children's PA levels varied up to ± 1.3 to 1.7 SD units between two measurements, indicating measurement error for all variables (247). Therefore, assessment of PA for a limited number of days might not indicate true activity level, but the error introduced is random; hence, it should not create bias (11). A seven-day approach of PA measurements in children is therefore generally accepted as sufficient (272), but increased

monitoring length and several time points might improve the validity of study conclusions, although it does increase participant burden and possibly affecting compliance (247).

Clustering of cardiometabolic risk factors

The magnitude of associations in terms of practical significance for the clustering of cardiometabolic risk is difficult to interpret. A study examining the utility of different continuous MetS scores in a cohort of younger adults followed from 15 to 25 years found that a 1 SD increase in z-score predicted at least a 30% increase in adult type 2 diabetes (217). In Study II, a 1 SD increase in VPA predicted a 0.06 SD lower clustered cardiometabolic risk over a short time period. Theoretically, if the entire risk reduction was due to a single individual risk factor, a 10-minute increase in VPA predicted a reduction in WC or SBP of 0.05 cm and 0.05 mmHg, respectively. Further, not meeting 60 minutes of MVPA daily as recommended predicted a 0.51 cm higher WC and 0.54 mmHg higher SBP. A previous study that found that a 10-minute difference in children's MVPA was associated with approximately 0.5 cm difference in WC (23), with more substantial results from the combined analyses. Waist circumference differed by as much as 5.6 cm between those in the top tertiles for MVPA (>35 minutes per day) compared with those in the bottom tertile (<18 minutes per day) even when combined with time spent sedentary tertiles (23). If these observed persists into adulthood, it may confer considerable health risks. For example, every 5 cm increase in WC is associated with an increased relative risk of 17%, and a 13% increase for all-cause mortality in men and women, respectively (276). Therefore, small differences between different PA groups observed in healthy children may translate to large differences when the children are older.

Applying a continuous cardiometabolic risk score as an indicator for adverse health has its clear advantages when compared to the aforementioned MetS definitions. Applying a continuously distributed score is more sensitive and less susceptible to errors than dichotomous approaches and maximises statistical power (277). However, the cluster approach could also be criticised: it may obscure and underestimate the true associations between PA, CRF, and the individual cardiometabolic risk factors, and is based on the assumption that each component is equally weighted in predicting future disease progression (149). Similar with the present definition for MetS, there exists no agreement regarding which and how many risk factors should be included nor the degree to how they should be weighted. Using a cluster approach is also sample-specific and depends on the sample from which it was derived, making it difficult to compare between studies (97, 149). The children 'at risk' in this thesis might not be 'at risk' when compared to other populations (i.e. urban populations, other countries or ethnicities); however, this is only true if the mean and SD from the specific population are used when variables are standardised. Thus, approaches have been made to construct age-adjusted z-scores for each risk factor based on

common means and SDs, and to define a cut-off point in the mean of summarised z-scores (97). Such harmonised approach could reduce misclassification of children as 'at risk', and enhance comparison between studies, ultimately providing estimates that are more precise and improve surveillance of cardiometabolic health over time.

Implications

In epidemiology, primary prevention is promised as the most effective strategy for public health, but different perspectives regarding the effectiveness of prevention exist. Rose (278) outlined the advantages and disadvantages of 'high risk' and 'population prevention strategy'. If we aim for 'high risk' prevention approach based on our findings, we should identify and intervene in children with low MVPA levels who have clustering of cardiometabolic risk factors and those with overweight and obesity. Children with overweight are at a higher risk of overweight in adulthood (279, 280); hence, intervening in subgroups of 'high risk' children should be effective. Childhood is a time when adverse cardiometabolic development most likely are reversible, and the 'high risk' approach is cost-effective, and benefits those individuals most in need. On the contrary, 70% of adults with obesity were not obese in their youth (279). The preventive actions targeting children 'at risk' will therefore not prevent the majority of disease in the population (278). Likewise, we do not know whether children with clustering of cardiometabolic risk will develop disease later in life, although clustering of cardiometabolic risk tracks into adolescence (218) and young adulthood (281). These aspects argues for a population prevention strategy being a 'preventive measure that brings much benefit to the population, but little to each participating individual' (278), although both 'high risk' and 'population prevention' strategies are needed in the effort to prevent poor health (278).

A population prevention strategy that receives agreement within this field of research is approaching schools as a prevention arena. This rationale is commonly based an ecological approach, as a child's behaviour is a consequence of the context and setting in which they live, learn, work, and play (282). Another important aspect is the possibility to reach the population of interest without having to stigmatise or discriminate subgroups by SES or body weight (252). The majority of children attend school, which leaves an extraordinary window of opportunity for PA initiatives (282). Paradoxically, school is a sedentary setting, and it is plausible that increasing sedentary time during adolescence is due to more demanding school and academic requirements (123). Several school-based PA interventions fail to increase PA significantly (1, 102, 203), and there are discrepancies as to whether these initiatives addressing challenges of physical inactivity are effective or not. Importantly, successful PA interventions are difficult to conduct given the long time it takes to influence some health outcomes (i.e., obesity and achieve weight loss), combined with issues of loss of follow-up and adherence to changes in PA behaviour or simply because their control groups are too active (213).

Despite these shortcomings and discrepancies, school-based PA interventions are considered the most effective strategy for increasing overall PA in youth (252). School-based PA interventions are suitable for all children, at risk or not, given the well-documented health benefits that children derive from PA (24, 133) and the number of hours that children spend at school. Increasing PA initiatives during school time seems therefore justifiable. On the opposite, schools represents only half of children and adolescents time awake, and there are other important PA domains. Some hypothesise that changes in transport (active to passive) could be a cause of increased sedentary time in youth (125). There is consistent evidence that children who actively commute to obtain higher PA levels at all intensities, than those who travel with motorised transport (283, 284). Children and adolescents who actively commute to school are spending more time in MVPA throughout the whole day (285), but also have reduced BMI (286) and improved cardiometabolic health (287). Simply being outdoors increases PA and reduces sedentary time (288), and each additional hour spent outdoors is associated with higher MVPA levels (289). Thus, facilitating for active transport, leisure time activities and safe local environments represents relevant initiatives in combating physical inactivity. Population prevention strategies should focus on long-term interventions that target multiple aspects of life (school, family and community), possibly inducing differences in PA levels and improving children's overall health (290).

Future research

To advance the knowledge of sedentary time and PA in young populations, we need long-term studies starting as early in life with multiple measurements of both exposures and outcomes including important covariates and confounders (diet, SES, puberty). This would allow additional modelling of the complex longitudinal relationships between intensity, domain and amount of sedentary time and PA with cardiometabolic health (22, 222). Moreover, accurate PA measurements and statistical techniques that can adequately examine the independent associations between sedentary time and the different PA intensities are warranted.

CONCLUSIONS

Study I: No evidence was found for a prospective association between sedentary time and cardiometabolic risk factors in youth. On the other hand, the evidence for a prospective association between MVPA and *clustering* of cardiometabolic risk factors is consistent, inverse, and supported by the meta-analyses. As long as youth spend sufficient time in MVPA, being sedentary causes little harm to cardiometabolic health. To advance the knowledge of independent associations of intensity-specific PA with cardiometabolic health, it is necessary to conduct long-term studies with multiple measurements including important confounders (SES, diet, and puberty).

Study II: The results extend previous observations in Study I: sedentary time is unrelated to individual cardiometabolic risk factors and clustered cardiometabolic risk. In opposite, PA of at least moderate intensity appears to be prospectively related to triglycerides, HOMA-IR, and clustered cardiometabolic risk. However, the association between MVPA and clustering of cardiometabolic risk factor are possibly confounded or mediated by adiposity.

Study III: CRF moderated the prospective association between PA and clustered cardiometabolic risk. This moderation was most pronounced for HOMA-IR, and independent of adiposity. The magnitude of association between MVPA, HOMA-IR, and clustered cardiometabolic risk was stronger in children with low CRF, with no associations appeared present in their high fit peers. Therefore, increasing time spent in MVPA is especially important for children with low CRF.

Study IV: Time spent sedentary does not predict any of the examined adiposity measures, while PA of at least moderate intensity predict lower skinfolds in boys. On the opposite, all adiposity measured predict higher sedentary time, while skinfolds predicts lower VPA. However, BMI and WC predicts lower overall PA, MVPA and VPA in boys only. Being sufficiently active (≥ 60 minutes MVPA per day) does not predict lower adiposity, while being overweight or obese predicts lower PA but not higher sedentary time in both sexes. Preventing accumulation of excess adiposity early in life might be important for sufficient PA levels in children.

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STUDY I

1 **Summary**

2 Sedentary pursuits and moderate-to-vigorous physical activity (MVPA) may be uniquely
3 related to cardiometabolic health. Excessive sedentary time is suggested as an independent
4 cardiometabolic risk factor, while MVPA is favourably associated with cardiometabolic
5 health. This systematic review and meta-analysis summarises the evidence on a prospective
6 relationship between objectively measured sedentary time, MVPA, and cardiometabolic
7 health indicators in youth.

8 PubMed, Embase, CINAHL, PhyscINFO, and SPORTDiscus were systematically searched
9 from January 2000 until April 2018. Studies were included if sedentary time and physical
10 activity were measured objectively and examined associations with body mass index, waist
11 circumference, triglycerides, high-density lipoprotein, insulin, blood pressure or the clustering
12 of these cardiometabolic risk factors.

13 We identified 30 studies, of which 21 were of high quality. No evidence was found for an
14 association between sedentary time and cardiometabolic outcomes. The association between
15 MVPA and individual cardiometabolic risk factors was inconsistent. The meta-analysis for
16 prospective studies found a small but significant effect size between MVPA at baseline and
17 clustered cardiometabolic risk at follow-up (ES -0.014 [95% CI, -0.024 to -0.004]). It can be
18 concluded that the prospective association between sedentary time and cardiometabolic health
19 is non-significant, while MVPA is beneficially associated with cardiometabolic health in
20 youth.

1 Introduction

2 Children and adolescents should accumulate at least 60 minutes of moderate-to-vigorous
3 physical activity (MVPA) daily to achieve optimal health benefits (1), but a large proportion
4 of youth do not meet these recommendations (2). Children are more active than adolescents;
5 however, physical activity (PA) consistently declines with age (2) while sedentary time
6 increases (3, 4). Consequently, sedentary time is suggested as an independent risk factor for
7 cardiometabolic health (5). However, the majority of studies linking sedentary time to adverse
8 cardiometabolic health in youth are cross-sectional and quantify sedentary time as screen time
9 (6). Television and screen time are confounded by dietary habits (7) and provide only a partial
10 picture of overall sedentary time (8); they are therefore a poor measure (9). Moreover,
11 objectively measured PA suggests that youth can be highly sedentary and sufficiently active
12 on the same day (10). Therefore, being sedentary *per se* may not directly affect
13 cardiometabolic health (5), and it is uncertain whether excessive sedentary time represents a
14 risk factor.

15 The prospective associations between sedentary time, PA, and cardiometabolic health in
16 youth have been extensively reviewed (4, 11-15). These reviews conclude that overall PA
17 may elicit a long-term beneficial effect on adiposity and some cardiometabolic health
18 indicators (12, 13) but is not necessarily the main predictor of adiposity in youth (15).
19 Furthermore, the evidence for a relationship between sedentary time and cardiometabolic
20 health or adiposity is unconvincing (4, 11, 14). Considering that high intensity PA produces
21 stronger associations with cardiometabolic health than overall PA (16-19), the
22 aforementioned reviews are limited by their failure to examine the independent associations
23 of objectively measured sedentary time and MVPA with cardiometabolic health, and fail to
24 include clustering of cardiometabolic risk factors as outcome. There have been an increasing
25 number of prospective studies using objective measurement of PA; thus, it is timely to

1 summarise the evidence for any association between sedentary time, MVPA, and
2 cardiometabolic health in youth.

3 **Methods**

4 Following the PRISMA-P 2015 guidelines (20, 21), five electronic databases (PubMed,
5 Embase, CINAHL, PhyscINFO, and SPORTDiscus) were searched from January 1, 2000
6 until November 10, 2016. The search was last updated for April 1, 2018, with no additional
7 studies found. The search aimed to identify intervention and prospective observational cohort
8 studies that were both published in peer-reviewed English-language journals and examined
9 the association between objectively measured sedentary time, MVPA, and cardiometabolic
10 outcomes in youth. The protocol was published in PROSPERO in November 2016 under
11 registration number CRD42016048860 and adhered to the preferred reporting items of the
12 PRISMA-P checklist (22).

13 **Study inclusion criteria and search strategy**

14 The search included four principal elements, which are described in detail in Table 1.

15 *Population:* Children and adolescents aged 6–18 years between baseline and follow-up from
16 populations without any diseases or disabilities except for the metabolic syndrome, type 2
17 diabetes, and populations with overweight or obesity.

18 *Exposure:* Objectively measured sedentary time and/or MVPA.

19 *Outcomes:* Waist circumference (WC); body mass index (BMI); blood pressure (BP); high-
20 density lipoprotein cholesterol (HDL); the ratio of total cholesterol and HDL (TC:HDL);
21 triglycerides (TG); fasting insulin, or the homeostasis model assessment for insulin resistance
22 (HOMA-IR); and/or cardiometabolic risk factors reported as a clustered score standardised by
23 age and sex.

1 *Study Design:* Longitudinal, observational prospective cohort, randomised controlled trials
2 (RCT), and intervention designs. The minimum study length was set to 6 months, and the
3 number of participants in each study was ≥ 50 .

4 Study selection

5 Two independent reviewers (TS, JS-J) reviewed the titles and abstracts of all included studies.
6 A third reviewer (GKR) contributed to the inclusion of full-text studies. Any disagreements
7 were discussed amongst all three reviewers, and reasons for exclusions were recorded. The
8 reference lists of included studies from the full-text review were scanned for studies that
9 could meet the inclusion criteria (backward tracking). Finally, a citation search was performed
10 to identify studies that cited the included studies (forward tracking).

11 Data Extraction

12 One researcher (TS) performed data extraction after the full-text phase. The following
13 information was extracted: study design, population characteristics (country, sex, age,
14 included/excluded participants, participation rate), measurement of PA including its data
15 reduction (cut points, epoch, non-wear time, wear time in terms of days or hours, examined
16 cardiometabolic risk factors, covariates included in the analyses (e.g., puberty, socio-
17 economic status, diet), performed statistical analyses, and main results.

18 Assessment of methodological quality

19 The quality of evidence was assessed by quality criteria adapted from existing tools (23-25).
20 The methodological quality list contains 13 items categorised in four dimensions: 1) study
21 population and participation, 2) study attrition, 3) data collection, and 4) data analyses. The
22 items distinguish between informativeness (four items) and validity/precision (eight items).
23 The criteria had a 'yes' (+), 'no' (-), or 'unclear' (?) answer format. If the study referred to
24 another publication describing the design or other relevant information about the study, the

1 publication was retrieved. For each study, a total methodological quality score was calculated
2 by counting the number of items scored positively on the validity/precision (V/P) criterion
3 and dividing that number by the total number of V/P criteria. If a study scored at least 0.75
4 (75%), the study was considered to be of high methodological quality. Studies scoring lower
5 than 0.75 were considered to be of low methodological quality. The quality score did not
6 exclude any studies from the review. One researcher (TS) conducted the quality scoring,
7 which was thereafter re-examined by two of the co-authors (Table 2 and 5).

8 Level of scientific evidence

9 Results for each outcome were coded using the approach first employed by Sallis et al. (26)
10 and subsequently applied to observational and prospective studies examining associations
11 with health (11). Results were classified as having ‘no evidence’ if 0–33% of studies reported
12 a significant association. If 34–59% of studies reported a significant association, or if fewer
13 than five studies reported results for the specific outcome, the result was classified as being
14 ‘inconsistent’. If $\geq 60\%$ of studies found a significant association, the result was classified as
15 ‘positive/adverse’ or ‘negative/inverse’, depending on the direction of the association, which
16 was defined by significance ($P < 0.05$). Notably, the scientific evidence coding was
17 performed amongst only studies considered of high quality (Table 6).

18 Meta-analysis

19 The studies were heterogeneous in their measurements of exposures. Few studies had two
20 measurement points of both sedentary time, PA, and blood-based outcomes, and none of the
21 outcomes were reported in \geq five studies using the same analytical approach with outcomes
22 expressed in the same units. Thus, statistical pooling was not possible for most outcomes, but
23 these researchers aimed to meta-analyse the association between MVPA and clustered
24 cardiometabolic risk from three prospective observational studies (17, 27, 28) and three

1 intervention/follow-up studies (29-31). The authors of one of the prospective studies was
2 contacted (27) to reanalyse their data in a similar fashion. The meta-analysis was conducted
3 using random effects models with unstandardised regression coefficients and 95% confidence
4 intervals (CI). Analyses were performed in Stata/SE 13.1 for Windows.

5 Results

6 The initial search identified 5,733 studies (Figure 1). After removal of duplicates, 4,599
7 studies were retrieved. After title review, 172 studies were assessed for abstract review. Sixty-
8 eight studies met the inclusion criteria and were eligible for full-text screening and data
9 extraction. In this process, eight additional studies were identified from the reference lists, and
10 one study was in press and nominated for inclusion by collaborators. After the full-text phase,
11 30 studies were included and eligible for evidence synthesis and quality scoring. Twenty-one
12 studies were prospective, seven studies were interventions or trials, and two studies were
13 long-term follow-ups of previous intervention studies.

14 Sample characteristics

15 Tables 3 and 4 present study characteristics and results sorted by outcomes. Table 3 gives an
16 overview of the prospective studies. Studies were conducted in North America ($n = 4$),
17 Australia ($n = 1$), and Europe ($n = 16$). In total, the prospective studies comprised 32,036
18 participants. Study populations ranged from 120 to 6,497 with participants aged 4.9 to 18.0.
19 The median follow-up time was 2.8 years. Table 4 depicts a summary of the seven
20 intervention studies and the two long-term follow-ups of previous interventions. The studies
21 were conducted in North America ($n = 1$), Australia ($n = 1$), Europe ($n = 6$), and South
22 America ($n = 1$). Study populations ranged from 88 to 1,527, with participants aged 6.8 to
23 14.0 years. The median study follow-up time was 2.0 years. The intervention studies

1 comprised 5,764 participants. Table 2 lists the quality of informativeness and the V/P for all
2 studies. Of the 30 included studies, 21 were categorised as high quality (Table 5).

3 Adiposity

4 One observational longitudinal study found that an increased time spent sedentary predicted
5 changes in BMI from age 9 to 15 that were independent of MVPA (32). At the 90th BMI
6 percentile, an additional hour spent sedentary per day was associated with a 0.84 unit increase
7 in BMI. Similar but weaker findings were observed at the 75th and 50th BMI percentiles (32).
8 In general, studies examining the prospective associations between sedentary time and
9 adiposity reported no evidence for any association (16, 27, 28, 33-38). Two studies found that
10 sedentary time predicted lower BMI (17) and WC (39), even after adjustment of MVPA.
11 Activity of at least moderate intensity was inversely associated with BMI (36, 38, 40, 41) and
12 WC (18, 39). Similarly, a declining MVPA was associated with increased BMI during two
13 years of follow-up (35). However, differences between boys and girls were present, as an
14 inverse association was evident between vigorous PA and WC in boys only (18). Moreover,
15 boys not meeting the threshold of 20 minutes of vigorous PA at baseline had an increased risk
16 for overweight 2 years later (OR = 4.14) (37). However, half of the studies found no
17 significant prospective associations between MVPA at baseline and BMI (42, 43) or WC (16,
18 27, 28, 33, 40, 42) in models that were ultimately adjusted.

19 No intervention study reported the *effect* of sedentary time on adiposity. For MVPA, three of
20 seven intervention studies reported a beneficial development in BMI (30, 44) and WC (45) in
21 the intervention group. By the end of a non-randomised intervention, Gorely et al. (44)
22 observed that children in the intervention schools performed 20 minutes more MVPA per day,
23 which was associated with a lower increase in BMI than was observed in the control group
24 (0.4 vs 0.9 BMI units per year of age). In the KISS study, lower BMI at follow-up was
25 observed in the intervention group (30). However, the favourable changes in BMI that were

1 reported by Gorely et al. (44) and Kriemler et al. (30) were not sustained at 1.5 and 3-year
2 follow-ups respectively (31, 46). Two intervention studies and two cluster RCTs found no
3 effect for MVPA on BMI (29, 47-49). Notably, these intervention studies did not induce
4 significant differences in MVPA between intervention and control groups, except for
5 Donnelly et al. (48). However, objective measurement of PA was only assessed in a sub-
6 sample ($n = 167$). As summarised in Table 6, there was no evidence for a prospective
7 association between total sedentary time and adiposity. The evidence for a prospective
8 association between MVPA and adiposity was inconsistent.

9 Blood Pressure

10 Three studies found no associations between baseline sedentary time and BP at follow-up (17,
11 27, 28), but one study reported an independent and beneficial association between both
12 sedentary time and MVPA with follow-up SBP (39). Stamatakis et al. (17) observed an
13 inverse association between MVPA and SBP, but that association was attenuated by
14 adjustment of important covariates and baseline value of SBP, which corresponded with the
15 four other studies reporting no prospective associations (17, 27, 28, 50). However, some
16 studies observed inverse associations in boys; Carson et al. (18) reported a dose-response
17 association across quartiles of baseline vigorous PA (Q1: 1.3 min/day vs Q4: 8.0 min/day)
18 with follow-up SBP. The EarlyBird cohort found that number of minutes spent ≥ 3 METs
19 were associated with lower mean arterial BP (MAP) in boys from ages 5 to 8 (42). From the
20 same cohort, diastolic BP (DBP) were marginally lower in active boys (≥ 50 minutes MVPA
21 per day) when compared with those that were less active throughout adolescence (age 9 to 16)
22 (51). Similarly, one study observed a favourable but non-significant effect on SBP in the
23 intervention group between baseline and post-intervention (29). However, at the 4-year
24 follow-up, the intervention boys had a smaller increase in SBP compared with the control
25 boys (29). The remaining intervention studies found no effect of MVPA on SBP or DBP (30,

1 31, 45). Taken together, there was no evidence for a prospective association between
2 sedentary time and BP, while the evidence appeared inconsistent for MVPA and BP (Table
3 6).

4 Biochemical variables

5 One prospective study found that sedentary time was associated with unfavourable changes in
6 HOMA-IR, but not independent of MVPA (27). Three studies reported no associations
7 between sedentary time and HOMA-IR (17, 28, 39). In contrast, MVPA was associated with
8 lower insulin/HOMA-IR in four studies (17, 27, 28, 39). Moreover, baseline MVPA (≥ 38.7
9 min per day) had a protective effect on the development of HOMA-IR 2 years later in a large
10 European cohort (52). In a follow-up from age 9 to 16, children in the more active groups
11 (boys: ≥ 50 minutes MVPA per day, girls: ≥ 35 minutes MVPA per day) attenuated the mid-
12 adolescent peak in HOMA-IR compared to the less active group, independent of body fat
13 percentage and pubertal status (51). However, at age 16 there were no differences between the
14 activity groups (51). Similarly, an Estonian study ($n = 120$) found no association between
15 MVPA and HOMA-IR in boys (53). One intervention study observed an effect of MVPA on
16 HOMA-IR in boys in the intervention group, but the effect did not persist to long-term
17 follow-up (29). Seabra et al. (45) did not observe any effect of MVPA on HOMA-IR.

18 One study reported an inverse association between sedentary time and HDL, independent of
19 MVPA (27), with no relationship observed between sedentary time and HDL in three studies
20 (17, 28, 39). Three of six studies concluded that MVPA was prospectively associated with
21 higher HDL/TC:HDL levels (17, 27, 39). Similarly, time spent in MVPA predicted lower TG
22 during 6 to 9 months of follow-up (27, 28, 39). However, associations between MVPA and
23 HDL that were independent of sedentary time were found in only one of these studies, but not
24 for TG (27). Conversely, the largest observational prospective study did not observe any
25 association between MVPA and TG (17). Two studies from the EarlyBird cohort found that

1 TG levels in more active girls (above median) were lower than in less active girls between
2 ages 5 and 8 (42); this effect also persisted throughout adolescence (51). Physical activity
3 intervention effects on HDL and TG were reported by Kriemler et al. (30), while Bugge et al.
4 (29) and Seabra et al. (45) did not observe any intervention effect on HDL/TC:HDL or TG.

5 Sedentary time was unrelated to clustered cardiometabolic risk in prospective observational
6 studies (17, 28), even when accounting for MVPA, sleep, and adiposity (27). In contrast, one
7 study observed an unexpected beneficial association between sedentary time and clustered
8 cardiometabolic risk, independent of MVPA (39). However, all studies examining MVPA and
9 clustered cardiometabolic risk found inverse associations (17, 27, 28, 39, 42), suggesting that
10 those with higher levels of MVPA had a favourable cardiometabolic risk profile. Few
11 intervention studies were identified that examined the effect of MVPA on clustered
12 cardiometabolic risk. Kriemler et al. (30) observed an effect of MVPA on the clustered
13 cardiometabolic risk in the intervention group between baseline and follow-up. However, the
14 effect was no longer evident at later follow-up (31). Bugge et al. (29) found no effects of
15 MVPA on clustered cardiometabolic risk at post-intervention or at long-term follow-up. The
16 meta-analyses that examined the relationship between baseline MVPA and clustered
17 cardiometabolic risk at follow-up pooled data of 5,489 participants from five independent
18 samples. The pooled effect for MVPA was small but significant for both prospective (ES –
19 0.014 [95% CI, –0.024 to –0.004]) (Figure 2) and intervention studies (ES –0.137 [95% CI, –
20 0.237 to –0.037]) (Figure 3).

21 In summary, there was no evidence for a prospective association between sedentary time,
22 individual biochemical risk factors, or clustered cardiometabolic risk. The evidence for an
23 association between MVPA and the individual biochemical risk factors was inconsistent.
24 However, a consistent and inverse prospective association was evident for MVPA and
25 *clustered* cardiometabolic risk (Table 6, Figure 2 and Figure 3).

1 Discussion

2 We have summarised the evidence for the prospective relationship between sedentary time,
3 MVPA, and cardiometabolic risk factors in youth. Thirty studies have been systematically
4 reviewed. First, the evidence for an association between sedentary time and cardiometabolic
5 risk factors is inconsistent, which is in line with the conclusions of previous systematic
6 reviews and meta-analyses (11, 14, 16, 23, 54). Second, the evidence for a prospective
7 association between MVPA and individual cardiometabolic risk factors is inconsistent.
8 However, MVPA is consistently and inversely associated with *clustered* cardiometabolic risk
9 score.

10 No evidence was found for an association between sedentary time and adiposity as well as for
11 inconsistent prospective associations with MVPA. These findings may be explained by the
12 fact that PA, sedentary time (55), and the prevalence of overweight and obesity indicate
13 moderate tracking (24, 56). Moreover, a prospective study found that body composition
14 tracked more strongly than PA, suggesting that PA has limited impact on body composition
15 (57). Thus, overall PA may not be a predictor of adiposity (15), and excessive energy intake
16 may be the major driver of obesity and being overweight in youth. Thus, PA may instead be a
17 moderator that influences the steepness of the adiposity increase (58). Some studies suggest
18 that the prospective association between sedentary time, MVPA, and adiposity is more
19 apparent in children with overweight or obesity, or amongst those at risk for being overweight
20 or obesity (32, 59). However, Trinh et al. (38) found that long-term reductions in BMI were
21 small, even with the largest change in MVPA amongst girls that were overweight or obese.
22 BMI children is widely used as an indicator of fatness in children, but is affected by growth
23 and puberty. Additionally, BMI also incorporates fat and lean body mass, which are likely to
24 be influenced by PA in opposite directions. The associations between MVPA and BMI
25 (reduced by a factor of around four) are generally weaker than those between MVPA and the

1 fat mass index calculated using DEXA measurements of body composition (41). Importantly,
2 only three of the seven intervention studies included in this review managed to increase
3 MVPA levels (30, 44, 45), which affects the conclusions on whether MVPA is causally
4 associated with adiposity. Thus, the lack of an intervention effect on MVPA (29, 47, 49), high
5 PA levels in control groups (60), short follow-ups (61), and issues with adherence contribute
6 to the limited intervention effects. Further, two studies reported that effects were lost at long-
7 term follow-ups (31, 46), suggesting that changes in PA behaviour are difficult to sustain after
8 intervention ended. However, adiposity predicts more sedentary time and lower MVPA (62-
9 64), and weight loss itself could hypothetically enhance PA. Therefore, a bi-directional
10 association or reverse causation between sedentary time, PA, and adiposity may also explain
11 the inconsistent associations (65, 66).

12 Sedentary time appears unrelated with BP and has an inconsistent association with MVPA.
13 This does not mean that sedentary time or MVPA is irrelevant for abnormal BP development,
14 but the associations are probably affected by the age-related continuous increase in BP (67).
15 Moreover, the estimated prevalence of hypertension in young populations is uncertain and
16 varies between 1% to 10% (68). However, childhood BP tracks into adulthood (69), and the
17 association between PA and BP may become evident later in life. Thus, MVPA at an early
18 age may have a preventive effect (70).

19 There was no evidence for an association between sedentary time and individual biochemical
20 outcomes, similar to what had been previously reported (14, 23). The prospective association
21 between MVPA and biochemical outcomes was inconsistent. Indeed, it was observed that
22 MVPA had favourable associations with insulin and lipid concentrations, but the low number
23 of high-quality studies examining these associations suggest that these observations should be
24 interpreted with caution. However, meta-analyses suggested a significant but small effect size
25 for an inverse association between baseline MVPA and follow-up clustered cardiometabolic

1 risk. The consistent and inverse associations found in our evidence synthesis support this
2 conclusion. Thus, it is likely that the inclusion of additional high quality studies may have
3 strengthened the observed effects.

4 The lack of association between sedentary time and cardiometabolic health amongst youth
5 could be explained by shorter lifetime exposure (17). Sedentary bouts in children are
6 relatively short (< 20 minutes) (71) and are possibly not extensive enough to have a negative
7 influence on cardiometabolic health. At present, the evidence for the detrimental effect of
8 prolonged or uninterrupted sedentary bouts is limited when accounting for MVPA (11, 23),
9 but few existing prospective studies examine sedentary patterns. A recurring question is
10 whether sedentary time and MVPA are independently associated with cardiometabolic health.
11 Of the prospective studies included, only seven mutually adjusted MVPA for sedentary time
12 (17, 18, 27, 32, 33, 39, 40). However, the quantity of time spent in different PA intensities is
13 co-dependent and difficult to separate statistically (i.e., multicollinearity). Some researchers
14 have even suggested that these adjustments could be erroneous and called for more
15 appropriate analytical methods (72). Nonetheless, the favourable associations between MVPA
16 and cardiometabolic risk factors are likely to be independent of time spent sedentary, while
17 detrimental associations between sedentary time and cardiometabolic risk are attenuated by
18 MVPA. Replacing 10 minutes of sedentary time with MVPA that uses isothermal
19 substitution modelling produces inverse, albeit theoretical, associations with WC, SBP,
20 insulin, and TG (73). Similar replacement by light PA does not produce similar associations
21 (73), indicating that change in sedentary time is most beneficial when replaced by high
22 intensity PA. Therefore, as long as youth spend a sufficient amount of time in MVPA, the
23 pattern of MVPA (12) and accumulation of sedentary time is not detrimental for
24 cardiometabolic health (11, 39).

1 These findings must be interpreted with the following methodological considerations in mind.
2 First, some degree of consensus exists regarding the reduction of accelerometer data, but there
3 are discrepancies. For example, MVPA cut points varied from ≥ 760 cpm (47) to $\geq 4,000$ cpm
4 (40) in the present review, which results in significantly different estimates of time spent in
5 MVPA. The threshold of 100 cpm is commonly used for sedentary time (74), although 200
6 cpm (17) and 1,100 cpm were also applied (35) in the included studies. Choosing a higher
7 cpm for sedentary time is likely to capture sitting *plus* standing (75) and to increase
8 misclassification of light PA into the sedentary category; however, choosing higher cpm for
9 sedentary time also leads to collinearity with MVPA (76). When examining sedentary time as
10 exposure, the definition of non-wear time is especially important; it is often defined between
11 10 to 60 minutes. A long non-wear time increases the risk of assessing sedentary time when
12 the monitor is in fact off (overestimation), or the opposite: a shorter definition misclassifies
13 ‘true’ sedentary time as if the monitor were off (underestimation). Taken together, these
14 choices of data reduction impair the true association between sedentary time, PA, as well as
15 cardiometabolic health, and complicate comparability between studies. An initiative to
16 overcome these methodological challenges is the International Children’s Accelerometry
17 Database, where raw accelerometer data from $> 37,000$ youth are pooled and analysed by the
18 same approach, which results in a large, heterogeneous, and representative sample (77, 78).

19 Second, the main challenge in synthesising the results is that different statistical models are
20 applied. The most common statistical models in prospective studies are the change model and
21 the determinant model (13). The change model consists of the absolute change of outcome
22 associated with the absolute change of exposure. However, this model is criticised because it
23 uses a masked cross-sectional analysis and because bias may arise by not adjusting for
24 baseline values of either exposures or outcomes (13). In the determinant model, a follow-up
25 outcome or change in outcome is regressed on a baseline value; however, not all studies

1 adjust for the baseline values of outcome. In the present review, only eight prospective studies
2 applied the determinant model and adjusted for baseline values. We believe that this statistical
3 approach is more appropriate because the baseline value of the outcome is the strongest
4 confounder in prospective analyses.

5 The main strength of this systematic review is that the evidence was synthesised from
6 prospective and intervention studies using a comprehensive search strategy with strict
7 inclusion criteria. Furthermore, this review differentiated its analyses according to sedentary
8 time and MVPA. By exclusively including studies with long-term design, bias was removed
9 from cross-sectional studies. Thus, the results were homogenous with regard to both study
10 design (i.e., temporality) and PA measured by accelerometry. To our knowledge, no study has
11 previously used a meta-analytical approach to examine the association between MVPA and
12 clustered cardiometabolic risk. Examining cardiometabolic risk factors as a cluster of z scores
13 is preferable as the cluster contains full information about all components; thus, a more
14 complete indication of cardiometabolic risk will be obtained than if only one risk factor is
15 elevated (79). Clustering of cardiometabolic risk is an undesirable condition and is an early
16 biological sign of poor cardiometabolic health that may track into adolescence (80) and young
17 adulthood (81), possibly increasing the risk of later cardiometabolic disease (79, 82). Some
18 limitations must be considered. First, accelerometers have limitations as they neither
19 distinguish between sitting and standing nor provide information about sedentary contexts.
20 Moreover, underestimation of acceleration due to increased running speed (83, 84) and
21 cycling (85) leads to misclassification of PA intensity. The intra-class correlation for repeated
22 measures of PA levels in children is approximately 0.5 (86, 87), which indicates substantial
23 instability in PA levels over time. These measurement errors may lead to regression dilution
24 bias, which attenuates the true relationship between the exposure and the outcome (88).
25 Second, few studies have assessed health indicators beyond adiposity. Additional studies

1 investigating other cardiometabolic risk factors (e.g., blood samples) as outcomes are
2 warranted. Third, the conclusions should be interpreted while keeping in mind the short
3 duration of follow-up, as the median follow-up time for prospective studies was 2.8 years
4 while interventions lasted 2.0 years. In relative terms, these periods represent about 10% to
5 20% of the lifetime of the majority of participants included.

6 Conclusion

7 No evidence was found for a prospective association between sedentary time and
8 cardiometabolic risk factors in youth. On the other hand, the evidence for a prospective
9 association between MVPA and *clustering* of cardiometabolic risk factors is consistent,
10 inverse, and supported by the meta-analyses. As long as youth spend sufficient time in
11 MVPA, being sedentary causes little harm to cardiometabolic health. To advance the
12 knowledge of independent associations of intensity-specific PA with cardiometabolic health,
13 it is necessary to conduct further long-term studies with multiple measurements including
14 important confounders (socio-economic status, diet, and puberty).

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16 The study had no sponsors.

17 Conflict of interest

18 The authors have no conflict of interest to declare.

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Figure 1: Flow chart

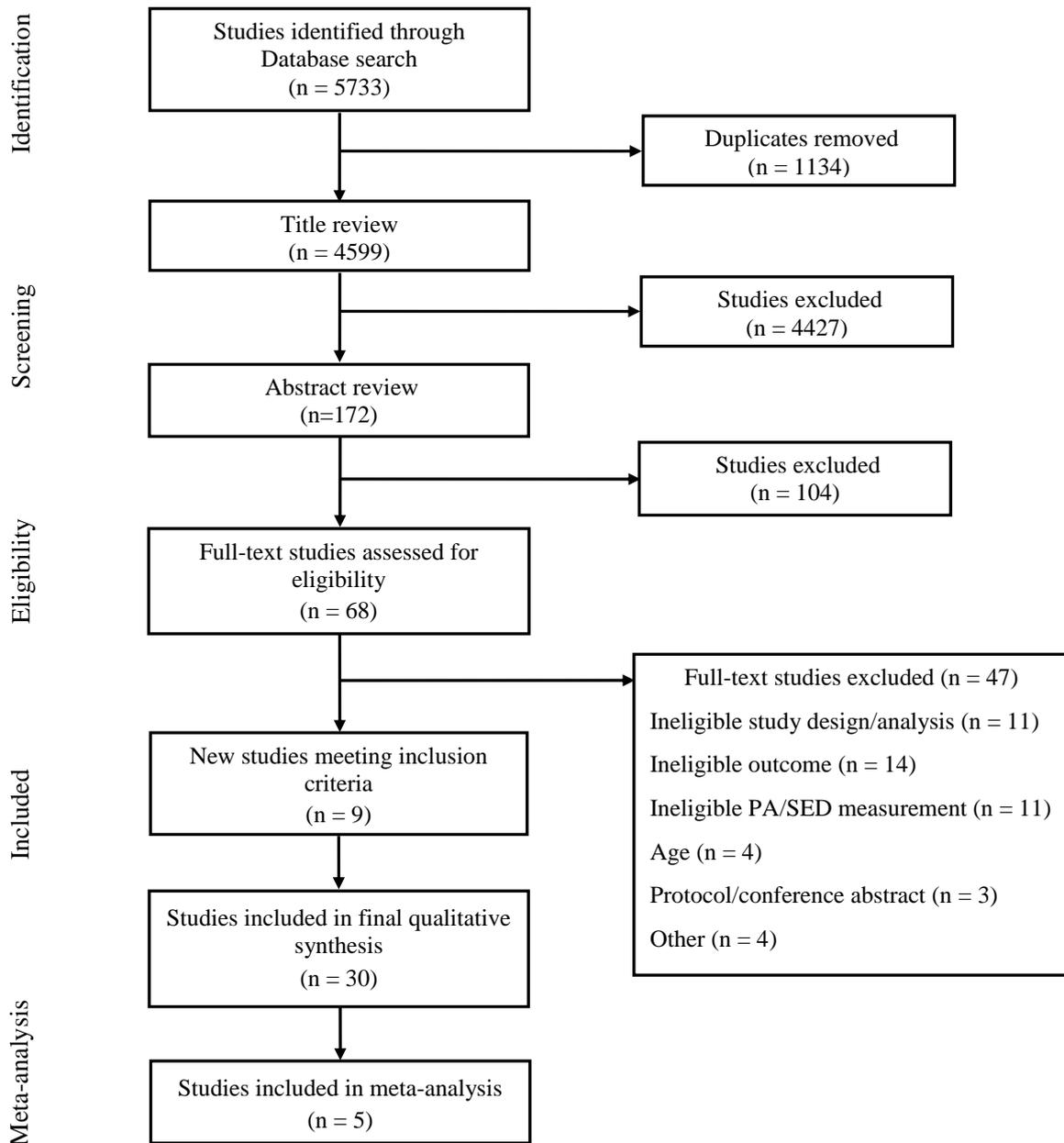


Table 1: Example of the complete search strategy

	Keywords
# 1	(‘cardiovascular disease risk factor’ OR ‘cardio-metabolic risk factor’ OR ‘metabolic risk factor’ OR ‘CVD risk factor’ OR ‘clustered cardio-metabolic risk’ OR ‘cluster’ OR ‘clustering’ OR ‘composite score’ OR ‘composite risk score’ OR ‘z score’ OR ‘sum of z score’ OR ‘mean of z score’ OR ‘metabolic syndrome’ OR ‘Mets’ OR ‘pre-diabetes’ OR ‘metabolic disorders’ OR ‘metabolic’ OR ‘insulin’ OR ‘glucose’ OR ‘insulin resistance’ OR ‘HOMA-IR’ OR ‘HOMA’ OR ‘high-density cholesterol’ OR ‘hyperlipidaemia’ OR ‘dyslipidaemia’ OR ‘hyperinsulinemia’ OR ‘hyperglycaemia’ OR ‘lipoprotein’ OR ‘HDL’ OR ‘HDL-cholesterol’ OR ‘low-density cholesterol’ OR ‘LDL’ OR ‘LDL-cholesterol’ OR ‘triglycerides’ OR ‘total cholesterol’ OR ‘waist circumference’ OR ‘WC’ OR ‘BMI’ OR ‘Body Mass Index’ OR ‘adiposity’ OR ‘visceral fat’ OR ‘central obesity’ OR ‘fat mass’ OR ‘skinfold’ OR ‘sum of skinfold’)
# 2	(‘physical activity’ OR ‘PA’ OR ‘moderate physical activity’ OR ‘moderate-to-vigorous physical activity’ OR ‘MVPA’ OR ‘vigorous physical activity’ OR ‘VPA’ OR ‘sedentary time’ OR ‘sedentary’ OR ‘sedated’ OR ‘inactivity’ OR ‘physical inactivity’ OR ‘inactive’ OR ‘sedentary behaviour’ OR ‘exercise’ OR ‘activity’ OR ‘intensity’ OR ‘moderate-and-vigorous intensity physical activity’ OR ‘physical activity energy expenditure’ OR ‘PAEE’)
# 3	(‘accelerometer’ OR ‘accelerometry’ OR ‘objectively measured’ OR ‘activity monitor’ OR ‘pedometer’ OR ‘heart rate monitor’ OR ‘HR monitoring’ OR ‘combined sensors’ OR ‘combined sensing’)
# 4	(‘longitudinal’ OR ‘prospective’ OR ‘RCT’ OR ‘randomized controlled trial’ OR ‘randomized controlled trial’ OR ‘cluster-randomized trial’ OR ‘cluster-randomized controlled trial’ OR ‘trial’ OR ‘intervention’ OR ‘cohort’ OR ‘observational study’)

Table 2: Criteria List for Assessment of the Methodological Quality of Prospective Studies based on Chinapaw et al. (23), Singh et al. (24), and Tooth et al. (25)

Criteria (rating of criteria: += yes, -= no, ? = not or insufficiently described)	I, V/P*	% of studies scoring +
Study population and participation (baseline): The study sample represents the population of interest on key characteristics:		
1 Adequate† description of sampling frame, recruitment methods, period of recruitment, and place of recruitment (setting and geographical location)‡	I	63.3
2 Participation rate at baseline at least 80%, or if the non-response was not selective (show that baseline study sample does not significantly differ from population of eligible subjects)	V	23.3
3 Adequate description of baseline study sample (i.e. individuals entering the study) for key characteristics (number of participants, age, sex, sedentary time, PA, and health outcome)‡	I	90.0
Study attrition: Loss to follow-up is not associated with key characteristics (i.e. the study data adequately represent the sample):		
4 Provision of the exact number of participants at each follow-up measurement	I	90.0
5 Provision of exact information on follow-up duration	I	96.7
6 Response at short-term follow-up (up to 12 months) was at least 80% of the number of participants at baseline and response at long term follow-up was at least 70% of the number of participants at baseline	V	50.0
7 Not selective non-response during follow-up measurement(s)§	V/P	63.3
Data collection:		
8 Adequate measurement of PA¶	V	100
9 PA was assessed at a time point prior to the measurement of the health outcome	V	100
10 Adequate measurement of the health outcome: objective measurement of the health outcome done and not by self-report	V	100
Data analyses:		
11 The statistical model used was appropriate¶¶	V/P	50.0
12 The number of cases was at least 10 times the number of the independent variables	V/P	96.7
13 Presentation of point estimates and measures of variability (confidence interval or standard error)	I	96.7

*I = criterion on informativeness, V/P = criterion on validity/precision.

†Adequate = sufficient information to be able to repeat the study.

‡++ is given only if adequate information is given on all items.

§++ is given only if non-selective dropout on key characteristics (age, sex, sedentary behaviour, health outcomes) is reported in the text or tables.

¶++ is given only if a multivariate regression model was used adjusting the baseline value of the outcome/RCT-design

¶¶++ is given only if at least three of the following points were mentioned: type of instrument, description of monitor placement, number of days worn, length of epoch, number of hour day⁻¹ worn, and number of minutes monitored, data reduction methods described.

Table 3: Prospective study characteristics and results sorted by outcome

Author	Country	N	Baseline Age	Study Length	Exposure	Outcome	PA Device	PA Data Reduction	Statistical Model and Covariates	Results
Basterfield et al., 2012	UK	403	Age 7.4	24 months	SED, MVPA	BMI (z score)	GTIM	SED < 1100 cpm MVPA > 3200 cpm Epoch: -- Non wear: manually deleting Wear time/day: 6 h Valid days: 3	Model: Multiple linear model. Exposure were %change in MVPA and SED, changes in adiposity Covariates: Sex, SES, FMI at baseline	Declining MVPA was associated with increased BMI z score in boys but not girls ($\beta \times 10^3$ -34.8, 95% CI, -61.8, -7.8, $P = 0.012$) Avoiding reductions in MVPA may reduce excessive fat gain. No associations for SED and later BMI (+/-)
Lätt et al., 2015	EE	136	Age 11.9 (♂)	2 years	SED, MVPA, VPA	BMI	GTIM	SED: < 100 cpm MVA > 2000 cpm VPA > 4000 cpm Epoch: 15 sec Non wear: 10 min Wear time/day: 8 h Valid days: 3	Model: Thresholds for PA were calculated by ROC and AUC curves. Logistic regression were used to calculate OR's overweight and obese at baseline and follow-up, based on PA thresholds at baseline and follow-up Covariates: Age and puberty	Boys not meeting thresholds of 5 and 20 min VPA/day at baseline had an increased risk of being overweight (OR = 4.1, 95% CI, 1.4, 11.6, and OR = 4.14, 95% CI, 1.4, 12.7, respectively), and obese (OR = 6.5, 95% CI, 2.1, 21.7, and OR = 8.8, 95% CI, 1.1, 68.5, respectively) two years later. No associations for SED (+/-)
Griffiths et al., 2016	UK	6497	Age 7	4 years	SED, MVPA	BMI	GTIM	SED < 100 cpm MVPA ≥ 2240 cpm Epoch: 15 sec Non wear: 20 min Wear time/day: 10 h Valid days: 2	Model: Linear regression models with baseline values of adiposity, SED and MVPA as covariate Covariates: Weekend, season, age, puberty, ethnicity, maternal BMI, maternal SES, maternal age at birth of cohort member, # cars, annual income, lone parenthood status country, urban/rural indicators, baseline value of the outcome	MVPA at age 11 were inversely associated with BMI at age 7. In boys, but not girls, BMI at age 11 were on average 2.5% (95% CI, 0.9, 4.2) lower for each 20 min increase in MVPA/day at age 7 No association for SED and later adiposity (+/-) 7-year-old children who are more physically active are less likely to be obese at that age and at age 11 years
Stevens et al., 2007	US	984	Age 11.9 (±)	2 years	MVPA	BMI	7164	SED < 100 cpm MVPA > 4.6 METs Epoch: 30 sec Non wear: 20 min Wear time/day: 80% of different time blocks of day	Model: Mixed-model linear regression with BMI and body fat% modelled as continuous variables on the mean and deviation scores for PA Covariates: Height, intervention assignment	No associations between MVPA and BMI over 2-year follow-up (-)

Treuth et al., 2009	US	984	Age 11.9 (±)	2 years	SED	BMI	7164	Valid days: 1 SED < 100 cpm Epoch: 30 sec Non wear: -- Wear time/day: 6 h Valid days: 1	Model: Mixed models with 1) the mean and 2) the deviation from each girl's SED were used to predict change in BMI in a repeated measures structure Covariates: Age, ethnicity, field centre/school	Changes in SED over time were not associated with changes in BMI. The estimates were in the expected direction, but not significant (-)
Trinh et al., 2013	AUS	182	Age 7.3	3 years	SED, MVPA	BMI (z score)	Actial (multiaxial)	SED < 100 cpm MVPA ≥ 900 cpm Epoch: 60 sec Non wear: 20 min Wear time/day: 10 h Valid days: 5	Model: Linear regression with the initial level of PA or change in PA used to predict change in BMI Covariates: Initial PA, intervention status, sex, age, SES, maternal BMI, maternal education	Every 10% change in time spent in MVPA, predicted -0.24 (95% CI, -0.43, -0.05) in BMI z score. No associations for SED ($P = 0.39$) (+)
Riddoch et al., 2009	UK	4150	Age 12	2 years	MVPA	BMI	N/A	MVPA > 3600 cpm Epoch:-- Non wear: 10 min Wear time/day: 10 h Valid days: 3	Model: Multilevel modelling with baseline adjustment of the outcome. The adjusted regression coefficient for the association between MVPA at age 12 and fatness at age 14 was calculated from random effects associated with MVPA and fatness Covariates: age, puberty, maternal education, occupation, pre-pregnancy BMI, smoking, total PA(cpm)	A 15 min increase in MVPA/day at age 12 were associated with -2.9% and -2.2% for BMI in boys and girls, respectively, at age 14 The changes in BMI with incremental changes in MVPA were -0.4% and -0.7% in boys and girls (+)
Ekelund et al., 2012	ICAD ^b	6413	Age 6-18	2.1 years	MVPA SED	WC	ICAD	SED < 100 cpm MVPA > 3000 cpm Epoch: 60 sec Non wear: 60 min Wear time/day: 8 h Valid days: 1	Model: Linear regression model Covariates: Age, sex, monitor wear time, follow-up time and the baseline value of the outcome variable	Neither time in MVPA or SED predicted WC, but WC predicted higher SED (β 0.40, 95% CI, 0.19, 0.61) (-)
Knowles et al., 2013	UK	427	Age 6.5	2 years	MVPA	BP	ActiHeart	MVPA ≈ 2000 cpm Epoch: 30 sec Non-wear: -- Wear time/day: -- Valid days: --	Model: Multiple linear regression with baseline adjustment of the outcome Covariates: Age, sex, ethnicity, change in age/height, height at baseline,	Every 15 min MVPA/day at baseline were not associated with SBP (β -0.11, 95% CI, -0.63, 0.41, $P = 0.68$) or DBP (β -0.18, 95% CI, -0.65, 0.29, $P = 0.45$) at follow-up (-)

Peplies et al., 2016	Europe ^a	3348	Age 6.4 ^a	2 years	MVPA	HOMA-IR	GTIM	SED < 100 cpm MPA > 2296 cpm VPA > 4012 cpm Epoch: 60 sec Non wear: 20 min Wear time/day: 8 h Valid days: 3	school, baseline BP, group allocation, duration of PA measurement, baseline BMI z score Model: Multivariate mixed logistic models using age- and sex-specific z score for HOMA-IR Covariates: Audio-visual media time, sex, age, SES, MVPA	MVPA has a protective effect for HOMA-IR in the two upper MVPA quartiles (≥ 38.7 min MVPA/day), but not a clear trend. MVPA reduces the risk of developing IR, also for children with normal weight at baseline which indicates that the effect of missing PA is not just mediated by obesity. Longitudinal reduction of HOMA-IR was accompanied with a parallel BMI decline (+)
Metcalf et al., 2015	UK	300	Age 8.9	7 years	MVPA	HOMA-IR, MAP, SBP, DBP, TG, HDL	7164	MVPA \approx 2500 cpm Non-wear: 17 min Epoch: 60 sec Wear time/day: 9 h Valid days: 4	Model: Multilevel modelling of longitudinal/repeated measure. MVPA level from 9-16 y were averaged and analysed both as a continuous and categorical variable (above/below 50 min MVPA/day in boys, 35 min MVPA/day in girls) Covariates: body fat%, age as a fixed and random effect, then polynomials of increasing order were added one by one as the age-related trends were not linear	HOMA-IR was lower in the 'active group' at age 12.5, independent of body fat%. For every 15 min MVPA/day, HOMA-IR was 5.5% lower (95% CI, -9.5, -1.3, $P = 0.01$) at age 12.5. However, no difference in HOMA-IR between activity groups at age 16 'More active' girls: 9.7% lower TG ($P = 0.05$), independent of puberty and body fat%. 'More active' boys: 1.20 mmHg lower DBP. No associations for HDL or SBP (+/-)
Lätt et al., 2016	EE	120	Age 11.9 (c)	2 years	MVPA	TG, HOMA-IR, TC:HDL	GTIM	MPA > 2000 cpm VPA > 4000 cpm Non-wear: 10 min Epoch: 60 sec Wear time/day: 10 h Valid days: 3	Model: Logistic regression model with follow-up outcomes regressed on change in MVPA Covariates: Puberty	MVPA do predict changes in either TG, HOMA-IR or TC:HDL (-)
Metcalf et al., 2008	UK	307	Age 4.9	3 years	MVPA	HOMA-IR, TG, TC:HDL, MAP, BMI, and CMRisk	MTI/CSA	MVPA \approx 2500 cpm (≥ 3 METs) Epoch: 60 sec Non wear: -- Wear time/day: 9 h	Model: Multiple linear regression (MLR) to find partial correlation between MVPA and changes in outcome. ANCOVA to compare changes in outcome	MLR: No associations between ≥ 3 METs for BMI or WC. Small to moderate inverse partial correlations between minutes spent >3 METs and changes in: TG (girls only: $r = -0.26$, $P = 0.02$) CMRisk (girls only: $r = -0.23$, $P = 0.03$) MAP (boys only: $r = -0.22$, $P = 0.02$)

Skrrede et al., 2017	NOR	700	Age 10	7 months	SED, MPA, VPA, MVPA	WC, SBP, TG, TC:HDL, HOMA-IR, CMRisk	GT3X	Valid days: min. 20 days over four assessments	according to activity group (high/low) Linear mixed models (LMM) to test if trends in BMI and CMRisk over four time points differed by more or less active children Covariates: Age at baseline, years/time to follow-up, SES, PA adjusted for season and sensitivity of each accelerometer, respective baseline value Model: Linear mixed model with baseline adjustment of the outcome at follow-up Covariates: Sex, school, SES, puberty, monitor wear time, WC, adjusted for baseline value of the outcome	ANCOVA: Active girls (>45 min MVPA/day) had more beneficial change in TG. Change in CMRisk in favour of the active group in both sex, but significant for boys only LMM: CMRisk above/below median activity diverged, and was linear over time (0.08 z scores/year, $P=0.001$) Notably, only 11% of girls and 42% of boys met recommended PA level (≥ 3 METs) (+/-)
Studies examining independent associations (SED and MPA/MVPA/VPA mutually adjusted)										
Carson et al., 2014	CA	315	Age 12.2	2 years	MPA, VPA	BMI (z score), WC, SBP	Actial	SED < 100 cpm MPA > 1500 cpm VPA > 6500 cpm Epoch: 15 sec Non wear: 60 min Wear time/day: 8 h Valid days: 3	Model: Multiple linear regression by associations between PA intensities at baseline (quartiles) and outcomes at follow-up. Q1 (low PA) was the reference group for all analyses. Covariates: Age, sex, dietary intake, monitor wear time, other intensities of PA, adjusted for baseline value of the outcome	Follow-up WC decreased in a dose-response manner across quartiles of baseline MPA $P_{trend} = 0.04$. Boys only; dose-response decrease in follow-up WC (Q1 vs Q4 = 79.0 vs 72.6 cm, $P_{trend} = 0.04$) and SBP (Q1 vs Q4 = 121.8 vs 115.3mm Hg; $P_{trend} = 0.07$) observed with increasing VPA (+)
Fisher et al., 2011	UK	280	Age 8.8	1 year	SED, MVPA	BMI, WC	GTIM	SED < 100 cpm MVPA > 4000 cpm Epoch: 60 sec Non wear: 10 min Wear time/day: 10 h	Model: Hierarchical multiple regression with baseline adjustment for the outcome Covariates: SES, ethnicity, sex, MVPA/SED/total PA,	Higher levels of MVPA at baseline were associated with lower BMI at follow-up (adjusted $\beta = -0.07$; $P = 0.002$), independent of SED. Similar pattern for MVPA and WC, but not significant (+)

Mitchell et al., 2013	US	424-740	Age 9	6 years	SED, MVPVA	BMI	7164	Valid days: 3 SED < 100 cpm MPA > 2296 cpm VPA > 4012 cpm Epoch: 60 sec Non wear: 60 min Wear time/day: 10 h Valid days: 3	adjusted for baseline value of the outcome Model: Longitudinal quantile regression to assess changes at the 10 th -90 th SED percentile from 9-15 y and change in BMI Covariates: BMI, time, SED, MVPVA, sex, race, maternal education, sleep and healthy eating	No evidence that SED associated with BMI percentile differed with increasing age, or that BMI change differ between sexes At the 90th BMI percentile, an additional hour spent in SED/day was associated with a 0.59 (95% CI, 0.19, 0.98) increase in BMI unit, adjusted for MVPVA and covariates. Similar findings from the 50 th percentile (+)
van Sluijs et al., 2016	UK	367	Age 9.8	4 years	SED, MPA, VPA	WC	GT1M	SED < 100 cpm MPA > 2000 cpm VPA > 4000 cpm Epoch: 5 sec Non wear: 10 min Wear time/day: 8 h Valid days: ≥ 3	Model: Linear (continuous outcome) or logistic (binary outcome) regression models. Including robust standard errors to account for clustering within schools. Covariates: Age, sex, SES, birth weight, maternal BMI, puberty at follow-up, sleep duration, height, baseline diet, adjusted for baseline value of the outcome	Either SED, MPA or VPA predicted change in WC: SED (β -0.10, 95% CI, -0.43, 0.23) MPA (β -0.54, 95% CI, -0.45, 1.53) VPA (β -0.09, 95% CI, -0.71, 0.52) (-)
Hjorth et al., 2014	DK	554	Age 10	200 days	SED, MVPVA	WC, MAP, HOMA-IR, TG, HDL, CMRrisk	GT3X	SED < 100 cpm MPA > 2296 VPA > 4012 Epoch: 60 sec Non wear: 60 min Wear time/day: 10 h Valid days: 4	Model: Linear regression with change in exposure vs change in outcome Covariates: Age, sex, puberty interaction, days of follow-up, baseline value of behaviour movement and outcome risk factor, baseline BMI z score	Change in MVPVA had beneficial influence on HDL (β 0.019, 95% CI, 0.012, 0.026), TG (β -0.02, 95% CI, -0.04, -0.004), and HOMA-IR (β -0.07, 95% CI, -0.11, -0.003) but not for WC. Associations for MVPVA with HOMA-IR and HDL were independent of SED. Change in SED reduced HDL (β -0.006, 95% CI, -0.009, -0.004), independent of MVPVA. Low MVPVA and short sleep at baseline associated with increased CMRrisk at follow-up. independent of SED (β -0.12, 95% CI, -0.22, -0.01), but attenuated by FMI. SED not associated with CMRrisk ($P = 0.39$) or adiposity (+/-)
Stamatakis et al., 2015	UK	2963 / 4369	Age 11.5	4 years	SED, MVPVA	BMI, WC, SBP, DBP, TG, HDL,	7164/GT1M	SED < 200 cpm MVPVA > 3600 cpm Epoch: 60 sec	Model: Multiple linear regression with baseline adjustment of the outcome at follow-up	In fully adjusted models, MVPVA was beneficially associated with insulin (β -0.024, 95% CI, -0.036, -0.013), HDL (β 0.006, 95% CI, 0.001, 0.011) and

Chinapaw et al., 2018	DK	460	Age 9.4	10 months	SED, MVPA	TG, TC:HDL, HOMA-IR, SBP, WC, CMRisk	GT3X	Non wear: 10 min Wear time/day: 10 h Valid days: 3	Covariates: Age, sex, monitor wear time, time between PA measurement and cardiometabolic risk factor, paternal social class, birth weight, maternal BMI, puberty, energy intake, baseline adjustment of outcome (baseline BMI for blood variables), SED adjusted for MVPA, but MVPA not adjusted for SED	CMRisk (β -0.014, 95% CI, -0.025, -0.004) Baseline SED at age 11 was not independently deleteriously associated with cardiometabolic markers at age 15, except for BMI (β -0.004, 95% CI, -0.007, -0.001). However, in a nonimputed data set, there were no associations between SED and BMI (+/-)
								SED < 100 cpm MVPA > 2296 cpm Epoch: 2 sec Non wear: 60 min Wear time/day: 8 h Valid days: 6	Model: Multilevel linear mixed models with school and class as random effects Covariates: age, sex, parental education, puberty and school (i.e. intervention or control), mutual adjustment for MVPA and SED. Outcome not adjusted for baseline value	In fully adjusted models, higher mean (T1+T2) MVPA levels were significantly associated with lower WC (β -18.4, 95% CI, -23.8, -13.0), SBP (β -5.6, 95% CI, -10.8, -0.5), HOMA-IR (β -10.2, 95% CI, -16.2, -4.2) and CMRisk (β -9.4, 95% CI, -13.0, -5.9), independent of SED Higher mean SED (T1+T2) were associated with lower WC (β -5.8, 95% CI, -7.6, -3.9), and CMRisk (β -2.1, 95% CI, -3.4, -0.9), independent of MVPA. Change in SED were associated with lower SBP (β -2.2, 95% CI, -4.0, -0.3) (+/-) Overweight children scored significantly worse on all cardiometabolic health indicators

^a 85% of participants were 6 to 9 years

^b Belgium, Cyprus, Estonia, Greece, Germany, Hungary, Italy, Spain and Sweden

^c ICAD: the International Children's Accelerometry Database: UK, Switzerland, Denmark, Estonia, Scotland, US, Norway, Brazil, Portugal

BMI, Body Mass Index; CMRisk, clustered cardiometabolic risk; cpm, counts per minute; DBP, diastolic blood pressure; FMI, fat mass index; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; MAP, mean arterial pressure; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; PA, physical activity; SED, sedentary time; SES, socio-economic status; SBP, systolic blood pressure; TC:HDL, ratio between total cholesterol and HDL; TG, triglycerides; VPA, vigorous physical activity; WC, waist circumference

-- No information given

- Or + indicates the whether the is an association (+), no association (-) or mixed findings (+/-)

Table 4: Intervention study characteristics and results sorted by outcome

Author	Country	N	Baseline Age	Study Length	Exposure	Outcome	PA Device	PA Data Reduction	Statistical Model and Covariates	Results
Andrade et al., 2014	EC	226* / 1378	Age 12.8	28 months	MVPA	BMI (z score)	GT-256 /GTIM	SED < 100 cpm MPA ≥ 760 cpm Epoch:-- Non-wear: -- Wear time/day: 9 h Valid days: 3	Model: ITT by linear mixed regression model Covariates: Baseline BMI z score, sex, SES, knowledge of PA recommendations	Intervention did not lead to favourable changes in BMI z score (-0.004, 95% CI, -0.09, 0.08). 95.0% of intervention children and 93.6% of control children met ≥60 min MVPA/day at baseline (-) *Only n = 226 wore accelerometer, n = 134 valid measurements
Donnelly et al., 2009	US	167** / 1527	Age 7-9	3 years	MVPA	BMI	7164	MVPA ≥ 4 METs Epoch: -- Non-wear: -- Wear time/day: -- Valid days: 4 d	Model: Adjusted t-test Covariates: --	Intervention children had 27% higher MVPA ($P < 0.001$), but did not reduce BMI (-) **Only n = 167 wore accelerometer (n = 77 intervention, n = 90 control)
Lubans et al., 2012	AUS	357	Age 13.2 (♂)	1 year	MVPA	BMI	7164/GT1M /GT3X	MVPA ≈ 2000 cpm Epoch: -- Non-wear: -- Wear time/day: 10 h Valid days: 4	Model: ITT by linear mixed regression model Covariates: Adjusted for clustered nature of the data	No intervention effect of MVPA on BMI (-0.19, 95% CI, -0.70, 0.33), but changes in favour of intervention group (-)
Gorely et al., 2009	UK	589	Age 8.8	10 months	MVPA	BMI, WC	GT1M + pedometer	MVPA ≈ 2500 cpm Epoch: 5 sec Non-wear: 20 min Wear time/day: 9 h Valid days: 4	Model: ITT by multilevel-modelling (ML-win) Covariates: --	Intervention group had significant lower increase in BMI (intervention 0.4 vs control 0.9 BMI units) per year of age and WC (intervention 1.8 cm vs control 2.8 cm) per year of age (+)
Gorely et al., 2011 ^a	UK	421	Age 7-11	18-20 months	MVPA	BMI, WC	GT1M	MVPA ≈ 2500 cpm Epoch: 5 sec Non-wear: 20 min Wear time/day: 9 h Valid days: 4	Model: ITT by multilevel-modelling (ML-win) Covariates: --	The beneficial effects on BMI reported by Gorely et al. (2009) were not sustained (-)
Seabra et al., 2016	PT	88	Age 10.5 (♂)	6 months	MVPA	BMI (z score), WC, SBP, DBP, HOMA-IR, TG, HDL	GT3X	SED < 100 cpm MPA ≥ 2296 cpm VPA > 4012 cpm Epoch: -- Non-wear: -- Wear time/day: -- Valid days: --	Model: one way ANOVA, chi-square tests, and calculated effect size Covariates: --	From baseline to follow-up, the interventions groups decreased BMI z score, WC TG, and HDL. The interventions groups decreased WC (-5.0 and -5.3 cm) compared to the control group (-0.2 cm) (+)

Bugge et al., 2012	DK	441-613	Age	3 & 4 years (7 years)	MVPA	BMI, WC, SBP, TG, HOMA-IR, CMRisk	7164 /GTIM	SED < 100 cpm MVPA > 1500 cpm Epoch: 10 sec Non-wear: 10 min Wear time/day: 8 h Valid days: 3	Model: General linear model Covariates: Sex, puberty, baseline level of outcome, school as cluster variable	Intervention boys had smaller increase in HOMA-IR from baseline to post-intervention (3 years) compared with control boys ($P = 0.004$). From baseline to follow-up (7 years) group boys had a smaller increase in SBP compared with control boys ($P = 0.010$) (+/-)
Kriemler et al., 2010	CH	502	Age 7 & 11	9 months	MVPA	BMI, WC, SBP, DBP, HDL, TG, CMRisk	MTI/CSA 7164	MVPA > 2000 cpm Epoch: 60 sec Non-wear: 15 min Wear time/day: 12 h Valid days: >2	Model: ITT by mixed linear model Covariates: group, sex, and grade as fixed factors; school class as a random effect; and the respective baseline z score as a covariate	1-children decreased BMI: -0.12 (95% CI, -0.19, -0.04) TG: -0.10 (95% CI, -0.18, -0.01) CMRisk: -0.18 (95% CI, -0.29, -0.06) HDL: 0.27 (95% CI, 0.09, 0.44) (+)
Meyer et al., 2014 ^b	CH	289	Age 10 & 14	3 years	MVPA	BMI, WC, SBP, DBP, HDL, TG, CMRisk	MTI/CSA 7164	MVPA > 2000 cpm Epoch: 60 sec Non-wear: 15 min Wear time/day: 12 h Valid days: 3	Model: Multilevel linear models with z scores at follow-up as dependent variables Covariates: Group, gender and grade as fixed factors, BMI z score and change in puberty, the respective baseline z score as covariate. Original school class were used as random effect	Beneficial effects on BMI, TG or CMRisk reported by Kriemler et al. (2010) were not sustained (-)

BMI, Body Mass Index; CI, confidence interval; CMRisk, clustered cardiometabolic risk; cpm, counts per minute; DBP, diastolic blood pressure; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; ITT, Intention-to-treat; MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; PA, physical activity; SED, sedentary time; SES, socio-economic status; SBP, systolic blood pressure; TC:HDL, ratio between total cholesterol and HDL; TG, triglycerides; VPA, vigorous physical activity; WC, waist circumference

-- No information given

- Or + indicates the whether the is an association (+), no association (-) or mixed findings (+/-)

^a Long-term follow-up after Gorely et al., 2009

^b Long-term follow-up after Kriemler et al., 2010

Table 5: Quality assessment of the included studies sorted by quality score (based on criteria as listed in Table 2)

	1	2*	3	4	5	6*	7*	8*	9*	10*	11*	12*	13	Score (%)
Prospective studies														
Bastierfield et al., 2012	+	+	+	+	+	+	+	+	+	+	-	+	+	88
Fisher et al., 2011	+	-	+	+	+	+	+	+	+	+	+	+	+	88
Skrede et al., 2017	+	-	+	+	+	+	+	+	+	+	+	+	+	88
Stevens et al., 2007	+	+	+	+	+	+	+	+	+	+	-	+	+	88
Treuth et al., 2009	+	+	+	+	+	+	+	+	+	+	-	+	+	88
van Shuijs et al., 2016	+	-	+	?	+	+	+	+	+	+	+	+	+	88
Carson et al., 2014	+	-	+	+	+	-	+	+	+	+	+	+	+	75
Chinapaw et al., 2018	+	+	+	+	+	-	+	+	+	+	-	+	+	75
Griffiths et al., 2016	+	-	+	+	+	+	+	+	+	+	+	+	+	75
Knowles et al., 2013	+	-	+	+	?	-	+	+	+	+	+	+	+	75
Mercalf et al., 2008	+	-	?	+	+	+	+	+	+	+	-	+	+	75
Mercalf et al., 2015	+	?	+	+	+	+	+	+	+	+	-	+	+	75
Stamatakis et al., 2015	+	+	?	+	+	-	?	+	+	+	-	+	+	75
Hjorth et al., 2014	+	+	+	+	+	-	+	+	+	+	-	+	+	63
Michelle et al., 2013	+	-	+	+	+	-	?	+	+	+	-	+	+	63
Peplies et al., 2016	?	-	+	+	+	+	?	+	+	+	-	+	+	63
Riddoch et al., 2009	+	-	+	+	+	-	+	+	+	+	-	+	+	63
Trinh et al., 2013	+	-	+	+	+	-	+	+	+	+	-	+	+	63
Lätt et al., 2015	-	?	+	+	+	-	-	+	+	+	-	+	+	50
Lätt et al., 2016	+	?	+	+	+	-	?	+	+	+	-	?	+	50
Ekelund et al., 2012	+	n/a	+	n/a	+	n/a	n/a	+	+	+	+	+	+	n/a
Intervention studies														
Bugge et al., 2012	+	-	+	+	+	+	+	+	+	+	+	+	+	88
Lubans et al., 2012	+	?	+	+	+	+	+	+	+	+	+	+	+	88
Seabra et al., 2016	+	-	+	+	+	+	+	+	+	+	+	+	+	88
Andrade et al., 2014	+	+	+	+	+	-	?	+	+	+	+	+	+	75
Gorely et al., 2009	?	?	+	+	+	+	+	+	+	+	?	+	+	75
Gorely et al., 2011	-	?	+	+	+	+	+	+	+	+	?	+	+	75
Kriemler et al., 2010	+	-	+	+	+	-	+	+	+	+	+	+	+	75
Meyer et al., 2014	+	-	+	+	+	-	+	+	+	+	+	+	+	75
Donnelly et al., 2009	?	-	-	-	+	-	?	+	+	+	+	+	-	63

*validity/precision criteria, + = publication met the quality criterion at issue; - = publication did not meet the quality criterion; ? = quality criterion was insufficiently described; score % = methodological quality score calculated by counting the number of V/P criteria that were met, divided by total the amount of V/P criteria.

Table 6: Level of evidence from studies examining associations between objectively measured total sedentary time, MVPA and cardiometabolic outcomes. Level of evidence coding were performed amongst studies with high quality only and based on ultimately adjusted analyses

Outcome	Beneficially associations with SED	Not associated with SED	n/N for outcome (%)	Level of evidence
BMI	<i>Obs.</i> : Stamatakis ^a	<i>Obs.</i> : Treuth, Griffiths ^a , Basterfield ^b	1/4 (25%)	No evidence
WC	<i>Obs.</i> : Chinapaw ^b	<i>Obs.</i> : Skrede ^a , Stamatakis ^a , van Sluijs ^a	1/4 (25%)	No evidence
Insulin/HOMA-IR	<i>n/a</i>	<i>Obs.</i> : Skrede ^a , Stamatakis ^b , Chinapaw ^b	0/3 (0%)	No evidence
TG	<i>n/a</i>	<i>Obs.</i> : Skrede ^a , Stamatakis ^b , Chinapaw ^b	0/3 (0%)	No evidence
HDL/TC:HDL	<i>n/a</i>	<i>Obs.</i> : Skrede ^a , Stamatakis ^b , Chinapaw ^b	0/3 (0%)	No evidence
Blood Pressure (MAP, SBP, DBP)	<i>Obs.</i> : Chinapaw ^b	<i>Obs.</i> : Skrede ^a , Stamatakis ^b	1/3 (33%)	No evidence
CMRisk	<i>Obs.</i> : Chinapaw ^b	<i>Obs.</i> : Skrede ^a , Stamatakis ^b	1/3 (33%)	No evidence
Outcome	Beneficially associations with MVPA	Not associated with MVPA	n/N for outcome (%)	Level of evidence
BMI	<i>Obs.</i> : Stamatakis ^a , Carson ^a , Griffiths ^a (♂), Fisher ^a , Basterfield ^b (♂) <i>Int.</i> : Kriemler ^c , Gorely ^d (2009) <i>Obs.</i> : Stamatakis ^a , Chinapaw ^b <i>Int.</i> : Bugge ^d , Gorely ^d (2009), Seabra ^d	<i>Obs.</i> : Metcalf ^b (2008), Stevens ^b , <i>Int.</i> : Meyer ^e , Bugge ^d , Gorely ^e (2011), Lubans ^c , Seabra ^d , Andrade ^d <i>Obs.</i> : Fisher ^a , Skrede ^a , Metcalf ^b (2008), van Sluijs ^a <i>Int.</i> : Meyer ^e , Bugge ^d , Gorely ^e (2011)	7/15 (43%)	Inconsistent
WC	<i>Obs.</i> : Stamatakis ^a , Chinapaw ^b <i>Int.</i> : Bugge ^d , Gorely ^d (2009), Seabra ^d	<i>Obs.</i> : Fisher ^a , Skrede ^a , Metcalf ^b (2008), van Sluijs ^a <i>Int.</i> : Meyer ^e , Bugge ^d , Gorely ^e (2011)	5/12 (41%)	Inconsistent
Insulin/HOMA-IR	<i>Obs.</i> : Skrede ^a , Stamatakis, Chinapaw ^b <i>Int.</i> : Bugge ^d (♂) (baseline to post-intervention)	<i>Obs.</i> : Metcalf ^b (2008), Metcalf ^b (2015), <i>Int.</i> : Seabra ^d , Bugge (long-term)	4/8 (50%)	Inconsistent
TG	<i>Obs.</i> : Skrede ^a , Metcalf ^b (♀) (2015), Metcalf ^a (♀) (2008), <i>Int.</i> : Kriemler ^c	<i>Obs.</i> : Stamatakis <i>Int.</i> : Meyer ^e , Bugge ^d , Seabra ^d	4/8 (50%)	Inconsistent
HDL/TC:HDL	<i>Obs.</i> : Stamatakis ^b <i>Int.</i> : Kriemler ^c	<i>Obs.</i> : Skrede ^a , Metcalf ^b (2015), Metcalf ^b (2008) <i>Int.</i> : Meyer ^e , Seabra ^d	2/7 (29%)	Inconsistent
Blood Pressure (MAP, SBP, DBP)	<i>Obs.</i> : Metcalf ^b (♂) (2008), Carson ^a (♂), Chinapaw ^b , Metcalf ^b (♂) (2015) <i>Int.</i> : Bugge ^d (♂)	<i>Obs.</i> : Knowles ^a , Skrede ^a , Stamatakis ^a <i>Int.</i> : Kriemler ^c , Meyer ^e , Seabra ^d	5/11 (45%)	Inconsistent
CMRisk	<i>Obs.</i> : Skrede ^a , Stamatakis, Chinapaw ^b , Metcalf ^a (2008) <i>Int.</i> : Kriemler ^c	<i>Int.</i> : Bugge ^d , Meyer ^e	5/7 (71%)	Negative/inverse

^a Prospective study with adjustment for baseline value of the outcome, ^b Prospective study not adjusting for baseline values of the outcome ^c Randomised controlled trial,

^d Non-randomised controlled interventions, ^e Long-term follow-ups, *Obs.* = observational prospective studies, *Int.* = intervention studies

Results/associations are coded using the approach first employed by Sallis et al. (26) and subsequently applied to observational studies examining associations with health outcomes. The result was classified as 'no evidence (0) if 0–33% of studies reported a significant association. If 34–59% of studies reported a significant association, or if fewer than five studies reported on the outcome, the result was classified as being inconsistent. If $\geq 60\%$ of studies found a significant association, the result was classified as positive/adverse or negative/inverse.

BMI, Body Mass Index; CMRisk, clustered cardiometabolic risk; DBP, diastolic blood pressure; HDL, high density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance; MAP, mean arterial pressure; MVPA, moderate-to-vigorous physical activity; SED, sedentary time; SBP, systolic blood pressure; TC:HDL, ratio between total cholesterol and HDL; TG, triglycerides; WC, waist circumference

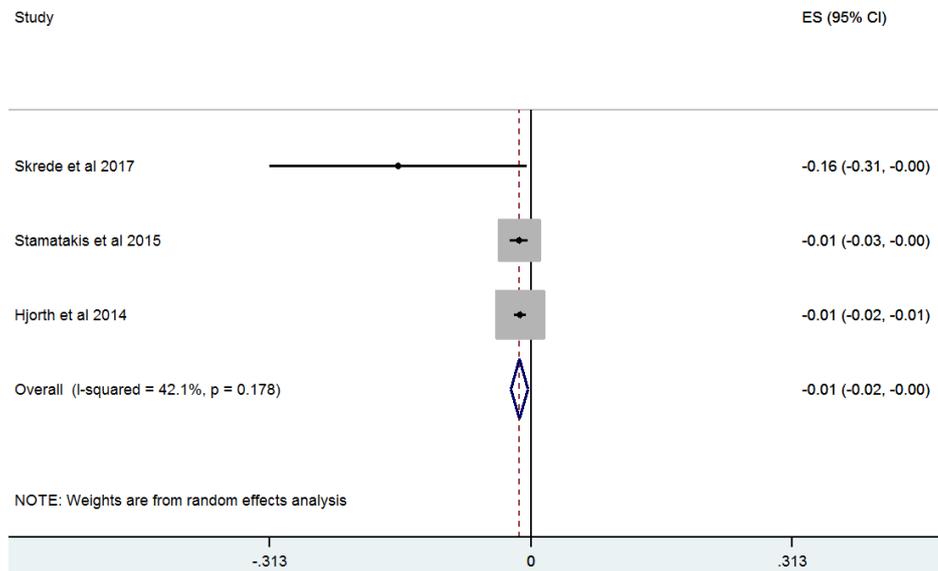


Figure 2: Forest plot for baseline MVPA and clustered cardiometabolic risk at follow-up from prospective studies. Estimates are adjusted for baseline value of the outcome.

Please note: Stamatakis et al. (17) adjusted for baseline BMI when clustered cardiometabolic risk was regressed as outcome.

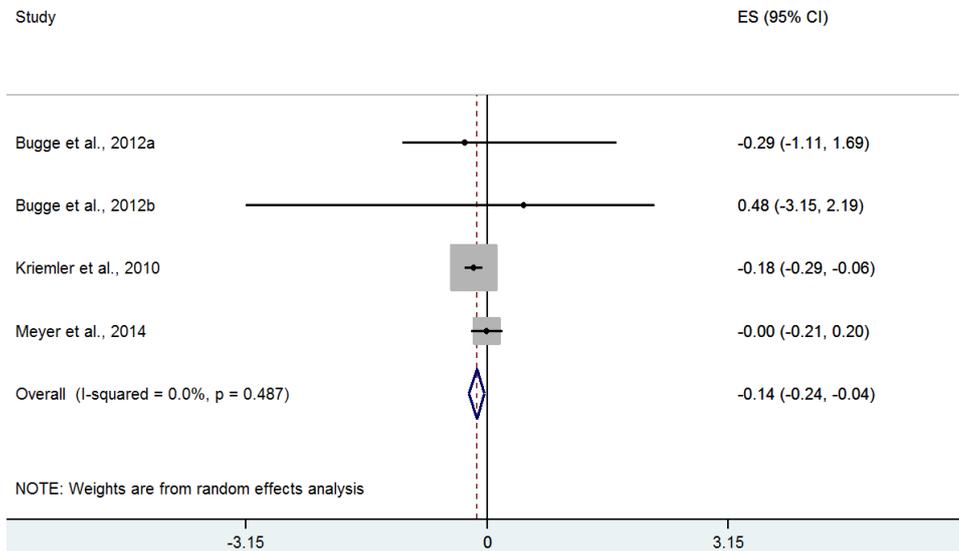


Figure 3: Forest plot for MVPA and clustered cardiometabolic risk by intervention studies. Estimates are based on the difference between intervention and control group at follow-up.

Please note: Bugge et al. (2012a) is baseline to post-intervention, and Bugge et al. (2012b) is baseline to long-term follow up, but reported in the same publication (29).

STUDY II

Moderate-to-vigorous physical activity, but not sedentary time, predicts changes in cardiometabolic risk factors in 10-y-old children: the Active Smarter Kids Study^{1,2}

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ABSTRACT

Background: Cross-sectional data have suggested an inverse relation between physical activity and cardiometabolic risk factors that is independent of sedentary time. However, little is known about which subcomponent of physical activity may predict cardiometabolic risk factors in youths.

Objective: We examined the independent prospective associations between objectively measured sedentary time and subcomponents of physical activity with individual and clustered cardiometabolic risk factors in healthy children aged 10 y.

Design: We included 700 children (49.1% males; 50.9% females) in which sedentary time and physical activity were measured with the use of accelerometry. Systolic blood pressure, waist circumference (WC), and fasting blood sample (total cholesterol, high-density lipoprotein cholesterol, triglycerides, glucose, fasting insulin) were measured with the use of standard clinical methods and analyzed individually and as a clustered cardiometabolic risk score standardized by age and sex (*z* score). Exposure and outcome variables were measured at baseline and at follow-up 7 mo later.

Results: Sedentary time was not associated with any of the individual cardiometabolic risk factors or clustered cardiometabolic risk in prospective analyses. Moderate physical activity at baseline predicted lower concentrations of triglycerides ($P = 0.021$) and homeostatic model assessment for insulin resistance ($P = 0.027$) at follow-up independent of sex, socioeconomic status, Tanner stage, monitor wear time, or WC. Moderate-to-vigorous physical activity ($P = 0.043$) and vigorous physical activity ($P = 0.028$) predicted clustered cardiometabolic risk at follow-up, but these associations were attenuated after adjusting for WC.

Conclusions: Physical activity, but not sedentary time, is prospectively associated with cardiometabolic risk in healthy children. Public health strategies aimed at improving children's cardiometabolic profile should strive for increasing physical activity of at least moderate intensity rather than reducing sedentary time. This trial was registered at clinicaltrials.gov as NCT02132494. *Am J Clin Nutr* 2017;105:1391–8.

Keywords: children, prediction of change, behavior, risk factors, physical activity, school

INTRODUCTION

The prevalence of childhood overweight and obesity has increased dramatically worldwide during the last decade (1). This may subsequently lead to the increased prevalence of cardiometabolic risk factors and the metabolic syndrome already observed at an early age (2). Clusters of cardiometabolic risk factors are risk factors that are not independently distributed in the population but rather cluster in subgroups of children (3) and may be a biological marker of poor cardiometabolic health in apparently healthy children (4).

Several cross-sectional studies have suggested a negative association between physical activity and clustered cardiometabolic risk (5–10), and time spent in moderate-to-vigorous physical activity (MVPA)⁵ seems to be independently associated with cardiometabolic health (8). In contrast, objectively measured time spent sedentary seems to be unrelated to cardiometabolic risk when time spent in MVPA is taken into account (8). The prospective associations between sedentary time, MVPA, and cardiometabolic health, however, are less evident. Only a few studies to our knowledge have examined whether sedentary time and/or physical activity prospectively predict cardiometabolic risk in children (11, 12), and it is unclear which aspects of physical activity may be more strongly associated with cardiometabolic risk. This knowledge is important when designing future interventions and informing public health policy.

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⁵Abbreviations used: MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; SBP, systolic blood pressure; SES, socioeconomic status; TC, total cholesterol; VPA, vigorous physical activity; WC, waist circumference.

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Therefore, we analyzed the independent prospective associations between objectively measured sedentary time, moderate physical activity (MPA), vigorous physical activity (VPA), and MVPA with both individual risk factors and clustered cardiometabolic risk in a sample of healthy children.

METHODS

We used data from the Active Smarter Kids study (NCT02132494), a 7-mo cluster-randomized controlled trial conducted from 2014 to 2015 (13). All children were fifth-graders aged 10 y from Sogn og Fjordane, Norway. In total, 1145 (97.4%) of eligible children from 57 schools (28 intervention schools and 29 control schools) agreed to participate in the study. Of these, 1129 provided data on at least some of the variables of interest. Children who were diagnosed as patients with type 1 diabetes were excluded ($n = 5$) before analyses. Valid data on objectively measured physical activity were available for 1006 children, of which 900 provided fasting blood samples. Forty-two children did not provide data on systolic blood pressure (SBP) and waist circumference (WC), leaving 858 children with valid measurements on all variables of interest at baseline. At follow-up, another 158 children were excluded because of invalid physical activity measurements ($n = 58$), lack of fasting blood samples ($n = 80$), or missing data on SBP or WC ($n = 20$), leaving 700 children with complete data on exposure and outcome variables at both baseline and follow-up. **Figure 1** shows the number of schools and children included in the study at baseline, those excluded, and reasons for exclusion. Main results from the Active Smarter Kids study intervention have recently been reported (14). Because there was no difference in either physical activity or sedentary time from baseline to follow-up between intervention and control schools (14), all data were pooled and analyzed as a cohort.

A detailed description of the study design and methodology has been published elsewhere (13). In summary, baseline measurements were obtained between April and October 2014, and follow-up measurements were obtained between April and June 2015. Weight was measured to the nearest 0.1 kg with the use of a SECA 899 electronic scale. Height was measured to the nearest 0.1 cm with the use of a portable SECA 217. BMI (in kg/m^2) was calculated and used to categorize children as normal weight, overweight, or obese according to age-adjusted BMI thresholds (15). WC was measured with a SECA 201 ergonomic circumference measuring tape. Two measurements were taken between the lowest rib and iliac crest with the child's abdomen relaxed at the end of a gentle expiration. If the 2 results differed by >1 cm, a new measurement was taken until 2 results were ≤ 1 cm. Children self-assessed their pubertal stage according to the Tanner method (16) with the use of a scale of color images (17). Children were given a standardized series of images with explanatory text in a private room. SBP was measured with the use of an Omron HBP-1300 automated blood pressure monitor. Before each blood pressure measurement, children rested for 10 min in a sitting position. Blood pressure was thereafter measured on the upper right arm with the use of an appropriately sized cuff. Four measurements were taken with a 1-min interval between each measurement, and the mean of the last 3 measurements was used for analyses. If a difference of >5 mm Hg between measurements was observed, we conducted an additional measurement, in which case the mean of the last 4 measurements was calculated and used

in the analyses. All anthropometric and blood pressure measurements were performed by trained personnel. Parental education status was self-reported by the children's parents and used as an indicator of socioeconomic status (SES).

A nurse or phlebotomist collected blood samples from the antecubital vein after an overnight fast. Serum samples were analyzed for constituents related to traditional cardiometabolic risk factors [insulin, glucose, triglycerides, total cholesterol (TC), and HDL cholesterol] with the use of standard laboratory methods. Blood samples from baseline and follow-up were analyzed at the same time in a single batch at an International Organization for Standardization-certified laboratory. The HOMA-IR was calculated as fasting insulin \times fasting glucose/22.5 (18). The TC:HDL cholesterol ratio was calculated because it has been shown to be the most informative cholesterol-related index (19).

Physical activity and sedentary time were measured with the use of ActiGraph GT3X accelerometers. The children were fit with accelerometers at school and instructed to wear the accelerometer on the right hip at all times for the next 7 consecutive days, except during water-based activities and while sleeping. Valid monitor wear time was defined as achieving ≥ 480 min/d accumulated between 0600 and 0000. Continuous bouts ≥ 20 min of zero counts were defined as nonwear time (20), and children recording ≥ 4 of 7 d were included in the analyses. Sedentary time (<100 counts/min), MPA (>2296 counts/min), and VPA (>4012 counts/min) were defined according to previously established and validated cutoffs (21, 22). All accelerometer data were analyzed in 10-s epochs with the use of Kinesoft analytic software.

Ethics

All procedures and methods conformed to the ethical guidelines defined by the World Medical Association's Declaration of Helsinki and its subsequent revisions (23). The Regional Committee for Medical Research Ethics approved the study protocol. Written informed consent from each child's parent or legal guardian and the responsible school authorities were obtained before all testing.

Statistics

Descriptive characteristics are presented as means \pm SDs for normally distributed data, medians (IQRs) for non-normally distributed data, or frequencies (percentages). The effect of time and the prospective associations between exposure and outcome were analyzed with the use of linear mixed models, including the random intercept of school to account for the cluster effect. All physical activity variables were log-transformed to improve the normality of distribution. Although some of the individual cardiometabolic risk factors were skewed, the change between baseline and follow-up were normally distributed and therefore not log-transformed. A continuous cardiometabolic risk score was calculated by summing the age- and sex-standardized variables for SBP, WC, triglycerides, TC:HDL cholesterol, and HOMA-IR and then divided by the number of variables. A nonobesity cardiometabolic risk score was also computed that omitted WC. All variables were transformed to z scores for ease of interpretation. We included an interaction term (sex \times baseline exposure) to test whether sex modified the associations. However, there were no sex-specific effects; thus, all analyses were performed in the total sample. First, we modeled the associations between baseline

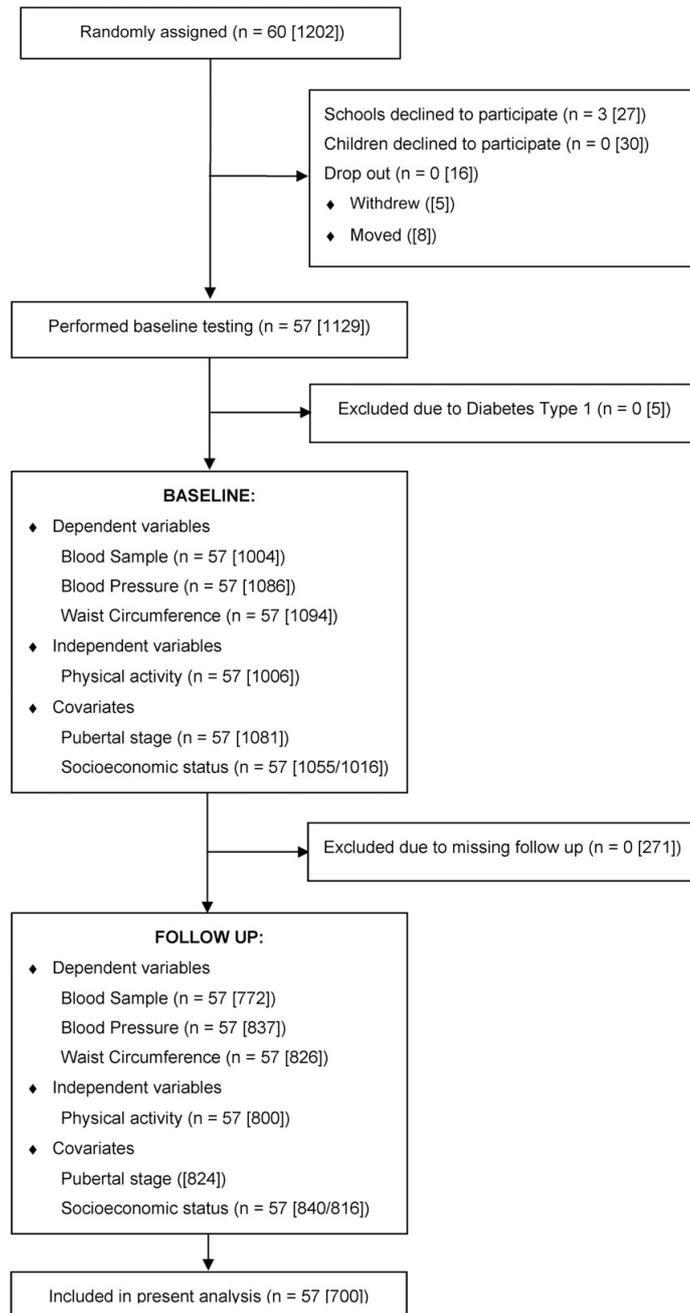


FIGURE 1 Flow of schools and children through the study. All numbers are shown as total number of schools and total number of children in brackets. Only children who had a complete set of data at baseline and follow-up were included in the final analysis.

sedentary time, MPA, VPA, and MVPA with individual cardiometabolic risk factors at follow-up adjusting for sex, Tanner stage, SES, monitor wear time, and the respective risk factor at

baseline (model 1). Second, we adjusted the analyses for WC to assess whether the associations were independent of adiposity when WC was not the outcome of interest (model 2). Because of

multicollinearity ($r = -0.59$ to -0.78) sedentary time, MPA, VPA, and MVPA were not mutually adjusted.

The associations between the subcomponents of physical activity and a clustered cardiometabolic risk at follow-up were modeled adjusting for clustered cardiometabolic risk at baseline and the covariates described previously. Thereafter, WC was excluded from the clustered cardiometabolic risk and added as a covariate in the next model to examine whether the prospective associations were independent of adiposity. For illustrative purposes, we categorized the children by quartiles of baseline MVPA and examined differences between these quartiles in clustered cardiometabolic risk in a finally adjusted model as described previously.

All analyses were performed with the use of SPSS version 23 (IBM). $P < 0.05$ was considered statistically significant.

RESULTS

Baseline and follow-up characteristics are presented in **Table 1**. Seven-hundred children (49.1% boys and 50.9% girls) with a mean \pm SD age of 10.2 ± 0.3 y were included in the analyses.

Those who were excluded between baseline and follow-up ($n = 395$) from the analysis were shorter ($P = 0.009$), but there were no differences in body weight ($P = 0.330$), WC ($P = 0.824$), or SBP ($P = 0.817$) at baseline between those included and those excluded.

At baseline, 78.4% of the children were categorized as having normal BMI. Children recorded 6.3 d (mean: 783.2 min/d) and 6.4 d (mean: 786.2 min/d) of valid physical activity measurements at baseline and follow-up, respectively. MPA and VPA decreased by 4.7 min/d (95% CI: 3.4, 6.0 min/d) and 4.6 min/d (95% CI: 3.5, 5.7 min/d), respectively, whereas MVPA decreased by 9.2 min/d (95% CI: 7.5, 10.9 min/d) between baseline and follow-up (all $P < 0.001$). Sedentary time increased by 27.1 min/d (95% CI: 31.1, 23.2 min/d) ($P < 0.001$). A statistically significant increase was observed for WC ($P = 0.004$), whereas triglycerides ($P = 0.012$) and TC:HDL cholesterol ($P = 0.002$) decreased. HOMA-IR and SBP did not change over time ($P > 0.133$).

Table 2 shows the prospective associations between sedentary time, physical activity, and individual cardiometabolic risk

TABLE 1
Baseline and follow-up characteristics of children from the Active Smarter Kids study¹

	Baseline (<i>n</i> = 700)	Follow-up (<i>n</i> = 700)	Correlation	Change score	<i>P</i> values
Age, y	10.2 \pm 0.3	—	—	—	—
Sex, %					
Boys	49.1	—	—	—	—
Girls	50.9	—	—	—	—
Height, cm	143.1 \pm 6.7 ²	147.0 \pm 7.0	0.98	3.9 \pm 1.3	<0.001
Weight, kg	35.6 (31.6–41.4) ³	37.9 (33.6–43.8)	0.98	2.4 \pm 1.7	<0.001
Tanner stage, <i>n</i> (%)			0.46		<0.001
1	206 (24.9)	91 (13.0)		–115	
2	413 (59.0)	446 (63.7)		+33	
≥ 3	75 (10.7)	162 (23.1)		+87	
Missing	6 (0.9)	1 (0.1)		–5	
SES, %					
Low	44.3	—	—	—	—
Middle	26.9	—	—	—	—
High	23.5	—	—	—	—
Missing	5.3	—	—	—	—
BMI, kg/m ²	17.3 (15.9–19.5)	17.5 (16.3–19.6)	0.96	0.13 \pm 0.8	0.369
Normal, %	78.4	81.2	—	—	—
Overweight, %	17.7	15.2	—	—	—
Obese, %	3.9	3.6	—	—	—
WC, cm	60.5 (56.8–66.5)	61.3 (58.0, 66.5)	0.93	1.1 \pm 2.8	0.004
SBP, mm Hg	105.4 \pm 8.3	104.7 \pm 8.1	0.53	–0.6 \pm 8.0	0.133
TGs, mmol/L	0.69 (0.54–0.89)	0.66 (0.54–0.85)	0.43	–0.04 \pm 0.36	0.012
TC:HDL cholesterol, mmol/L	2.77 (2.41–3.25)	2.67 (2.36–3.12)	0.83	–0.10 \pm 0.40	0.002
HOMA-IR	1.78 (1.25–2.47)	1.89 (1.26–2.63)	0.63	0.3 \pm 6.7	0.374
Monitor wear time, min/d	783.2 \pm 49.9	786.2 \pm 50.5	0.33	3.0 \pm 58.0	0.247
Overall PA, counts/min	706 (554–883)	606 (484–740)	0.36	–123 \pm 285	<0.001
Sedentary, min/d	467.0 (428–503)	496 (458–530)	0.54	27.1 \pm 53.3	<0.001
MPA, min/d	44.4 (31.5–48.2)	39.1 (31.5–48.2)	0.53	–4.7 \pm 12.0	<0.001
VPA, min/d	29.8 (20.5–48.5)	25.6 (18.0–35.5)	0.53	–4.6 \pm 14.7	<0.001
MVPA, min/d	74.6 (58.7–93.6)	65.9 (51.4–82.1)	0.56	–9.2 \pm 23.2	<0.001

¹ The change from baseline to follow-up was analyzed with the use of a linear mixed model with school as the random intercept. $P < 0.05$ was considered significant. MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; PA, physical activity; SBP, systolic blood pressure; SES, socioeconomic status; TC, total cholesterol; TG, triglyceride; VPA, vigorous physical activity; WC, waist circumference.

² Mean \pm SD (all such values).

³ Median; IQR in parentheses (all such values).

factors from the adjusted analyses. Sedentary time showed no significant associations with any of the cardiometabolic risk factors at follow-up ($P > 0.052$). MPA was significantly and inversely associated with triglycerides [$\beta = -0.086$ (95% CI: $-0.160, -0.013$); $P = 0.021$] and HOMA-IR [$\beta = -0.070$ (95% CI: $-0.132, -0.008$); $P = 0.027$] at follow-up and remained significant after further adjusting for WC. Prospective associations between MVPA and individual risk factors were similar as for MPA but attenuated for HOMA-IR after adjusting for WC. VPA was associated with triglycerides at follow-up, but this association was attenuated ($P = 0.052$) when adjusting for WC.

We thereafter examined the prospective association between sedentary time and physical activity with clustered cardiometabolic risk adjusting for the same covariates as described previously (Table 3). Sedentary time and MPA were not associated with clustered cardiometabolic risk in any of the models. Time spent in VPA [$\beta = -0.060$ (95% CI: $-0.113, -0.007$); $P = 0.028$] and MVPA [$\beta = -0.056$ (95% CI: $-0.109, -0.002$); $P = 0.043$] were inversely associated with cardiometabolic risk at follow-up. However, when excluding WC from the clustered cardiometabolic risk score and adjusting the analyses for WC, these associations were attenuated. Figure 2 shows the clustered cardiometabolic risk at follow-up stratified by baseline quartiles of MVPA. A significant difference was observed between the first and fourth quartiles for clustered metabolic risk.

DISCUSSION

This study examined the prospective associations between sedentary time and physical activity and cardiometabolic risk factors in children aged 10 y. Baseline physical activity of at least moderate intensity was significantly and inversely associated with cardiometabolic risk factors at follow-up independent of adiposity and confounding factors, indicating a causal relation. Our results highlight the importance of promoting physical activity of at least moderate intensity for favorable cardiometabolic health development in children.

Only a few previous studies to our knowledge have examined the prospective associations between sedentary time, physical activity, and clustered cardiometabolic risk in children (11, 12, 24). Andersen et al. (24) did not observe any associations between physical activity assessed at 6 y and clustered cardiometabolic risk at 9 y. Hjorth et al. (11) suggested a prospective association between time spent in MVPA and some individual cardiometabolic risk factors and with clustered cardiometabolic risk. However, these analyses modeled the association between changes (follow-up minus baseline) in the exposure (i.e., MVPA) with changes in the outcome. This is effectively a cross-sectional analysis and cannot determine the direction of association. Stamatakis et al. (12) did not observe any prospective association between baseline sedentary time and cardiometabolic risk, whereas time in MVPA was inversely associated with individual

TABLE 2
Prospective associations between sedentary time, MPA, VPA, and MVPA at baseline as exposure and individual risk factors at follow-up as outcomes¹

	Model 1 ² (n = 700)	P value	Model 2 ³ (n = 700)	P value
Sedentary				
WC	-0.016 (-0.049, 0.017)	0.342	—	—
SBP	-0.015 (-0.097, 0.068)	0.731	-0.024 (-0.107, 0.059)	0.570
TGs	0.083 (-0.001, 0.168)	0.052	0.061 (-0.022, 0.143)	0.150
TC:HDL cholesterol	-0.008 (-0.061, 0.045)	0.757	-0.015 (-0.068, 0.038)	0.571
HOMA-IR	0.013 (-0.059, 0.085)	0.722	-0.001 (-0.070, 0.070)	0.989
MPA				
WC	0.011 (-0.018, 0.040)	0.456	—	—
SBP	-0.006 (-0.067, 0.079)	0.870	0.016 (-0.058, 0.090)	0.669
TGs	-0.107 (-0.182, -0.033)	0.005	-0.086 (-0.160, -0.013)	0.021
TC:HDL cholesterol	-0.005 (-0.052, 0.042)	0.821	0.001 (-0.046, 0.047)	0.993
HOMA-IR	-0.083 (-0.147, -0.020)	0.010	-0.070 (-0.132, -0.008)	0.027
VPA				
WC	-0.001 (-0.031, 0.028)	0.926	—	—
SBP	-0.008 (-0.081, 0.063)	0.816	0.009 (-0.066, 0.084)	0.810
TGs	-0.120 (-0.194, -0.046)	<0.001	-0.073 (-0.148, 0.001)	0.052
TC:HDL cholesterol	-0.030 (-0.077, 0.016)	0.208	-0.019 (-0.069, 0.029)	0.439
HOMA-IR	-0.058 (-0.122, -0.005)	0.075	-0.027 (-0.090, 0.037)	0.413
MVPA				
WC	0.005 (-0.024, 0.035)	0.725	—	—
SBP	-0.001 (-0.073, 0.073)	0.991	0.014 (-0.060, 0.089)	0.704
TGs	-0.127 (-0.202, -0.051)	<0.001	-0.090 (-0.165, -0.015)	0.019
TC:HDL cholesterol	-0.019 (-0.066, 0.029)	0.437	-0.001 (-0.057, 0.038)	0.694
HOMA-IR	-0.075 (-0.139, -0.010)	0.022	-0.051 (-0.115, -0.012)	0.113

¹ All values are β coefficients (95% CIs) unless otherwise indicated. Individual risk factors were analyzed as z scores (not log-transformed). $P < 0.05$ was considered significant. MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; SBP, systolic blood pressure; SES, socioeconomic status; TC, total cholesterol; TG, triglyceride; VPA, vigorous physical activity; WC, waist circumference.

² Data were analyzed with the use of a linear mixed model with school as the random intercept; β coefficients were adjusted for baseline values for sex, monitor wear time, Tanner stage, SES, and cardiometabolic risk factor.

³ WC was omitted from the clustered cardiometabolic risk and added as a covariate; β coefficients were adjusted for baseline values for sex, monitor wear time, Tanner stage, SES, cardiometabolic risk factor, and WC.

TABLE 3

Prospective associations between sedentary time, MPA, MVPA, and VPA at baseline as exposure and clustered cardiometabolic risk at follow-up as outcomes¹

	Model 1 ² (n = 700)		Model 2 ³ (n = 700)	
	Cardiometabolic risk	P	Cardiometabolic risk	P
Sedentary	0.012 (−0.047, 0.072)	0.683	0.001 (−0.066, 0.068)	0.984
MPA	−0.044 (−0.097, 0.008)	0.099	−0.051 (−0.110, 0.008)	0.093
VPA	−0.060 (−0.113, −0.007)	0.028	−0.044 (−0.105, 0.016)	0.152
MVPA	−0.056 (−0.109, −0.002)	0.043	−0.052 (−0.113, 0.008)	0.091

¹ All values are β coefficients (95% CIs) unless otherwise indicated. MPA, moderate physical activity; MVPA, moderate-to-vigorous physical activity; SES, socioeconomic status; VPA, vigorous physical activity; WC, waist circumference.

² Data were analyzed with the use of a linear mixed model with school as the random intercept; β coefficients were adjusted for baseline values for sex, monitor wear time, Tanner, and SES, clustered cardiometabolic risk.

³ WC was omitted from the clustered cardiometabolic risk and added as covariate; β coefficients were adjusted for baseline values for sex, monitor wear time, Tanner, SES, cardiometabolic risk factor, and WC.

risk factors and clustered cardiometabolic risk. However, the cardiometabolic risk factors were only measured at follow-up. Thus, the analyses failed to adjust for the baseline value of the outcome, which limits any inference of temporality (12). Finally, a weak inverse partial correlation between time in MVPA and clustered cardiometabolic risk has been observed in a cohort of British children aged 5–8 y (25). However, clustered cardiometabolic risk was modeled as the change between baseline and follow-up measurements and correlated with the main exposure (i.e., MVPA), which was expressed as the mean of 4 measurements over the 4-y period, also limiting an inference of a temporal association.

Despite the strength of measuring sedentary time and physical activity objectively in the studies summarized previously, all studies seem to have limitations in their analytic approach assessing the temporal sequence between sedentary time, physical activity, and cardiometabolic risk factors. Our results extend these previous observations and suggest that sedentary time is unrelated to individual cardiometabolic risk factors and clustered cardiometabolic risk and that physical activity of at least moderate intensity seems to be prospectively related to some individual risk factors and clustered cardiometabolic risk also when adjusting for the baseline value of the outcome. However, the association with clustered cardiometabolic risk may be confounded by adiposity.

We observed significant prospective associations between baseline MPA and 2 of the individual cardiometabolic risk factors: HOMA-IR and triglycerides. This is in agreement with previous cross-sectional studies that have suggested that most of the variation in the cardiometabolic risk explained by physical activity seems to be attributed to reductions in fasting insulin and triglycerides (6). Interestingly, the associations between VPA and these risk factors were attenuated after adjusting for adiposity. This may be explained by the low amount of time spent in VPA in the overweight and obese children and thus an attenuating effect of adiposity when included as a confounder. However, the effect of physical activity might partly be mediated by adiposity (26), implying that the adjustment for WC is overly conservative. Physical activity of at least moderate intensity influences a range of biological mechanisms that may affect cardiometabolic risk without influencing adiposity. An acute effect of physical activity is improved insulin action and glucose transport (27). Furthermore,

physical activity increases blood flow and oxygen supply through the increased density of capillaries and vasodilatation by nitric oxide, hence improving fat metabolism (28, 29). Physical activity may also reduce the sympathetic tone and thus affect blood pressure (30). We did not find any associations between sedentary time and any of the individual or clustered cardiometabolic risk factors. A systematic review (31) has reported that all the included studies investigating sedentary time and the metabolic syndrome in children had a consistent positive relation. However, these studies were cross-sectional in design, varied substantially in the risk factors assessed, and mainly addressed associations between television-viewing time and cardiometabolic risk factors. Our observation is in agreement with previous large-scale cross-sectional studies that have suggested that objectively measured sedentary time is unrelated to cardiometabolic risk factors (8, 12).

The magnitude of associations in terms of practical significance for the cluster of cardiometabolic risk is difficult to interpret. A recent study that examined the utility of different

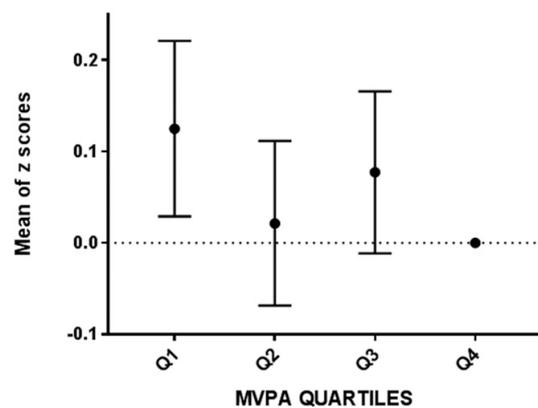


FIGURE 2 Clustered cardiometabolic risk (z scores) at follow-up stratified by baseline quartiles of MVPA in healthy children ($n = 175$ for each quartile). Data were analyzed with the use of a linear mixed model with school as the random intercept and adjusted for sex, socioeconomic status, Tanner stage, monitor wear time, and baseline cardiometabolic risk. Error bars represent SEs. The medians for quartiles 1–4 were 48.3, 66.6, 82.2, and 107.7 min/d, respectively. MVPA, moderate-to-vigorous physical activity; Q, quartile.

continuous metabolic syndrome scores in a cohort of younger adults followed between 15 and 25 y found that a 1-SD increase in the *z* score predicted a $\geq 30\%$ increased risk for type 2 diabetes (32). In our study, a 1-SD increase in VPA predicted a 0.06-SD lower clustered cardiometabolic risk over a short time period. In theory, if the entire risk reduction was caused by a single individual risk factor, a 10-min increase in VPA predicted a reduction in WC or SBP of 0.05 cm and 0.05 mm Hg, respectively. Furthermore, not meeting 60 min of MVPA daily as recommended predicted a 0.51-cm higher WC and 0.54-mm Hg higher SBP. Although it is uncertain how elevated risk in a child is related to later cardiovascular disease (4, 32), the clustering of cardiometabolic risk factors seems fairly stable throughout the first decades of life and tracks into adulthood (33). Therefore, small differences between different activity groups observed in healthy children may translate to large differences by age.

This study has several strengths. First, the prospective design, including measurements at 2 time points and analyses adjusted for baseline levels of the outcome variable, allowed a stronger interference for potential causal relations between physical activity and cardiometabolic risk in young children. Second, our analyses accounted for several putative confounding factors (sex, Tanner stage, SES, monitor wear time, and WC). Third, the compliance with physical activity measurements was high (≥ 6 d at both time points). However, our results should also be interpreted with some limitations in mind. It is unlikely that 6 d of objective physical activity measurements reflect the true within- and between-individual variation. If this error is random, it will attenuate the observed associations. Mattocks et al. (34) reported that the intraclass correlation coefficient is 0.5 in healthy children. The intraclass correlation coefficient can then be used for correcting the measurement error, and if the assumption is that all measurement errors stem from interindividual variability, the observed associations between physical activity and individual and clustered risk factors may be twice as strong. Although accelerometers are an appropriate and objective measurement of physical activity, they cannot distinguish between important different sedentary behaviors (e.g., standing compared with sitting) or the context and/or type of activity. A limitation is that we were unable to mutually adjust the associations between physical activity and sedentary time with cardiometabolic risk factors because of high multicollinearity between variables. Furthermore, a large number of children were excluded from the analysis because only those who had complete data for outcome and exposure at both time points were included. However, differences between included and excluded children were minor at baseline. The follow-up time was rather short and comprised slightly less than one school year. Thus, future studies with longer durations of follow-up are needed. Last, our sample was highly heterogeneous in terms of ethnicity and environmental living conditions.

In conclusion, physical activity of at least moderate intensity is prospectively and inversely associated with cardiometabolic risk factors in healthy children. This association seems to be independent of adiposity and confounding factors for triglycerides and HOMA-IR. In contrast, sedentary time is unrelated to both individual and clustered cardiometabolic risk.

The authors' responsibilities were as follows—EA, SAA, GKR, and UE: designed the research; TS, MS, EA, KNA, and GKR: conducted the research; TS, EA, and UE: analyzed the data; TS, EA, GKR, and UE: wrote

the manuscript and had primary responsibility for the final content; and all authors: read and approved the final manuscript. None of the authors reported a conflict of interest related to the study.

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STUDY III



Does cardiorespiratory fitness moderate the prospective association between physical activity and cardiometabolic risk factors in children?

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Abstract

Background/Objectives Physical activity (PA) and cardiorespiratory fitness (CRF) are independently associated with reduced cardiometabolic risk in children, and may affect risk through different pathways. This study aims to examine if CRF moderate the prospective association between PA, sedentary time, and cardiometabolic outcomes in 10-year-old children.

Subjects/Methods In total, 718 children of 1129 (drop out $n = 7$) had valid measures of PA (accelerometry), CRF (the Andersen running test), and a cardiometabolic risk profile measured at baseline and follow-up 7 months later. Cardiometabolic outcomes were systolic blood pressure, waist circumference (WC), total cholesterol, high-density lipoprotein, triglycerides, glucose, and insulin (HOMA-IR). The cardiometabolic risk factors were analysed individually, and as a clustered risk score (z score). A linear mixed model was used to examine the prospective associations between different PA exposures (overall PA, sedentary time, moderate-to-vigorous PA (MVPA), vigorous PA) and cardiometabolic outcomes, including the interaction term $PA \times CRF$ in the model to assess moderation by CRF.

Results CRF modified the association for baseline overall PA ($P < 0.039$) and MVPA (min/day) with clustered cardiometabolic risk at follow-up ($P < 0.023$). Moreover, CRF modified the association between overall PA and MVPA with HOMA-IR independent of WC ($P < 0.022$). When stratified by CRF level (median split; high/low), MVPA predicted lower HOMA-IR [MVPA $\beta -0.133$ (95% CI: $-0.223, -0.043$); $P = 0.004$] and clustered cardiometabolic risk [MVPA $\beta -0.094$ (95% CI: $-0.169, -0.019$); $P = 0.014$] in children with low CRF, but not among their fitter peers ($P > 0.232$). There was neither direct association between sedentary time and cardiometabolic risk factors in any analyses, nor moderation by CRF.

Conclusion CRF significantly moderated the prospective association between PA and the clustered cardiometabolic risk, but not for time spent sedentary. The magnitude of association between MVPA and clustered cardiometabolic risk was stronger in children with low CRF, and no associations appeared present in their high-fit peers.

Introduction

Unfavourable levels of cardiometabolic risk factors appear to manifest already during childhood [1], which may increase the risk for cardiometabolic disease later in life [2]. Physical activity (PA) of at least moderate intensity is

inversely associated with cardiometabolic risk in children [3–6]. Similarly, cardiorespiratory fitness (CRF) is a strong and independent predictor of cardiometabolic risk [7–9]. However, in studies using objective assessment of PA, moderate-to-vigorous intensity PA (MVPA) and CRF appear independently associated with cardiometabolic risk in children, possibly affecting cardiometabolic risk through partly different pathways [9]. The association between CRF and cardiometabolic risk is mediated by adiposity [9], partly due to correlation with body weight and computation of CRF [7, 9], while PA show independent associations with cardiometabolic risk [9]. Moreover, CRF has a genetic component [10], suggesting that some individuals may be predisposed to a higher CRF. Thus, associations between

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PA and cardiometabolic risk factors might be different pronounced in those with low and high CRF.

Although, CRF might potentially moderate the association between PA and cardiometabolic risk, only two cross-sectional studies have examined such an influence of CRF on this relationship [4, 11]. While both these studies suggested stronger associations between PA and cardiometabolic risk [4] and abdominal adiposity [11] in those with lower CRF, the cross-sectional analyses preclude inference about temporality and indication of causality. Further, it is unknown whether prospective associations between sedentary time with cardiometabolic risk might also be modified by CRF. Therefore, the aim of this study was to examine whether CRF modified the prospective association between objectively measured PA and sedentary time with traditional cardiometabolic risk factors in healthy 10-year-old children.

Methods

Study design

We used data from the Active Smarter Kids study (ASK), a 7-month cluster-randomised controlled trial conducted during the school year of 2014–2015 in the Western Norway [12]. Sixty schools were approached (including at least 7 children each class) and 57 schools (1129 children) agreed to participate (recruitment success of 95% of schools, 94% of children). As neither PA nor sedentary time differed from baseline to follow-up between intervention and control schools [13] all data were pooled and analysed as a prospective observational cohort in this study. A detailed description of the study design, methodology and sample size calculation is published previously [12]. Thus, only procedures relevant for the present study are summarised here. Baseline measurements were obtained between April and October 2014, and follow-up measurements between April and June 2015.

Data collection

CRF was assessed using the intermittent Andersen shuttle-run test [14], which is a reliable ($r = 0.63$ – 0.73) and valid method to estimate CRF [15]. Children ran from one end line to another (20 m apart, one hand in floor behind line at each turn) in an intermittent pattern consisting of 15 s running and 15 s breaks. The Andersen test lasts for 10 min (in total; 5 min running, 5 min breaks), where distance covered in metres was registered.

PA and sedentary time was measured using GT3X/GT3X+ accelerometers (ActiGraph, LLC, Pensacola, Florida, USA). All children was fitted with accelerometers

at school and instructed to wear the accelerometer on the right hip at all times for 7 consecutive days, except during water-based activities and while sleeping. Valid monitor wear-time was defined as achieving ≥ 480 min/day accumulated between 06:00 AM and 00:00 PM. Continuous bouts ≥ 20 min of zero counts was defined as non-wear time [16]. Children recording ≥ 4 of 7 days were included in the analyses [17]. Sedentary time (< 100 counts per minute (cpm)), MPA (> 2296 cpm) and VPA (> 4012 cpm) were defined according to previously established and validated cut points [18, 19]. All accelerometer data were analysed in 10-s epochs using the KineSoft analytical software (KineSoft version 3.3.80, Loughborough, UK).

Body weight was measured to the nearest 0.1 kg using an electronic scale (SECA 899, SECA GmbH, Hamburg, Germany). Height was measured to the nearest 0.1 cm using a portable stadiometer (SECA 217, SECA GmbH, Hamburg, Germany). Body mass index (BMI; $\text{kg} \times \text{m}^2$) were calculated and children categorised as normal weight, overweight, or obese according to age-adjusted BMI thresholds [20]. Waist circumference (WC) was measured with an ergonomic circumference measuring tape (SECA 201, SECA GmbH, Hamburg, Germany). Two measurements were taken between the lowest rib and the iliac crest with the child's abdomen relaxed at the end of a gentle expiration. If the two results differed > 1 cm, a new measurement was taken until two results were ≤ 1 cm apart. Children self-assessed their pubertal stage according to the Tanner method [21] using a scale of colour images (stage 1–5) [22] in a private room. Stage 2 marks the onset of pubertal development. Systolic blood pressure (SBP) was measured using an automated blood pressure monitor (Omron HBP-1300, Omron Healthcare, Inc., Vernon Hills, IL, US). Before each blood pressure measurement, the children rested for 10 min in a sitting position. Blood pressure was measured on the upper right arm with an appropriate sized cuff. Four measurements were taken with a 1-min interval between each measurement and the mean of the last three measurements were used for analyses. If a difference > 5 mmHg between measurements was observed, we conducted one additional measurement, in which case the mean of the last four was calculated and used in analyses. All anthropometric and blood pressure measurements were performed by trained test personnel. Parental education level was self-reported by the children's parents and used as an indicator of socio-economic status (SES) and was categorised into three groups; low: < 2 y of high school, middle: < 4 y of college/university or ≥ 4 y of college/university).

A nurse or phlebotomist collected blood samples from the antecubital vein after an overnight fast. Serum samples were analysed for constituents related to traditional cardiometabolic risk factors (insulin, glucose, and the standard

Table 1 Characteristics of the children ($n = 718$) presented for total sample and by the sex-specific median split for CRF

	Sample in total at baseline	Sample in total at follow-up	Low CRF below median split baseline	High CRF above median split baseline
Age (years)	10.2 (0.3)	---	10.2 (0.3)	10.3 (0.3) ^a
Boys/girls (%)	50.3/49.7	—	58.6/41.4	44.2/58.4 ^a
Height (cm)	143.0 (6.7) ^b	147.0 (7.1)	143.3 (6.9)	142.9 (6.6)
Weight (kg)	35.5 (31.6–41.2) ^c	37.8 (33.6–43.7)	37.8 (32.4–45.1)	34.1 (31.1–28.1) ^a
BMI ($\text{kg} \times \text{m}^2$)	17.3 (15.9–19.5)	17.4 (16.1–19.5)	18.6 (16.3–21.3)	16.7 (15.5–18.1) ^a
<i>SES^{a,d} (n & %)</i>				
Low	666 (46.4)	—	187 (61.5)	134 (44.1)
Middle	325 (22.6)	—	48 (15.8)	76 (25.0)
High	350 (24.4)	—	40 (13.2)	77 (25.3)
Missing	95 (6.6)	—	29 (9.5)	17 (5.6)
<i>Pubertal status (n & %)</i>				
Stage 1	210 (29.4)	—	89 (29.3)	121 (29.2)
Stage 2	428 (59.9)	—	168 (55.3)	260 (62.8)
Stage ≥ 3	77 (10.7)	—	45 (14.8)	32 (7.7)
Missing	3 (0.4)	—	2 (0.7)	1 (0.2)
Clustered risk score	-0.22 (-0.64–0.45)	-0.21 (-0.70–0.45)	0.07 (-0.50–0.94)	-0.38 (-0.74–0.16) ^a
WC (cm)	60.3 (56.8–65.5)	61.3 (58.0–66.5)	63.8 (58.4–70.9)	59.0 (56.0–62.3) ^a
SBP (mmHg)	105.4 (8.4)	104.7 (8.1)	105.3 (8.4)	105.5 (8.5)
TG (mmol/L)	0.69 (0.54–0.88)	0.66 (0.54–0.85)	0.73 (0.57–0.97)	0.66 (0.53–0.54) ^a
TC:HDL (mmol/L)	2.77 (2.42–3.22)	2.66 (2.35–3.11)	2.89 (2.52–3.49)	2.69 (2.37–3.1) ^a
HOMA-IR	1.77 (1.25–2.47)	1.89 (1.26–2.63)	1.92 (1.39–2.86)	1.67 (1.21–2.23) ^a
Monitor wear time (min/day)	784.0 (51.1)	784.4 (53.8)	781.3 (51.7)	786.1 (50.6)
SED (min/day)	467.2 (58.0)	492.6 (54.4)	473.0 (61.9)	462.9 (54.6)
VPA (min/day)	30.0 (20.7–40.6)	25.8 (18.0–51.9)	24.7 (17.0–35.0)	32.9 (23.0–43.0) ^a
MVPA (min/day)	74.7 (59.2–93.7)	66.4 (51.9–82.5)	67.6 (53.3–84.8)	79.2 (63.7–98.2) ^a
CPM (counts/min)	710 (560–880)	611 (487–742)	652 (515–809)	747 (583–906) ^a
Andersen-test (metres)	901 (102)	941 (98)	819 (77)	961 (71) ^a

CRF cardiorespiratory fitness, CPM counts per minute, HOMA-IR homeostatic model assessment of insulin resistance, MVPA moderate-to-vigorous physical activity, SBP systolic blood pressure, SED sedentary, SES socio-economic status, TC:HDL the ratio of total cholesterol and high-density lipoprotein cholesterol, TG triglycerides, VPA vigorous physical activity, WC waist circumference

^aSignificant difference between low/high CRF

^bMean and SD (all such values)

^cMedian and IQR (all such values)

^dSES reported by both parents

lipid panel) using standard laboratory methods. Blood samples from baseline and follow-up were analysed at the same time in a single batch at an ISO certificated laboratory. The HOMA-IR was calculated as (fasting insulin \times fasting glucose)/22.5 as suggested by Matthews et al. [23]. The total cholesterol (TC) to HDL (TC:HDL) ratio were calculated for the analyses, which is the most informative cholesterol-related index [24].

Ethics

Our procedures and methods conform to the ethical guidelines defined by the World Medical Association's Declaration of Helsinki [25] and its subsequent revisions. The Regional Committee for Medical Research Ethics committee in Norway approved the study protocol (2013/1893/REK). Written informed consent from each child's

Table 2 Prospective associations between sedentary time and PA with individual cardiometabolic risk factors (model 1) ($n = 718$)

	SED (min/day)	VPA (min/day)	MVPA (min/day)	CPM
<i>WC</i>				
Overall association	-0.019 (-0.053, 0.015) $P = 0.274$	0.004 (-0.027, 0.035) $P = 0.809$	0.010 (-0.021, 0.042) $P = 0.508$	0.010 (-0.020, 0.040) $P = 0.509$
Interaction (CRF × PA exposure)	-0.020 (-0.047, 0.008) $P = 0.150$	0.014 (-0.011, 0.039) $P = 0.275$	0.017 (-0.009, 0.042) $P = 0.192$	0.007 (-0.020, 0.032) $P = 0.613$
<i>SBP</i>				
Overall association	-0.018 (-0.101, 0.065) $P = 0.671$	0.010 (-0.064, 0.085) $P = 0.785$	-0.019 (-0.057, 0.094) $P = 0.626$	0.029 (-0.043, 0.100) $P = 0.426$
Interaction (CRF × PA exposure)	-0.018 (-0.054, 0.082) $P = 0.682$	0.002 (-0.061, 0.064) $P = 0.957$	0.001 (-0.065, 0.063) $P = 0.958$	-0.029 (-0.093, 0.036) $P = 0.384$
<i>TC:HDL</i>				
Overall association	0.019 (-0.045, 0.036) $P = 0.497$	-0.020 (-0.069, 0.029) $P = 0.421$	-0.010 (-0.060, 0.039) $P = 0.687$	-0.003 (-0.051, 0.044) $P = 0.894$
Interaction (CRF × PA exposure)	-0.032 (-0.076, 0.013) $P = 0.164$	0.028 (-0.012, 0.069) $P = 0.172$	0.022 (-0.020, 0.063) $P = 0.311$	0.033 (-0.010, 0.076) $P = 0.128$
<i>TG</i>				
Overall association	0.045 (-0.042, 0.132) $P = 0.306$	-0.077 (-0.155, 0.001) $P = 0.050$	-0.080 (-0.159, -0.001) $P = 0.047$	-0.061 (-0.136, 0.014) $P = 0.112$
Interaction (CRF × PA exposure)	-0.065 (-0.135, 0.005) $P = 0.069$	0.061 (-0.003, 0.125) $P = 0.063$	0.057 (-0.009, 0.123) $P = 0.091$	0.071 (0.004, 0.137) $P = 0.037$
Low CRF	N/A	N/A	N/A	-0.130 (-0.235, -0.026) $P = 0.015$
High CRF	N/A	N/A	N/A	-0.003 (-0.098, 0.099) $P = 0.995$
<i>HOMA-IR</i>				
Overall association	0.009 (-0.066, 0.084) $P = 0.807$	-0.020 (-0.098, 0.038) $P = 0.389$	-0.048 (-0.117, 0.020) $P = 0.165$	0.002 (-0.068, 0.063) $P = 0.941$
Interaction (CRF × PA exposure)	-0.035 (-0.095, 0.025) $P = 0.254$	0.081 (0.026, 0.136) $P = 0.004$	0.088 (0.032, 0.145) $P = 0.002$	0.081 (0.024, 0.138) $P = 0.005$
Low CRF	N/A	-0.130 (-0.220, -0.040) $P = 0.005$	-0.153 (-0.245, -0.062) $P = 0.002$	-0.085 (-0.175, 0.005) $P = 0.065$
High CRF	N/A	0.031 (-0.099, 0.037) $P = 0.377$	0.022 (-0.057, 0.123) $P = 0.474$	0.067 (-0.019, 0.152) $P = 0.129$

All values are standardised β coefficients (95% CIs), analysed with linear mixed model included school as the random intercept, and further adjusted for sex, group allocation, pubertal status (Tanner), SES, monitor wear time, respective baseline cardiometabolic risk factor, and baseline Andersen-test. Individual cardiometabolic risk factors are analysed as z scores (not log transformed).

CRF cardiorespiratory fitness, CPM counts per minute, HOMA-IR homeostatic model assessment of insulin resistance, MVPA moderate-to-vigorous physical activity, PA physical activity, SBP systolic blood pressure, SED sedentary, SES socio-economic status, TC:HDL the ratio of total cholesterol and high-density lipoprotein cholesterol, TG triglycerides, VPA vigorous physical activity, WC waist circumference.

Bold entries denotes statistical significance ($P < 0.05$).

Table 3 Prospective associations between sedentary time and PA with individual cardiometabolic risk factors, adjusted for adiposity (model 2) ($n = 718$)

	SED (min/day)	VPA (min/day)	MVPA (min/day)	CPM
<i>SBP</i>				
Overall association	0.021 (-0.106, 0.062) $P = 0.606$	-0.018 (-0.057, 0.093) $P = 0.634$	-0.024 (-0.052, 0.200) $P = 0.537$	-0.032 (-0.040, 0.103) $P = 0.383$
Interaction (CRF × PA exposure)	0.014 (-0.054, 0.083) $P = 0.682$	-0.005 (-0.068, 0.057) $P = 0.865$	-0.007 (-0.071, 0.057) $P = 0.826$	-0.034 (-0.100, 0.030) $P = 0.293$
<i>TC:HDL</i>				
Overall association	0.023 (-0.075, 0.028) $P = 0.428$	-0.013 (-0.062, 0.037) $P = 0.621$	-0.005 (-0.055, 0.046) $P = 0.854$	-0.003 (-0.050, 0.044) $P = 0.889$
Interaction (CRF × PA exposure)	-0.028 (-0.072, 0.017) $P = 0.224$	0.022 (-0.018, 0.064) $P = 0.276$	0.017 (-0.026, 0.059) $P = 0.433$	0.028 (-0.014, 0.070) $P = 0.192$
<i>TG</i>				
Overall association	0.040 (-0.044, 0.125) $P = 0.347$	-0.056 (-0.132, 0.020) $P = 0.146$	-0.068 (-0.146, 0.009) $P = 0.085$	-0.054 (-0.126, 0.019) $P = 0.147$
Interaction (CRF × PA exposure)	-0.054 (-0.122, 0.014) $P = 0.121$	0.046 (-0.017, 0.109) $P = 0.155$	0.044 (-0.021, 0.110) $P = 0.183$	0.057 (-0.008, 0.122) $P = 0.085$
<i>HOMA-IR</i>				
Overall association	0.005 (-0.167, 0.030) $P = 0.886$	-0.017 (-0.084, 0.050) $P = 0.618$	-0.042 (-0.110, 0.025) $P = 0.218$	0.001 (-0.066, 0.063) $P = 0.964$
Interaction (CRF × PA exposure)	-0.020 (-0.079, 0.040) $P = 0.520$	0.064 (0.010, 0.119) $P = 0.020$	0.074 (0.018, 0.130) $P = 0.009$	0.066 (0.009, 0.119) $P = 0.022$
Low CRF	N/A	-0.098 (-0.187, -0.009) $P = 0.031$	-0.133 (-0.223, -0.043) $P = 0.004$	-0.071 (-0.160, 0.017) $P = 0.117$
High CRF	N/A	0.054 (-0.035, 0.143) $P = 0.233$	0.032 (-0.056, 0.121) $P = 0.466$	0.057 (-0.026, 0.141) $P = 0.180$

All values are standardised β coefficients (95% CIs), analysed with linear mixed model included school as the random intercept, and further adjusted for sex, group allocation, pubertal status (Tanner), SES, monitor wear time, respective baseline cardiometabolic risk factor, baseline Andersen-test and waist circumference as a measure of adiposity. Individual cardiometabolic risk factors are analysed as z scores (not log transformed). Bold entries denotes statistical significance ($P < 0.05$).

CRF cardiorespiratory fitness, CPM counts per minute, HOMA-IR homeostatic model assessment of insulin resistance, MVPA moderate-to-vigorous physical activity, PA physical activity, SBP systolic blood pressure, SED sedentary, SES socio-economic status, TC:HDL the ratio of total cholesterol and high-density lipoprotein cholesterol, TG triglycerides, VPA vigorous physical activity

parent or legal guardian and the responsible school authorities were obtained prior to all testing in 2014.

Statistical analysis

Descriptive characteristics are presented as the mean and standard deviation (SD), median and interquartile range (IQR), or frequencies (%). All PA variables, except sedentary time, were log-transformed to improve the normality of the distributions. Although some of the individual cardiometabolic risk factors were skewed, the residuals of

the change between baseline and follow-up for the cardiometabolic risk factors were normally distributed and the respective outcome were therefore kept un-transformed. All variables were standardised to z scores for ease of interpretation, thus, all regression coefficient are given in SD units. No sex-specific interactions (sex × baseline exposure) were found, and all analyses were performed in the whole sample, adjusted for sex.

The statistical analyses were performed in three steps using two models. First, we modelled the prospective associations between baseline sedentary time, VPA, MVPA

Table 4 Prospective associations between sedentary time and PA with clustered cardiometabolic risk factors (model 1 and 2) ($n = 718$)

MODEL 1 ^a	SED (min/day)	VPA (min/day)	MVPA (min/day)	CPM
Clustered cardiometabolic risk score				
Overall association	-0.007 (0.068, 0.055) $P = 0.830$	-0.026 (-0.081, 0.030) $P = 0.364$	-0.021 (-0.077, 0.035) $P = 0.453$	-0.002 (-0.051, 0.056) $P = 0.931$
Interaction (CRF × PA exposure)	-0.047 (-0.096, 0.002) $P = 0.058$	0.055 (0.010, 0.100) $P = 0.017$	0.054 (0.008, 0.100) $P = 0.023$	0.049 (0.002, 0.096) $P = 0.039$
Low CRF	N/A	-0.099 (-0.171, -0.025) $P = 0.009$	-0.094 (-0.169, -0.019) $P = 0.014$	-0.042 (-0.116, 0.032) $P = 0.268$
High CRF	N/A	0.040 (-0.033, 0.115) $P = 0.280$	0.040 (-0.034, 0.112) $P = 0.289$	0.043 (-0.027, 0.112) $P = 0.232$
MODEL 2 ^b	SED (min/day)	VPA (min/day)	MVPA (min/day)	CPM
Clustered non-obesity cardiometabolic risk score				
Overall association	-0.011 (-0.081, 0.059) $P = 0.761$	-0.024 (-0.087, 0.040) $P = 0.463$	0.031 (-0.095, 0.032) $P = 0.333$	-0.001 (-0.068, 0.054) $P = 0.820$
Interaction (CRF × PA exposure)	-0.033 (-0.089, 0.023) $P = 0.246$	0.047 (-0.005, 0.098) $P = 0.077$	0.047 (-0.005, 0.100) $P = 0.079$	0.042 (-0.011, 0.096) $P = 0.118$

All values are standardized β coefficients (95% CIs), analysed with linear mixed model included school as the random intercept

CRF cardiorespiratory fitness, CPM counts per minute, MVPA moderate-to-vigorous physical activity, PA physical activity, SED sedentary, VPA vigorous physical activity

Bold entries denotes statistical significance ($P < 0.05$).

^aAdjusted for sex, group allocation, pubertal status (Tanner), SES, monitor wear time, baseline clustered cardiometabolic risk score, and Andersen-test

^bAdjusted as model 1, but WC omitted from the cardiometabolic risk score and added as covariate

and overall PA (cpm) with individual cardiometabolic risk factors at follow-up adjusted for the baseline value of the respective risk factor, CRF, sex, pubertal stage, SES, monitor wear time and group allocation (Step 1, model 1). Thereafter, we examined potential interactions between the different PA exposures (sedentary time, VPA, MVPA, overall PA) and CRF by including the interaction term CRF × PA exposure by baseline values in the model (Step 2, model 1). If a significant interaction ($P < 0.05$) was observed, we stratified the analyses by sex-specific median split for CRF to explore the difference in magnitude of the prospective association between the exposure variables in low and high CRF groups (Step 3, model 1). In model 2, we repeated the three steps in Model 1 with additional adjustments for WC to examine whether the associations were independent of abdominal adiposity. Finally, we repeated the two models using a continuous clustered cardiometabolic risk score. The score was calculated as the sum (z score) of age and sex standardized variables (z SBP + z WC + z Triglycerides + z TC:HDL + z HOMA-IR/5). A non-obesity cardiometabolic risk score was also computed, omitting WC from the calculation of the risk score. In all

models, sedentary time and PA variables were analysed one by one to avoid multi-collinearity. To account for possible clustering of observations within schools, all analyses were performed using linear mixed models, including school as a random effect.

Analyses were performed using the SPSS software, version 24 (IBM SPSS Statistics for Windows, Armonk, NY: IBM Corp., USA). A P -value of < 0.05 was used to indicate statistical significance.

Results

Children's characteristics at baseline are presented in Table 1. Of 1129 participants, only seven children dropped out of the study and 718 children (50.3% boys) aged 10.2 ± 0.3 had valid measurements for exposure and outcome at both time points. Excluded children (total $n = 411$) were shorter [1.00 cm (95% CI 0.15, 1.8); $P = 0.021$], but there were no differences in baseline BMI ($P = 0.533$), WC ($P = 0.755$) or SBP ($P = 0.716$) compared to the included children. The majority of the children were normal weight

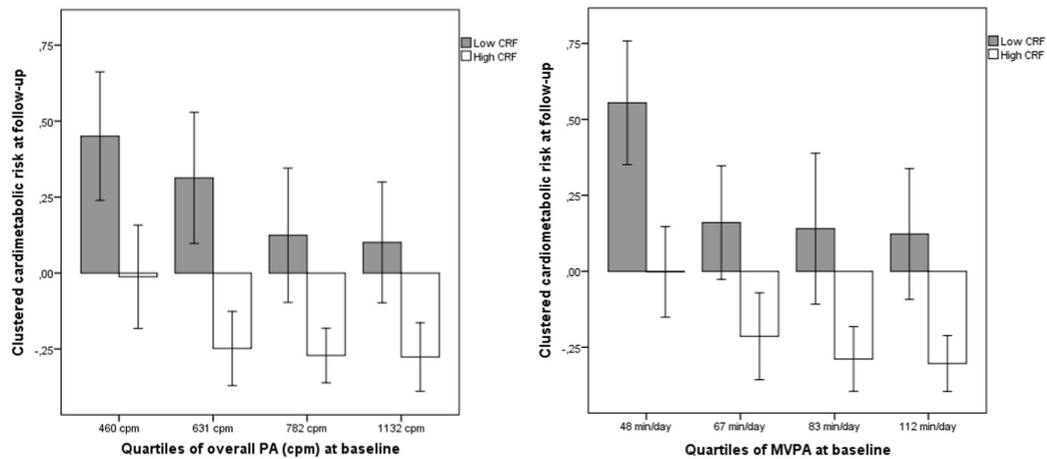


Fig. 1 Prospective association between quartiles (Q1–Q4) of overall PA (cpm) and MVPA (min/day) with clustered cardiometabolic risk

(95% CI), stratified by CRF below and above the sex-specific median. Figures are adjusted for all covariates.

(78.1%), and 3.6% were categorised as obese. At baseline and follow-up, the children had >6 days of valid PA measurement and mean 784 ± 51 min/day monitor wear time. Boys spent more time in MVPA [15 min (95% CI 12, 19); $P < 0.001$] and covered a longer distance during the Andersen-test compared to the girls [60 m (95% CI 46, 75); $P < 0.001$], but there were no differences in time spent sedentary ($P = 0.691$). At baseline, children with high CRF (above the median split) had more beneficial values in all PA and cardiometabolic measures ($P < 0.05$), except for SBP. There were no differences between groups for pubertal stage and monitor wear time. The sex-specific median split by the Andersen-test (940 m for boys, 875 m for girls) correspond to a peak oxygen uptake of 58.2 ml/kg/min and 50.8 ml/kg/min, respectively [26].

MVPA were associated with lower TG at follow-up, independent of CRF [$\beta -0.080$ (95% CI: $-0.159, -0.001$); $P = 0.047$], but this association was attenuated by WC [$\beta 0.044$ (95% CI: $-0.021, 0.010$) $P = 0.085$] (Table 2). CRF modified the prospective associations between overall PA and time spent in at least moderate PA with HOMA-IR ($P < 0.005$) at follow-up (Table 2), also when adjusted for WC ($P < 0.022$). In children with low CRF, both VPA and MVPA at baseline were significantly associated with lower HOMA-IR [MVPA $\beta -0.153$ (95% CI: $-0.245, -0.062$); $P = 0.002$] at follow-up, also when adjusted for WC [MVPA $\beta -0.133$ (95% CI: $-0.223, -0.043$); $P = 0.004$]. CRF did not modify the prospective associations between sedentary time or the other PA variables and cardiometabolic risk factors (Tables 2 and 3).

Further, CRF modified the associations between time spent in VPA, MVPA and overall PA with the clustered

cardiometabolic risk score ($P < 0.039$) (Table 4). In low-fit children, we observed a significant association between baseline VPA and clustered cardiometabolic risk score at follow-up [$\beta -0.099$ (95% CI: $-0.171, -0.025$); $P = 0.009$]; and a similar association were observed for MVPA [$\beta -0.094$ (95% CI: $-0.169, -0.019$); $P = 0.014$], but not for overall PA. However, neither sedentary time nor any of the PA variables were associated with the non-obesity clustered cardiometabolic risk score at follow-up when adjusted for WC. Figure 1 illustrates the prospective association between high and low CRF with clustered cardiometabolic risk at follow-up adjusted for all covariates, based on quartiles of overall PA and MVPA at baseline.

Discussion

We found a moderation by CRF between overall PA and time spent in at least moderate intensity PA with cardiometabolic outcomes. In children with low CRF (below the median split), both MVPA and VPA predicts lower HOMA-IR and clustered cardiometabolic risk score, while these associations were not observed in high-fit children. We found no evidence for any associations between sedentary time and cardiometabolic outcomes. We are only aware of one previous study examining if CRF modifies the relationship between PA and clustered cardiometabolic risk [4]. In line with our findings, a significant interaction between CRF and overall PA was found, suggesting a stronger relationship between PA and clustered cardiometabolic risk in children with low CRF [4]. Our observations extend these previous observations [4] by examining

intensity-specific PA in a prospective design adding temporality to the associations. Our findings are also supported by PA intervention studies in children suggesting that short term increases of PA (>6 months) can improve cardiometabolic risk factors [27]. For example, a previous study conducted in obese children suggested improvements in TG, insulin and body fat % following a 4 -month exercise training intervention although, benefits were attenuated when the exercise intervention ceased [28]. Unfortunately, intervention effects are usually lost in studies with long-term follow-ups [29, 30].

The null associations between sedentary time and the cardiometabolic outcomes is in line with previous literature on prospective associations for objectively measured sedentary time and cardiometabolic health in children [6, 31, 32]. However, examining sedentary time by accelerometers do have certain limitations. First, accelerometers are not specifically designed to measure sedentary behaviour, and cannot distinguish between sitting and lying—or context of the behaviour. Second, we did not examine prolonged bouts or patterns in time spent sedentary, which is suggested be a more appropriate exposure in children [33].

Previous studies have shown that the association between PA and cardiometabolic risk appears to be independent of adiposity, while adiposity may mediate the association between CRF with cardiometabolic risk [9, 34]. Similarly, we found that overall PA and MVPA could lead to beneficial changes in HOMA-IR, independent of adiposity in less fit children. The mechanisms why PA, especially higher intensities of PA, is more strongly associated with cardiometabolic risk among low fit children may be due to short-term effects of PA. For example, insulin levels is more sensitive to acute changes in PA than adiposity [35], and the main independent pathway between PA and insulin levels is likely due to an effect on muscle tissue [36]. PA increases muscle contraction and blood flow, which in turn enhances glucose uptake via increased translocation of GLUT4 in the muscle cell membrane, and may thereafter affect insulin levels [37, 38]. Although hypothesised, the translocation of GLUT4 appear not to differ between varying intensities of PA [39], therefore; PA of an intensity that may not increase aerobic capacity, could induce important effects on glycaemic control. On the other hand, CRF is based on the ability of the circulatory and respiratory systems to supply fuel during sustained PA, and includes more stable physiological traits (i.e., higher resting energy expenditure, increased capillary density, specific muscle characteristics). These traits induced by CRF also benefit cardiometabolic health [9], and may be more pronounced in high-fit children.

We did not observe any effect modification by CRF when modelling the prospective association between PA

variables and the non-obesity clustered cardiometabolic risk score. This may be explained by lack of power (interaction terms $P < 0.08$) or the confounding effect of central adiposity when WC was modelled as a confounder rather than included in the cardiometabolic risk score. Indeed, central adiposity is a strong determinant of cardiometabolic risk in healthy children [40] and public health interventions should aim at increasing both PA of at least moderate intensity and reducing central adiposity [34].

The relationship between CRF and PA is not linear, and a ceiling effect might be present for the high-fit children. This could partly explain the effect modification by CRF, rather than genetic predisposition. Although, the heritability for CRF is >50% [10], CRF is also influenced by recent PA behaviour, and high-intensity PA is needed to increase CRF [41]. In contrast, habitual PA is weakly correlated to CRF in children [9]. Some PA interventions in healthy children successfully manage to increase CRF and subsequently detect favourable changes in cardiometabolic outcomes [42, 43]. However, these favourable effects on cardiometabolic risk markers might as well be explained by an increase in daily high-intensity PA, rather than higher CRF per se, or a combination of both. Another challenging aspect is the different degrees of measurement precision when comparing objective measured PA with CRF; while CRF measured by the Andersen-test has an intra-class correlation coefficient (ICC) of 0.84 [15], the ICC for PA is ~0.50 [44, 45]. These measurement errors lead to regression dilution bias which attenuates the relationship between exposure and outcome [46]. Therefore, the associations for PA are probably stronger than those observed, and it is difficult to judge the true relative importance of PA over CRF [4].

Our study has several strengths; the objective measurements of PA and sedentary time, more than six valid days of PA measurements at baseline, a complete cardiometabolic risk profile at two time points 7 months apart, and adjustment for important confounders such as pubertal stage and parental SES. The prospective analyses with baseline adjustments of the outcome are robust, and provide inference of temporality between exposures and outcomes. However, some limitations needs to be taken into account. CRF was assessed indirectly by the Andersen-test. However, a recent clinical validation of three different measures of CRF (VO_{2peak} , the Andersen-test, and time to exhaustion) with clustered cardiometabolic risk in 10-year-old children, found that the Andersen-test showed strongest associations across all markers of cardiometabolic health [47]. We did not include any measure of sleep or diet, which may be both predictors and confounders between PA and cardiometabolic outcomes in youth [48]. It should be noted that we did not adjust for multiple testing, which may inflate type I error. However, correction for multiple comparisons is

debated, as it may increase the risk of type 2 error [49]. Taken together, we cannot exclude that our observations are due to residual confounding by poorly measured and other unmeasured factors. Finally, the study was carried out in one rural Norwegian county where the majority of the children are Caucasian, and the generalisation of our results to other populations are therefore limited.

Conclusion

CRF moderated the prospective association between PA and the clustered cardiometabolic risk; this moderation was most pronounced for HOMA-IR, and independent of adiposity. The magnitude of association between MVPA, HOMA-IR and clustered cardiometabolic risk was stronger in children with low CRF, and no associations appeared present in their high-fit peers. Therefore, increasing MVPA is especially important for children with low CRF.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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STUDY IV

Title: Bi-directional prospective associations between objectively measured sedentary time, physical activity and adiposity in 10 year old children

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Short running head: Bi-directional association adiposity and activity

Clinical Trial Registry: www.clinicaltrials.gov ID nr: NCT02132494

Abbreviations: BMI, body mass index; CI, confidence interval; cpm, counts per minute; ICC, intra-class correlation; MR, Mendelian Randomization; MVPA, moderate-to-vigorous physical activity; PA, physical activity; SES, socio-economic status; SD, standard deviation; VPA, vigorous physical activity; WC, waist circumference

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1 Abstract

2 **Background:** Insufficient physical activity (PA) level is considered as one important cause of
3 increasing overweight and obesity in children. However, this assumption is mainly supported by
4 observational studies. In contrast, PA interventions rarely succeed in reducing body weight or body
5 mass index (BMI) in children. Therefore, a bi-directional association between PA and adiposity may
6 explain the inconsistency between observational and experimental studies.

7 **Objective:** To examine if the prospective association between sedentary time, different PA intensities
8 and adiposity are bi-directional.

9 **Design:** Of 1,129 participants participating in the Active Smarter Kids Study (drop out: n=7), 869 ten-
10 year-old Norwegian children provided valid measurements for PA and adiposity at both time points
11 (seven months apart). PA was measured by accelerometry (GT3X/GT3X+), while adiposity was
12 assessed by three different measures: BMI, waist circumference (WC) and skinfolds. PA and adiposity
13 were examined as exposure and outcome to examine the bi-directional association. Analyses were
14 performed by linear mixed model with school as random intercept, further adjusted for sex, pubertal
15 stage, birth weight, parental weight, socio-economic status, and baseline value of the outcome.

16 **Results:** Neither overall PA nor time spent sedentary predicted lower BMI or WC at follow-up ($P \geq$
17 0.080), but time spent in moderate-to-vigorous PA (MVPA) and vigorous PA (VPA) at baseline
18 predicted lower skinfolds at follow-up among boys (MVPA β -0.066 [95% CI -0.105, -0.027] $P =$
19 0.001), but not in girls ($P = 0.889$). When adiposity was modelled as exposure, baseline BMI and WC
20 predicted lower overall PA, MVPA and VPA in boys, but not in girls. Skinfolds predicted lower VPA
21 both girls (β -0.098 [95% CI -0.194, -0.002] $P = 0.045$) and boys (β -0.276 [95% CI -0.372, -0.180]
22 $P < 0.001$). All adiposity measures predicted more time spent sedentary at follow-up in girls and boys
23 ($P \leq 0.043$).

24 **Conclusions:** Time spent sedentary does not predict change in BMI, WC or skinfold, but time spent in
25 PA of at least moderate intensity predicts lower skinfolds in boys. All three adiposity measures
26 predicted higher sedentary time, lower overall PA, MVPA and VPA – mainly evident in boys.

27 **Keywords:** exercise; fatness; youth; longitudinal; body composition

28

29 Introduction

30 Overweight and obesity levels among children and adolescents have more or less continuously
31 increased worldwide during the last decades (1) with estimates suggesting more than 60 million
32 children will be overweight or obese by 2020 (2). Reasons for the childhood obesity epidemic is a
33 complex mix of social, cultural, genetic and behavioral factors (3). At a fundamental level, weight
34 gain occurs when energy intake exceeds energy expenditure over time (4). Physical activity (PA)
35 readily increases energy expenditure; thus, and low levels of PA is considered a modifiable risk factor
36 for overweight and obesity (5). Moreover, attaining at least one hour of moderate-to-vigorous PA
37 (MVPA) is in cross-sectional studies associated with lower odds of obesity, independent of sedentary
38 time (6). However, these observations cannot determine the temporality between PA and adiposity,
39 which is emphasized by meta-analyses concluding that PA interventions are have limited effects on
40 body weight (7) and body mass index (BMI) in children (8, 9). Therefore, a bi-directional association
41 between PA and adiposity may explain the inconsistency between observational and experimental
42 findings. A few prospective studies have observed that a high percentage body fat at baseline predicts
43 lower levels of PA at follow-up (10-12). Moreover, abdominal obesity appears to predict higher time
44 spent sedentary (13). These studies contradicts the traditional view; fatness might be a determinant for
45 PA, and physical inactivity could be the result of fatness rather than its cause. At least one study have
46 suggested a causal association between adiposity and lower levels of PA in children using the
47 Mendelian Randomization approach (14). Thus, the bi-directional hypothesis may explain why
48 attempts to tackle excessive weight gain in childhood by increasing PA have been largely unsuccessful
49 (9). If these findings are true, new perspectives are needed to develop intervention strategies to
50 promote PA and to prevent overweight in children at an early age, before excess adiposity is
51 accumulated. Although several studies (10-13) have suggested a bi-directional prospective association
52 between adiposity and PA in childhood, more evidence is needed to examine this hypothesis,
53 especially related to time spent being sedentary time and of vigorous intensity PA (VPA). Therefore,
54 the aim of this study was to examine whether sedentary time, different PA intensities predicts
55 adiposity, or vice versa, using a prospective study design in a sample of healthy 10-year old
56 Norwegian children.

57 Materials and methods

58 Study design

59 The study comprises data from the Active Smarter Kids study (ASK), a seven-month cluster-
60 randomized controlled school trial conducted during the school year of 2014–2015 in Western Norway
61 (15). As PA levels did not differ from baseline to follow-up between intervention and control schools,
62 data were pooled and analyzed as a prospective observational cohort in the present study. A detailed
63 description of the study design, methodology and sample size calculation is available elsewhere (16).

64 Thus, only procedures relevant for the present study are summarized here. Baseline measurements
65 were conducted between April and October 2014, and follow-up measurements between April and
66 June 2015. In the present study, children who provided valid measurement for all exposures and
67 outcomes (PA and adiposity) at both time points were included. Figure 1 shows the flow of schools
68 and children through the study.

69 Data collection

70 Physical activity and sedentary time were measured using GT3X/GT3X+ accelerometers (ActiGraph,
71 LLC, Pensacola, Florida, USA). All children were fitted with accelerometers at school site and
72 instructed to wear the accelerometer on the right hip at all times for seven consecutive days, except
73 during water-based activities and while sleeping. Valid monitor wear-time was defined as achieving
74 ≥ 480 minutes day accumulated between 06:00 AM and 00:00 PM. Continuous bouts ≥ 20 minutes of
75 zero counts were defined as non-wear time (17). Children recording \geq four of seven days were
76 included in the analyses. Sedentary time (< 100 counts per minute (cpm)), MVPA (≥ 2296 cpm) and
77 VPA (≥ 4012 cpm) were defined according to previously established and validated cut points (18, 19).
78 All accelerometer data were analyzed in 10-second epochs using the Kinesoft analytical software
79 (KineSoft version 3.3.80, Loughborough, UK).

80 Body weight was measured to the nearest 0.1 kg using an electronic scale (SECA 899, SECA GmbH,
81 Hamburg, Germany). Height was measured to the nearest 0.1 cm using a portable altimeter (SECA
82 217, SECA GmbH, Hamburg, Germany). BMI (kg / m^2) were calculated and children categorized as
83 normal weight, overweight or obese according to age-adjusted thresholds (20). WC was measured
84 with an ergonomic circumference measuring tape (SECA 201, SECA GmbH, Hamburg, Germany).
85 Two measurements were taken between the lowest rib and the iliac crest with the abdomen relaxed at
86 the end of a gentle expiration. If the two results differed > 1 cm, a new measurement was taken until
87 two results were ≤ 1 cm apart.

88 Body fat were assessed by the sum of four skinfolds, which is a reliable and valid method for use in
89 population-based studies in children (21). We collected skinfold thickness from four sites (biceps,
90 triceps, subscapular, and suprailiac) on the non-dominant side of the body using a Harpenden skinfold
91 caliper (Bull; British Indicators Ltd., West Sussex, England). We collected two measurements at each
92 site in sequence. If the difference between measures was larger than two mm, a third measurement was
93 conducted; the mean of the two nearest measurements were recorded and the sum (mm) of four
94 skinfolds was used in analyses. Trained test personnel performed all anthropometric measurements,
95 but as skinfold measurements are prone to have high measurement error, we recruited seven persons
96 specifically trained to perform skinfold measurements at baseline and follow-up. Before baseline
97 testing they formed intra- and inter-reliability tests specific for the skinfold measurements.

98 Children self-assessed their pubertal stage according to the Tanner method (22) using a scale of color
99 images (stage 1–5) (23) in a private room. Stage 2 marks the onset of pubertal development. Parents
100 self-reported their education level, body weight and their child’s birth weight. Parental education level
101 was used as an indicator of socio-economic status (SES) and was categorized into three groups; low: <
102 2 years of high school, middle: < 4 years of college/university or \geq 4 years of college/university).

103 Ethics

104 Our procedures and methods conform to the ethical guidelines defined by the World Medical
105 Association’s Declaration of Helsinki (24) and its subsequent revisions. The Regional Committee for
106 Medical Research Ethics committee in Norway approved the study protocol (2013/1893/REK).
107 Written informed consent from each child’s parent or legal guardian and the responsible school
108 authorities were obtained prior to all testing in 2014.

109 Statistical analysis

110 Descriptive characteristics are presented as mean and standard deviation (SD), median and
111 interquartile range, or frequencies (%). All adiposity and PA variables, except sedentary time, were
112 log-transformed to improve the normality of the distributions. Although the individual variables were
113 skewed, the residuals of the change between baseline and follow-up were normally distributed and the
114 outcome variables were therefore kept un-transformed when *both* time points were used
115 simultaneously in the analyses (i.e. when outcome were adjusted by baseline value. All adiposity and
116 PA variables were standardized to z scores for ease of interpretation, thus, all regression coefficient
117 are given in SD units. First, we modelled the prospective association between baseline MVPA, VPA
118 and sedentary time (independent variables) and the three different adiposity measures (dependent
119 variables) using a linear mixed model including school as a random effect. The models were adjusted
120 for sex, pubertal stage, SES, birth weight, parental weight and baseline value of the outcome
121 (adiposity). Second, we modelled the prospective association between baseline adiposity (BMI, WC
122 and skinfolds) (independent variables) with MVPA, VPA and sedentary time (dependent variables),
123 adjusted for the same covariates as in previous model and baseline value of the outcome (MVPA,
124 VPA or SED). We also tested for interaction by sex (*baseline exposure* (PA or adiposity) \times *sex*). If a
125 significant interaction ($P < 0.05$) were observed, the analyses were additionally stratified by sex.
126 Lastly, BMI were split into normal weight versus overweight/obese according to Cole et al. {Cole,
127 2000 #182}, and MVPA into groups achieving the current recommendations for PA in youth, i.e.
128 above/below 60 minutes daily MVPA. Thereafter, we examined if BMI (normal weight vs
129 overweight/obese) and MVPA (above/below 60 minutes) categories at baseline differed in PA and
130 adiposity outcomes (continuous) at follow-up, respectively. In all models, sedentary time and PA
131 variables were analyzed one by one to avoid multi-collinearity, and school were included as random
132 intercept to account for clustering within data.

133 Analyses were performed using the SPSS software, version 24 (IBM SPSS Statistics for Windows,
134 Armonk, NY: IBM Corp., USA). A P -value of < 0.05 indicated statistical significance.

135 Results

136 Children's characteristics at baseline are presented in Table 1. Of 1,129 participants, only $n=7$ children
137 dropped out during the study and $n = 869$ children provided valid measurements for PA and adiposity
138 at both time points. Excluded children (total $n=253$) did not differ in any of the adiposity measures at
139 baseline ($P \geq 0.280$), but baseline overall PA (cpm) were lower ($P=0.030$). At baseline, the majority of
140 the children were normal weight (77.4%), while 18.6% were categorized as overweight and 3.9% were
141 obese.

142 Neither overall PA nor time spent sedentary predicted lower BMI or WC at follow-up ($P \geq 0.080$)
143 (Table 2), but time spent in MVPA and VPA at baseline predicted lower skinfolds at follow-up ($P <$
144 0.022). There were an interaction by sex for MVPA ($P = 0.017$), but were borderline significant for
145 VPA ($P = 0.069$). However, both MVPA and VPA predicted lower skinfolds at follow-up among boys
146 (MVPA $\beta -0.066$ [95% CI $-0.105, -0.027$] $P = 0.001$), but not in girls ($\beta 0.003$ [95% CI $-0.041,$
147 0.048] $P = 0.889$).

148 On the contrary, all adiposity measures predicted lower overall PA, MVPA, VPA and higher sedentary
149 time at follow-up ($P < 0.043$) (Table 3). We observed significant interactions by sex between all
150 baseline adiposity measures and PA outcomes ($P < 0.048$), but not for sedentary time ($P \geq 0.477$).
151 Baseline BMI and WC predicted lower overall PA, MVPA and VPA in boys ($P < 0.001$), but not in
152 girls ($P \geq 0.112$). When skinfolds was modelled as the exposure, time spent in VPA was lower at
153 follow-up in both girls ($\beta -0.098$ [95% CI $-0.194, -0.002$] $P = 0.045$) and boys ($\beta -0.276$ [95% CI $-$
154 $0.372, -0.180$] $P < 0.001$).

155 Lastly, we examined the bi-directional prospective associations between PA and adiposity by
156 dichotomizing the sample into according to PA recommendations (60 minutes MVPA per day) and
157 BMI into normal-weight and overweight/obese at baseline to examine if these groups differed (Table
158 4). There were no difference in adiposity at follow up between children categorized as active or
159 inactive at baseline ($P > 0.235$). Overweight and obese children had significantly lower follow-up
160 overall PA ($\beta -0.235$ [95% CI $-0.405, -0.065$] $P = 0.007$), MVPA ($\beta -0.199$ [95% CI $-0.347, -0.052$]
161 $P = 0.008$) and VPA ($\beta -0.266$ [95% CI $-0.423, -0.110$] $P = 0.001$) than normal-weight children,
162 while there were difference between groups in relationship with sedentary time at follow-up.

163 Discussion

164 During seven months follow-up, either time spent sedentary or any PA exposure predicted lower BMI
165 or WC, but baseline MVPA and VPA predicted lower skinfolds in boys. All measures of adiposity at
166 baseline (BMI, WC and skinfolds) predicted lower overall PA, MVPA, and VPA in boys. However,
167 the association between baseline skinfolds and lower VPA at follow-up were also observed in girls.
168 All baseline adiposity measures predicted higher sedentary time at follow-up in both sex.

169 Our findings corroborate with the few previous studies examining bi-directional associations between
170 PA, sedentary time and adiposity. Kwon et al. (11) and Metcalf et al. (12) measured adiposity as body
171 fat (%) by dual-energy X-ray absorptiometry (DEXA) in children aged 5 to 11, and found that
172 adiposity level may be a determinant of lower PA levels, but not vice versa. Metcalf et al. (12) also
173 examined the associations using BMI and WC as exposure variables, but the associations were weaker
174 and non-significant using BMI and WC. However, an ICAD meta-analysis found that children's
175 MVPA and sedentary time were not associated with WC at follow-up, but a higher WC at baseline
176 predicted higher amounts of sedentary time at two years follow-up (13). Moreover, a higher fat mass
177 index at baseline was associated with lower PA and higher sedentary time in a sample of Danish 10
178 year olds during six months follow-up (10). These studies imply that PA and sedentary time does not
179 predict change in adiposity – but rather supports the hypothesis that the association between PA,
180 sedentary time, and weight gain could be in the opposite direction. However, it is difficult to directly
181 compare results from previous studies with ours due to differences in follow-up duration (months
182 versus years) and different anthropometric assessment methods aggravate comparisons. For example,
183 DEXA distinguishes fat mass from lean tissue and provide a measure of total fat mass and body fat
184 percentage. BMI does not make the distinction, which is crucial because PA could readily increase
185 lean/muscle tissue. Two prospective studies using an isotemporal substitution modelling approach
186 found different magnitude of associations between PA and adiposity. There were no prospective
187 associations with BMI when substituting sedentary time (10 minutes) with VPA (25), while replacing
188 sedentary time (30 minutes) with an equal amount of time in MVPA were associated with a favorable
189 body composition (DEXA) in children (26). Hence, the lack of distinction between fat mass and lean
190 body mass in the present study could explain why the observed associations between PA and BMI
191 were weaker than those between PA and skinfolds (12), likely due to different degree of measurement
192 precision of adiposity.

193 In contrast to previous studies, the present study observe interactions by sex. These findings could be
194 explained by that obese boys are less active than non-obese boys (27). Moreover, PA was
195 progressively lower across the weight spectrum in boys, but PA was consistently low across all weight
196 categories in girls (28). As boys have a higher PA level than girls (29), a possible effect of regression-
197 to-the-mean phenomenon could be present, meaning that those with high levels of baseline PA can

198 potentially experience a large decrease in PA levels compared with those starting with lower PA levels
199 (30), and so are likely to be greater in boys than in girls (31). However, the possibility of a bi-
200 directional association is plausible. Children with overweight and obesity favor participation in
201 sedentary behaviors (32), and consistently engage in less overall PA and MVPA (29, 33). A study
202 using the Mendelian Randomization (MR) approach to infer causality suggested that increasing
203 adiposity (BMI and fat mass index) led to a reduction in children's (age 11) overall PA and MVPA,
204 and increase in sedentary time (14). However, they were not able to exclude that low PA may also lead
205 to increases in adiposity (14). A recent study with similar MR approach, found that BMI may have a
206 causal influence on sedentary time, but not on total PA or MVPA at age 3 (34).

207 In a broader perspective, it is suggested that motor skill competence in early childhood is a critically,
208 yet underestimated, causal mechanism partially responsible for physical inactivity (35). Motor skills is
209 an important determinant of PA (36); thus, poorer fundamental movement skills in overweight and
210 obese children compared to their normal-weight counterparts might influence their PA levels
211 negatively (37). Also, self-efficacy may influence PA levels, and obese children is shown to be less
212 confident in their ability to overcome barriers to PA, ask parents to provide opportunities for PA, and
213 choose physically active pursuits over sedentary ones (38).

214 It is a common belief that the secular and longitudinal PA declines with increasing sedentary time
215 largely contributes to childhood overweight and obesity rates. However, our findings do not support
216 this assumption. This does not mean that PA is a useless strategy combating childhood overweight and
217 obesity, but underscores the difference between preventing weight gain and achieve weight loss (39).
218 Indeed, PA is important for various health outcomes beyond adiposity (9, 13, 40), but increasing PA
219 does not solve the complex health issue of weight loss in children. Overweight and obesity is a result
220 long-term energy imbalance (41), and PA is rather a moderator influencing steepness of adiposity
221 increase balance (42). However, as overweight and obesity is established early in life in many children
222 (43), other important determinants and risk factors include birth weight and rapid weight gain during
223 infancy, parental obesity, maternal smoking, breastfeeding, TV-viewing, sleep duration and diet (i.e.
224 sugar consumption) (44, 45). It is difficult to establish a causal association and relative importance
225 between determinants and obesity (44). However, as the rising rates is so severe and sudden, it is
226 likely that environmental factors and not genetics play a greater role. Hence, targeting early life
227 determinants *and* daily PA are cornerstones in the prevention of excessive adiposity in childhood (44,
228 45).

229 Accelerometers are considered a criterion method for measuring PA intensity, but is limited by
230 misclassification and underestimation of PA intensity (46). Moreover, when repeated measurements of
231 PA in the same individuals are performed, the substantial intra-individual variability with an intra
232 class correlation (ICC) of about 0.5 suggest that PA levels are highly variable over time (47). Because

233 PA and sedentary time usually are measured less precisely than BMI, WC and skinfolds, it is not
234 surprising that baseline BMI and WC predicts follow-up PA, whereas, because of measurement error,
235 the reverse may not be true (48). Therefore, examining direction of associations between exposures
236 and outcomes measures with different degree of measurement error is problematic. When the more
237 imprecise variable is modelled as the outcome, the magnitude of effect is estimated accurately, but
238 with wider confidence intervals. In contrast, when the more imprecise variable is modelled as the
239 exposure it tends to attenuate the regression coefficient (49). Unfortunately, increasing sample size do
240 not solve the issue and may only result in a *more precisely erroneous* estimate of the effect size (49).

241 The main strengths of the current study is the objective measurements of PA and clinically important
242 adiposity measures in a relatively large sample of children, and prospective analyses with baseline
243 adjustments of the outcome, but the short time frame between baseline and follow-up could raise
244 questions as to whether the present observations are meaningful, lasting effects in either directions.
245 However, we do not know the temporal association between PA and adiposity *before* our baseline
246 measurements. Hence, these associations between sedentary time, PA and adiposity could be evident
247 in studies with longer follow up (39). Nonetheless, seven months is a fair amount of time in these
248 children's life, and the 'short-term' observations could be stronger in magnitude if the study had
249 longer follow-up. Thus, repeated measurements of PA and more precise measures of adiposity (i.e.
250 DEXA) over a longer period would allow additional modelling of the complex longitudinal
251 relationships between sedentary time, PA and adiposity development. Experimental trials and
252 additional observational studies using the MR approach are needed to examine the causal associations
253 between sedentary time, PA and adiposity in children. Unfortunately, PA interventions are difficult to
254 conduct given the long duration it takes to develop obesity and achieve weight loss in children,
255 combined with issues of compliance. As in all observational research, we cannot exclude the
256 possibility that our observations are explained by residual and unmeasured confounding factors.
257 Lastly, the study was carried out in a rural Norwegian County where the majority of the children are
258 Caucasian, and the generalization of our results to other populations are therefore limited.

259 Conclusion

260 Time spent sedentary does not predict any of the examined adiposity measures, while PA of at least
261 moderate intensity predict lower skinfolds in boys. On the opposite, all adiposity measured predict
262 higher sedentary time, while skinfolds predicts lower VPA. However, BMI and WC predicts lower
263 overall PA, MVPA and VPA in boys only. Preventing accumulation of excess adiposity early in life
264 might be important for sufficient PA levels in children.

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268 students who participated in data collection.

269 Conflict of interest

270 All authors declare no conflict of interest.

271 Authors' contributions

272 The authors' responsibilities were as follows – GKR and SAA, designed the Active Smarter Kids
273 Study and provided financial support. TS, EAa, SAA and GKR conducted the research. TS, EAa, and
274 UE analyzed the data. TS wrote the first draft of the manuscript. TS, EAa, GKR, and UE had primary
275 responsibility for the final content. All authors have read, provided feedback and approved submission
276 of the manuscript.

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Table 1: Children's characteristics at baseline and follow-up ($n = 869$)

	n	Baseline: Autumn 2014	Follow-up: Spring 2015	Change baseline to follow-up
Age (years)	869	10.2 (0.3)	--	--
Boys / girls (%)	869	48.9 / 51.1	--	--
Height (cm)	869	142.9 (6.8) ^a	146.9 (7.1)	$P < 0.001$
Body weight (kg)	869	35.3 (31.6, 41.0) ^b	37.8 (33.7, 43.6)	$P < 0.001$
Children's birth weight (g)	820	3591 (623)	--	--
Mother's body weight (kg)	787	70.0 (12.0)	--	--
Father's body weight (kg)	784	86.8 (12.4)	--	--
SES (%)	799 ^c / 830 ^d			
Low		22.9 / 44.6	--	--
Middle		41.2 / 32.2	--	--
High		31.4 / 19.3	--	--
Missing		4.5 / 8.1	--	--
Pubertal status (%)	861-866			$P < 0.001$
Stage 1		29.2	13.3	--
Stage 2		59.4	63.2	--
Stage ≥ 3		10.4	33.1	--
Missing		0.9	0.3	--
BMI ($\text{kg} \times \text{m}^2$)	869	17.3 (15.9, 19.4)	17.5 (16.1, 19.6)	$P = 0.231$
Normal weight (%)		77.4	79.1	--
Overweight (%)		18.6	17.2	--
Obese (%)		3.9	3.7	--
WC (cm)	869	60.3 (56.8, 65.5)	61.3 (58.0, 66.5)	$P < 0.001$
Skinfold (mm)	869	41.8 (29.9, 63.0)	41.8 (30.5, 60.0)	$P = 0.333$
Monitor wear time (min/day)	869	782.0 (50.8)	785.8 (50.5)	$P = 0.133$
SED (min/day)	869	467.2 (58.3)	494.5 (53.1)	$P < 0.001$
MVPA (min/day)	869	74.2 (58.6, 92.4)	65.0 (50.2, 81.7)	$P < 0.001$
VPA (min/day)	869	29.1 (20.5, 39.1)	25.1 (17.3, 34.4)	$P < 0.001$
Overall PA (cpm)	869	695 (556, 875)	593 (480, 733)	$P < 0.001$

^a Mean and SD (all such values)

^b Median and interquartile range (all such values)

^c Mother reporting (n)

^d Father reporting (n)

BMI; body mass index, cpm; counts per minute, MVPA; moderate-to-vigorous physical activity, SED; sedentary time, SES; socio-economic status, VPA; vigorous physical activity, WC; waist circumference

P -value in bold is statistic significant to the level of $P < 0.05$.

Table 2: Prospective associations between PA at baseline and adiposity at follow-up ($n = 869$)

		Outcome at follow-up		
		BMI	WC	S4SF
Exposure at baseline	Overall PA (cpm)	0.019 (−0.002, 0.040)	0.009 (−0.019, 0.036)	−0.022 (−0.051, 0.008)
		$P = 0.080$	$P = 0.536$	$P = 0.153$
	<i>cpm</i> × <i>sex</i>	$P = 0.916$	$P = 0.686$	$P = 0.369$
	SED	−0.016 (−0.040, 0.008)	−0.007 (−0.038, 0.024)	0.010 (−0.024, 0.045)
		$P = 0.191$	$P = 0.649$	$P = 0.552$
	<i>SED</i> × <i>sex</i>	$P = 0.938$	$P = 0.977$	$P = 0.990$
	MVPA	0.009 (−0.013, 0.030)	0.003 (−0.025, 0.031)	−0.036 (−0.067, −0.005)
		$P = 0.435$	$P = 0.809$	$P = 0.022$
	<i>MVPA</i> × <i>sex</i>	$P = 0.563$	$P = 0.806$	−0.069 (−0.126, −0.012)
				$P = 0.017$
	<i>Boys</i>	<i>n/a</i>	<i>n/a</i>	−0.066 (−0.105, −0.027)
				$P = 0.001$
<i>Girls</i>	<i>n/a</i>	<i>n/a</i>	0.003 (−0.041, 0.048)	
			$P = 0.889$	
VPA	0.017 (−0.004, 0.039)	0.003 (−0.024, 0.032)	−0.043 (−0.074, −0.012)	
	$P = 0.116$	$P = 0.782$	$P = 0.006$	
<i>VPA</i> × <i>sex</i>	$P = 0.335$	$P = 0.877$	−0.053 (−0.111, 0.005)	
			$P = 0.069^*$	
<i>Boys</i>	<i>n/a</i>	<i>n/a</i>	−0.064 (−0.105, −0.026)	
			$P = 0.001$	
<i>Girls</i>	<i>n/a</i>	<i>n/a</i>	−0.011 (−0.057, 0.036)	
			$P = 0.643$	

The model are adjusted for sex, SES, parental weight, pubertal stage, child's birth weight, monitor wear time, and baseline value of the outcome.

BMI; body mass index, cpm; counts per minute, MVPA; moderate-to-vigorous physical activity, n/a; not applicable; SED; sedentary, S4SF; sum of four skinfolds, VPA; vigorous physical activity, WC; waist circumference

P -value in bold is statistic significant to the level of $P < 0.05$.

Table 3: Prospective associations between adiposity at baseline and PA at follow-up ($n = 869$)

	Outcome at follow-up			
	Overall PA (cpm)	SED	MVPA	VPA
	BMI	-0.124 (-0.198, -0.050) $P = 0.001$	0.088 (0.020, 0.157) $P = 0.011$	-0.092 (-0.156, -0.028) $P = 0.005$
BMI × sex	-0.137 (-0.273, -0.001) $P = 0.048$	$P = 0.508$	-0.209 (-0.326, -0.093) $P < 0.001$	-0.140 (-0.263, -0.017) $P = 0.025$
Boys	-0.193 (-0.295, -0.092) $P < 0.001$	<i>n/a</i>	-0.199 (-0.287, -0.112) $P < 0.001$	-0.208 (-0.301, -0.115) $P < 0.001$
Girls	-0.056 (-0.156, -0.043) $P = 0.266$	<i>n/a</i>	0.010 (-0.076, 0.095) $P = 0.822$	-0.068 (-0.159, 0.023) $P = 0.141$
WC	-0.150 (-0.225, -0.074) $P < 0.001$	0.072 (0.007, 0.148) $P = 0.043$	-0.102 (-0.169, -0.036) $P = 0.002$	-0.151 (-0.220, -0.082) $P < 0.001$
WC × sex	-0.139 (-0.277, -0.001) $P = 0.048$	$P = 0.477$	-0.207 (-0.326, -0.089) $P = 0.001$	-0.148 (-0.273, -0.024) $P = 0.020$
Boys	-0.221 (-0.324, 0.118) $P < 0.001$	<i>n/a</i>	-0.209 (-0.298, -0.120) $P < 0.001$	-0.227 (-0.323, -0.133) $P < 0.001$
Girls	-0.081 (-0.183, 0.019) $P = 0.112$	<i>n/a</i>	-0.002 (-0.089, -0.085) $P = 0.969$	-0.079 (-0.171, -0.012) $P = 0.090$
S4SF	-0.175 (-0.252, -0.098) $P < 0.001$	0.088 (0.016, 0.160) $P = 0.016$	-0.120 (-0.189, -0.051) $P = 0.001$	-0.187 (-0.258, -0.116) $P < 0.001$
S4SF × sex	-0.168 (-0.311, -0.024) $P = 0.022$	$P = 0.894$	-0.262 (-0.392, -0.133) $P < 0.001$	-0.178 (-0.307, -0.049) $P = 0.007$
Boys	-0.258 (-0.363, -0.154) $P < 0.001$	<i>n/a</i>	-0.240 (-0.331, -0.149) $P < 0.001$	-0.276 (-0.372, -0.180) $P < 0.001$
Girls	-0.090 (-0.195, -0.015) $P = 0.094$	<i>n/a</i>	-0.019 (-0.110, 0.073) $P = 0.689$	-0.098 (-0.194, -0.002) $P = 0.045$

The model are adjusted for sex, SES, parental weight, pubertal stage, child's birth weight, monitor wear time, and baseline value of the outcome.

BMI; body mass index, cpm; counts per minute, MVPA; moderate-to-vigorous physical activity, *n/a*; not applicable, SED; sedentary, S4SF; sum of four skinfolds, VPA; vigorous physical activity, WC; waist circumference

P -value in bold is statistic significant to the level of $P < 0.05$.

Table 4: Prospective associations between baseline MVPA (\geq / $<$ 60 minutes) and adiposity at follow-up ($n = 869$)

		Outcome at follow-up		
		BMI	WC	S4SF
Exposure at baseline	MVPA	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
	< 60 min			
	MVPA	0.016 (-0.028, 0.067)	-0.021 (-0.080, 0.037)	-0.039 (-0.105, 0.026)
	\geq 60 min	<i>P</i> = 0.467	<i>P</i> = 0.469	<i>P</i> = 0.235

The model are adjusted for sex, SES, pubertal stage, child's birth weight, parental weight, monitor wear time, and baseline value of the outcome.

BMI; body mass index, MVPA; moderate-to-vigorous physical activity; S4SF, sum of four skinfolds; WC, waist circumference

Table 5: Prospective associations between normal weight versus overweight/obese (BMI) at baseline and PA intensities at follow-up ($n = 869$)

		Outcome at follow-up			
		Overall PA (cpm)	SED	MVPA	VPA
Exposure at baseline	BMI	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
	< 25				
	BMI	-0.235 (-0.405, -0.065)	0.105 (-0.053, 0.262)	-0.199 (-0.347, -0.052)	-0.266 (-0.423, -0.110)
	\geq 25	<i>P</i> = 0.007	<i>P</i> = 0.192	<i>P</i> = 0.008	<i>P</i> = 0.001

The model are adjusted for sex, SES, pubertal stage, child's birth weight, parental weight, monitor wear time, and baseline value of the outcome.

BMI; body mass index, cpm; counts per minute, MVPA; moderate-to-vigorous physical activity, PA; physical activity, SED; sedentary time, VPA; vigorous physical activity

P-value in bold is statistic significant to the level of $P < 0.05$.

Figure 1:

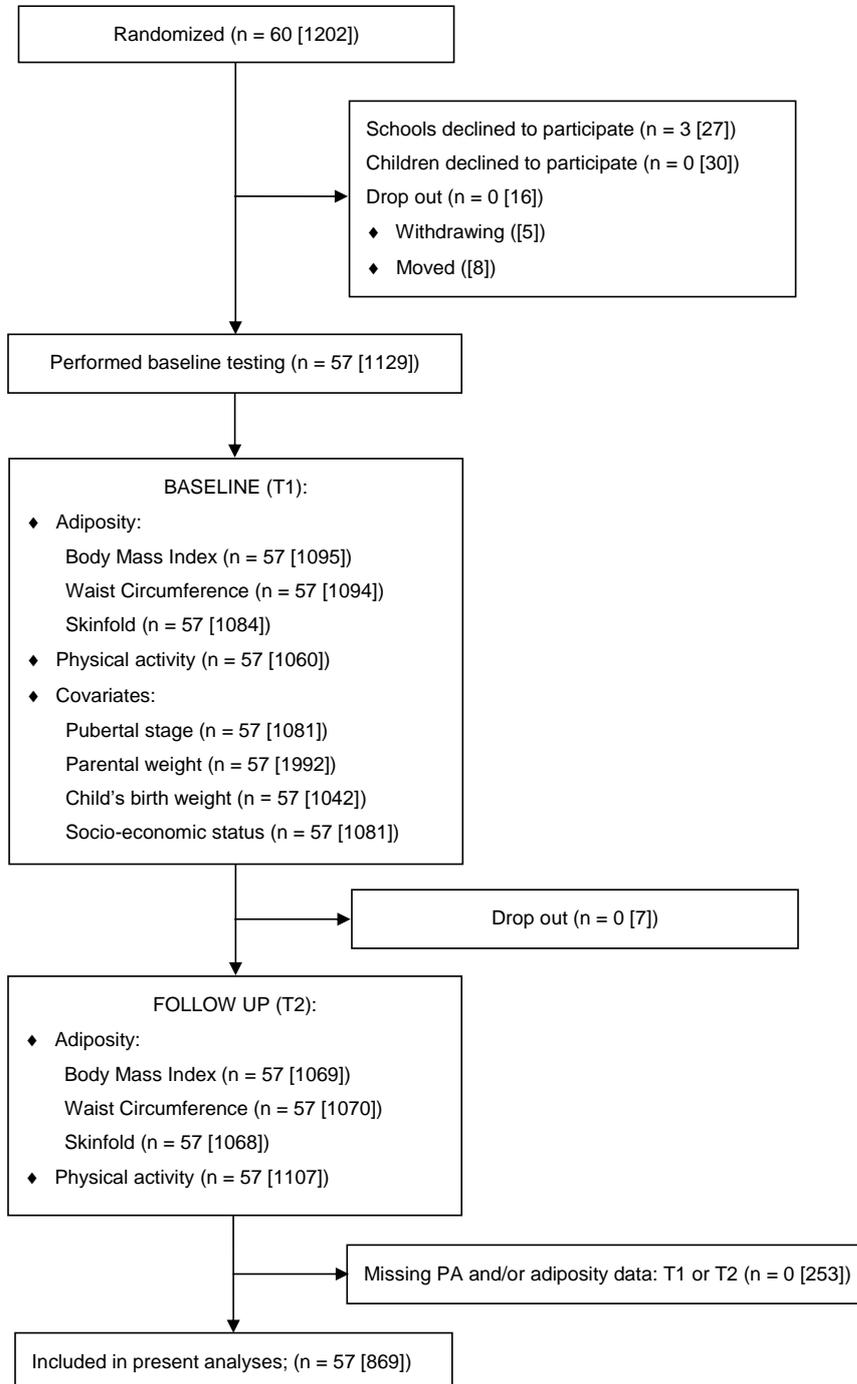


Table 1: Children's characteristics at baseline and follow-up ($n=869$)

	n	Baseline: Autumn 2014	Follow-up: Spring 2015	Change baseline to follow-up
Age (years)	869	10.2 (0.3)	--	--
Boys / girls (%)	869	48.9 / 51.1	--	--
Height (cm)	869	142.9 (6.8) ^a	146.9 (7.1)	P < 0.001
Body weight (kg)	869	35.3 (31.6, 41.0) ^b	37.8 (33.7, 43.6)	P < 0.001
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Mother's body weight (kg)	787	70.0 (12.0)	--	--
Father's body weight (kg)	784	86.8 (12.4)	--	--
SES (%)	799 ^c / 830 ^d			
Low		22.9 / 44.6	--	--
Middle		41.2 / 32.2	--	--
High		31.4 / 19.3	--	--
Missing		4.5 / 8.1	--	--
Pubertal status (%)	861-866			P < 0.001
Stage 1		29.2	13.3	--
Stage 2		59.4	63.2	--
Stage ≥ 3		10.4	33.1	--
Missing		0.9	0.3	--
BMI ($\text{kg} \times \text{m}^2$)	869	17.3 (15.9, 19.4)	17.5 (16.1, 19.6)	P = 0.231
Normal weight (%)		77.4	79.1	--
Overweight (%)		18.6	17.2	--
Obese (%)		3.9	3.7	--
WC (cm)	869	60.3 (56.8, 65.5)	61.3 (58.0, 66.5)	P < 0.001
Skinfold (mm)	869	41.8 (29.9, 63.0)	41.8 (30.5, 60.0)	P = 0.333
Monitor wear time (min/day)	869	782.0 (50.8)	785.8 (50.5)	P = 0.133
SED (min/day)	869	467.2 (58.3)	494.5 (53.1)	P < 0.001
MVPA (min/day)	869	74.2 (58.6, 92.4)	65.0 (50.2, 81.7)	P < 0.001
VPA (min/day)	869	29.1 (20.5, 39.1)	25.1 (17.3, 34.4)	P < 0.001
Overall PA (cpm)	869	695 (556, 875)	593 (480, 733)	P < 0.001

^a Mean and SD (all such values)

^b Median and interquartile range (all such values)

^c Mother reporting (n)

^d Father reporting (n)

BMI; body mass index, cpm; counts per minute, MVPA; moderate-to-vigorous physical activity, SED; sedentary time, SES; socio-economic status, VPA; vigorous physical activity, WC; waist circumference

Table 2: Prospective associations between PA at baseline and adiposity at follow-up ($n = 869$)

		Outcome at follow-up		
		BMI	WC	S4SF
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		$P = 0.080$	$P = 0.536$	$P = 0.153$
	<i>cpm</i> × <i>sex</i>	$P = 0.916$	$P = 0.686$	$P = 0.369$
	SED	-0.016 (-0.040, 0.008)	-0.007 (-0.038, 0.024)	0.010 (-0.024, 0.045)
		$P = 0.191$	$P = 0.649$	$P = 0.552$
	<i>SED</i> × <i>sex</i>	$P = 0.938$	$P = 0.977$	$P = 0.990$
	MVPA	0.009 (-0.013, 0.030)	0.003 (-0.025, 0.031)	-0.036 (-0.067, -0.005)
		$P = 0.435$	$P = 0.809$	$P = 0.022$
	<i>MVPA</i> × <i>sex</i>	$P = 0.563$	$P = 0.806$	-0.069 (-0.126, -0.012)
				$P = 0.017$
	<i>Boys</i>	<i>n/a</i>	<i>n/a</i>	-0.066 (-0.105, -0.027)
				$P = 0.001$
	<i>Girls</i>	<i>n/a</i>	<i>n/a</i>	0.003 (-0.041, 0.048)
				$P = 0.889$
	VPA	0.017 (-0.004, 0.039)	0.003 (-0.024, 0.032)	-0.043 (-0.074, -0.012)
		$P = 0.116$	$P = 0.782$	$P = 0.006$
<i>VPA</i> × <i>sex</i>	$P = 0.335$	$P = 0.877$	-0.053 (-0.111, 0.005)	
			$P = 0.069^*$	
<i>Boys</i>	<i>n/a</i>	<i>n/a</i>	-0.064 (-0.105, -0.026)	
			$P = 0.001$	
<i>Girls</i>	<i>n/a</i>	<i>n/a</i>	-0.011 (-0.057, 0.036)	
			$P = 0.643$	

The model are adjusted for sex, SES, parental weight, pubertal stage, child's birth weight, monitor wear time, and baseline value of the outcome.

BMI; body mass index, cpm; counts per minute, MVPA; moderate-to-vigorous physical activity, n/a; not applicable; SED; sedentary, S4SF; sum of four skinfolds, VPA; vigorous physical activity, WC; waist circumference

Table 3: Prospective associations between adiposity at baseline and PA at follow-up ($n=869$)

		Outcome at follow-up			
		Overall PA (cpm)	SED	MVPA	VPA
Exposure at baseline	BMI	-0.124 (-0.198, -0.050) $P = 0.001$	0.088 (0.020, 0.157) $P = 0.011$	-0.092 (-0.156, -0.028) $P = 0.005$	-0.136 (-0.205, -0.068) $P < 0.001$
	<i>BMI</i> × <i>sex</i>	-0.137 (-0.273, -0.001) $P = 0.048$	$P = 0.508$	-0.209 (-0.326, -0.093) $P < 0.001$	-0.140 (-0.263, -0.017) $P = 0.025$
	<i>Boys</i>	-0.193 (-0.295, -0.092) $P < 0.001$	<i>n/a</i>	-0.199 (-0.287, -0.112) $P < 0.001$	-0.208 (-0.301, -0.115) $P < 0.001$
	<i>Girls</i>	-0.056 (-0.156, -0.043) $P = 0.266$	<i>n/a</i>	0.010 (-0.076, 0.095) $P = 0.822$	-0.068 (-0.159, 0.023) $P = 0.141$
	WC	-0.150 (-0.225, -0.074) $P < 0.001$	0.072 (0.007, 0.148) $P = 0.043$	-0.102 (-0.169, -0.036) $P = 0.002$	-0.151 (-0.220, -0.082) $P < 0.001$
	<i>WC</i> × <i>sex</i>	-0.139 (-0.277, -0.001) $P = 0.048$	$P = 0.477$	-0.207 (-0.326, -0.089) $P = 0.001$	-0.148 (-0.273, -0.024) $P = 0.020$
	<i>Boys</i>	-0.221 (-0.324, 0.118) $P < 0.001$	<i>n/a</i>	-0.209 (-0.298, -0.120) $P < 0.001$	-0.227 (-0.323, -0.133) $P < 0.001$
	<i>Girls</i>	-0.081 (-0.183, 0.019) $P = 0.112$	<i>n/a</i>	-0.002 (-0.089, -0.085) $P = 0.969$	-0.079 (-0.171, -0.012) $P = 0.090$
	S4SF	-0.175 (-0.252, -0.098) $P < 0.001$	0.088 (0.016, 0.160) $P = 0.016$	-0.120 (-0.189, -0.051) $P = 0.001$	-0.187 (-0.258, -0.116) $P < 0.001$
	<i>S4SF</i> × <i>sex</i>	-0.168 (-0.311, -0.024) $P = 0.022$	$P = 0.894$	-0.262 (-0.392, -0.133) $P < 0.001$	-0.178 (-0.307, -0.049) $P = 0.007$
	<i>Boys</i>	-0.258 (-0.363, -0.154) $P < 0.001$	<i>n/a</i>	-0.240 (-0.331, -0.149) $P < 0.001$	-0.276 (-0.372, -0.180) $P < 0.001$
	<i>Girls</i>	-0.090 (-0.195, -0.015) $P = 0.094$	<i>n/a</i>	-0.019 (-0.110, 0.073) $P = 0.689$	-0.098 (-0.194, -0.002) $P = 0.045$

The model are adjusted for sex, SES, parental weight, pubertal stage, child's birth weight, monitor wear time, and baseline value of the outcome.

BMI; body mass index, cpm; counts per minute, MVPA; moderate-to-vigorous physical activity, *n/a*; not applicable, SED; sedentary, S4SF; sum of four skinfolds, VPA; vigorous physical activity, WC; waist circumference

Table 4: Prospective associations between baseline MVPA (\geq / $<$ 60 minutes) and adiposity at follow-up ($n=869$)

		Outcome at follow-up		
		BMI	WC	S4SF
Exposure at baseline	MVPA	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
	< 60 min			
	MVPA	0.016 (-0.028, 0.067)	-0.021 (-0.080, 0.037)	-0.039 (-0.105, 0.026)
	\geq 60 min	$P = 0.467$	$P = 0.469$	$P = 0.235$

The model are adjusted for sex, SES, pubertal stage, child's birth weight, parental weight, monitor wear time, and baseline value of the outcome.

BMI; body mass index, MVPA; moderate-to-vigorous physical activity; S4SF, sum of four skinfolds; WC, waist circumference

Table 5: Prospective associations between normal weight versus overweight/obese (BMI) at baseline and PA intensities at follow-up ($n=869$)

		Outcome at follow-up			
		Overall PA (cpm)	SED	MVPA	VPA
Exposure at baseline	BMI	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>	<i>Ref.</i>
	< 25				
	≥ 25	-0.235 (-0.405, -0.065) $P = 0.007$	0.105 (-0.053, 0.262) $P = 0.192$	-0.199 (-0.347, -0.052) $P = 0.008$	-0.266 (-0.423, -0.110) $P = 0.001$

The model are adjusted for sex, SES, pubertal stage, child's birth weight, parental weight, monitor wear time, and baseline value of the outcome.

BMI; body mass index, cpm; counts per minute, MVPA; moderate-to-vigorous physical activity, PA; physical activity, SED; sedentary time, VPA; vigorous physical activity

APPENDIX I

Approval letter from the Regional Committees for Medical and Health Research Ethics

Region: REK sør-øst	Saksbehandler: Anette Solli Karlsen	Telefon: 22845522	Vår dato: 04.03.2014	Vår referanse: 2013/1893/REK sør-øst A
			Deres dato: 28.01.2014	Deres referanse:

Vår referanse må oppgis ved alle henvendelser

Sigmund Anderssen
Høgskulen i Sogn og Fjordane

2013/1893 ASK - Active Smarter Kids

Forskningsansvarlig: Høgskulen i Sogn og Fjordane
Prosjektleder: Sigmund Anderssen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst) i møtet 13.02.2014. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikklovens § 4.

Opprinnelig prosjektbeskrivelse

Målsettingen i dette prosjektet er å undersøke effekten av en time daglig fysisk aktivitet i skolehverdagen for elever i femte klasse.

En eventuell effekt skal måles på skoleprestasjoner i matematikk, lesing og engelsk, på kognitive prestasjoner og på helsevariabler som lipider og hjernederivert nevroτροφisk faktor (Brain Derived Neurotrophic Factor, BDNF), som påvirker hjernecellers utvikling og funksjon.

Prosjektet har et klynge randomisert design. Skolen er enheten med to grupper, en intervensjons- og en kontrollgruppe. Forsøket har en varighet på åtte måneder. I alt 1196 barn som går i femte klasse i ulike skoler i Sogn og Fjordane skal spørres om deltakelse. Halvparten av skoleklassene vil bli randomisert til intervensjonsgruppen med daglig fysisk aktivitet, mens den andre halvdel vil komme i kontrollgruppen og får fysisk aktivitet som vanlig i skolen, dvs. to timer per uke. Den fysiske aktiviteten, som intervensjonsgruppen tilbys er variert, og etter endt forsøk, vil kontrollgruppen bli tilbudt den samme intervensjonen dvs. når de går i 6. klasse. Med et slikt design vil alle få det samme tilbudet. Hele utvalget vil undersøkes ved baseline og etter åtte måneder med en rekke fysiske tester, med antropometriske mål, høyde, vekt midjemål og hudtykkelse, med blodtrykk, flere kognitive tester, spørreskjema om livskvalitet, kosthold, samt vil det bli tatt blodprøver for å måle lipidmønstre i blod, glukose og BDNF.

Det er utarbeidet et informasjonsskriv med samtykkeerklæring som er adressert både til foreldrene og til barna. Noen av deltakerne, dvs. barn og lærere, vil bli spurt om å delta i en kvalitativ studie, hvor intervju skal tas opp på bånd, transkriberes og analyseres. I denne kvalitative delen av studien vil man også benytte seg av fotografi, dvs. man ønsker å ta bilder i de fysiske aktivitetene i prosjektet, og disse vil bli forelagt deltakerne og brukt i intervjusituasjonen.

Saksbehandling

Søknaden ble behandlet i møte 24.10.2013, og det ble fattet et utsettende vedtak. Komiteen ba om tilbakemelding på følgende punkter:

1. Datamaterialet vil bli anonymisert for forskerne i prosjektet 31.12 2016, men en navneliste vil bli

oppbevart hos en tredje person, dvs. hos NSD. Man opplyser også i informasjonsskrivet at man planlegger å be barna nå de er fylt 16 år om deres samtykke til å anvende data for senere forskning. Hva denne forskningen vil medføre står det ingenting om, og det går heller ikke klart fra prosjektprotokollen hva som planlegges. Prosjektbeskrivelsen omtaler ikke en slik eventuell oppfølging.

2. I informasjonsskrivet ber man om at data fra undersøkelsen kan kobles mot nasjonalt helseregister, medisinsk fødselsregister og mor/barn-registeret. Denne koblingen er ikke begrunnet noe sted, og man kan heller ikke i prosjektbeskrivelsen finne noen omtale av en slik kobling som man ber deltakerne samtykke til i informasjonsskrivet.
3. Det fins ingen opplysninger i informasjonsskrivet om den kvalitative delen av studien og heller ingen informasjon til lærerne som vil bli bedt om å delta i den delen av studien er vedlagt.
4. Prosjektledelsen har på side 8 i søknadsskjemaet diskutert ulike mulig ulemper som prosjektet kan ha på barna og argumentere for at prosjektet ikke kan ha slike ulemper som de diskuterer. En mulig ulempe er muligens uteglemt i diskusjonen og det er relatert til gruppepress. Hva med elever som ikke vil delta, for eksempel en elev i en klasse på 20 som ikke vil være med. Om hele klassen er randomisert til 1 times fysisk aktivitet hver dag, hva skjer med den ene elevens undervisningstilbud og hva kan han/hun eventuelt utsette for av mobbing/gruppepress? Det savnes en diskusjon av dette aspektet og hvordan man skal ivareta «ikke-deltakere».
5. Komiteen ber om en nærmere redegjørelse om behovet for en beredskap i forbindelse med informasjon som kan komme opp som resultat av prosjektet. Kan det tenkes uventede funn i analysene av blodprøver? Kan det tenkes svar på spørsmål i spørreskjemaet som kan tyde på det trenges en eller annen form for oppfølging?
6. Norsk versjon engelsk spørreskjema må ettersendes.

Prosjektleder har sendt tilbakemelding, denne ble mottatt 28.01.2014.

Om komiteens merknader fremkommer det av tilbakemeldingen:

1. Det kan i fremtiden være aktuelt å se på langtidseffektene av intervensjonen. Kontrolldeltakerne vil bli tilbudt samme intervensjon som studiegruppen, noe som i første omgang vil vanskeliggjøre en sammenligning mellom gruppene. Av denne grunn omfatter ikke protokollen en oppfølging på det nåværende tidspunkt. I midlertid vil en oppfølging av deltakerne i et longitudinelt design muligjøre en evaluering av langtidseffekter, og for å sikre at man kan be barna om deltakelse i et slikt eventuelt oppfølgingsstudie ønsker man nå å legge dette inn i informasjonsskrivet. Formuleringene i informasjonsskrivet er endret slik at dersom barnet planlegges undersøkt på nytt eller dersom data vil bli benyttet etter barna er fylt 16 år, så vil man be om et nytt samtykke for dette.
2. Det skal innhentes data fra medisinsk fødselsregister og MoBa-registeret, og disse koblingene er nå spesifisert i informasjonsskrivet.
3. Det foreligger nå en beskrivelse av den kvalitative delen av prosjektet, og det er utformet separate informasjonsskriv for deltakerne i denne delen.
4. Randomiseringen til intervensjon eller kontroll vil foregå på skolenivå, og ved intervensjonsskolene vil den ekstra timen med fysisk aktivitet inngå som en ordinær del av det pedagogiske tilbudet. Det vil derfor ikke oppleves som press på enkeltelever i forhold til deltakelse i prosjektet eller ikke. For de elever som av ulike årsaker søker fritak fra fysisk aktivitet, vil skolen på ordinær måte finne andre undervisningstilbud.
5. Eventuelle funn som måtte avdekkes ved deltakelse i prosjektet vil håndteres gjennom den enkeltes skolehelsetjeneste på ordinær måte.
6. Tidligere engelske skjema foreligger nå i norsk oversettelse, dette gjelder deler av MSLQ skjemaet (management strategies, learning self-efficacy) og CCC-instrumentet (cross-curricular competencies).

Prosjektleders tilbakemelding er å anse som tilfredsstillende i forhold til komiteens merknader.

Vedtak

Komiteen godkjenner at prosjektet gjennomføres i samsvar med det som fremgår av søknaden.

Godkjenningen gjelder til 31.12.2017.

Av dokumentasjonshensyn skal opplysningene oppbevares i 5 år etter prosjektslutt. Forskningsfilen skal oppbevares avidentifisert, dvs. atskilt i en nøkkel- og en datafil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato. Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for «Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse- og omsorgssektoren».

Prosjektet skal sende sluttmelding på eget skjema, se helseforskningsloven § 12, senest et halvt år etter prosjektslutt.

Dersom det skal gjøres endringer i prosjektet i forhold til de opplysninger som er gitt i søknaden, må prosjektleder sende endringsmelding til REK.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10 tredje og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst A. Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Med vennlig hilsen

Knut Engedal
Professor dr. med.
Leder

Anette Solli Karlsen
Komitesekretær

Kopi til: erik.kyrkjebo@hisf.no; post@hisf.no

APPENDIX II

Study information and consent form given to parents and children

Kjære foreldre eller føresette ved 5. klasstrinn i Sogn og Fjordane, skuleåret 2014/15

Føresurnad om deltaking forskingsprosjektet «ASK - Active Smarter Kids»

KVA ER «ASK»?

ASK er eit stort utviklings- og forskingsprosjekt som skal undersøke korleis auka fysisk aktivitet i samspel med dei tradisjonelle faga påverkar skuleprestasjon, skuletrivsel og helse gjennom eitt skuleår (2014/15) for 5. klasseelevar.

Kva er formålet med ASK-prosjektet?

ASK-prosjektet er eit såkalla intervensjonsprosjekt som betyr at ein innfører noko nytt, for deretter å måle verknaden. For å måle verknad av ASK-modellen får halvparten av skulane intervensjonen (som er dagleg fysisk aktivitet) og den andre halvparten fortsetter som før. Skular der det er sju elevar eller meir på 5. klasstrinn i skuleåret 2014/15 vil bli inkludert i prosjektet. Skulane i kontrollgruppa 2014/15 vil få tilbod om same opplegg som prosjektgruppa, men eit år seinare (i 6. klasse, skuleåret 2015/16). Alle 26 kommunane i Sogn og Fjordane har sagt ja til deltaking i utviklings- og forskingsprosjektet ASK. Prosjektet vert gjennomført i samråd skuleregionane i Sogn og Fjordane og utdanningsaktørar i fylket. Kunnskapen som denne studien gjev vil vere viktig for å evaluere graden av kor fysisk aktive barn og unge bør vere med tanke på både læring og helse. ASK-prosjektet vil difor kunne gje samfunnet verdifull informasjon og kunnskap om organisering av skulekvardagen og metodar for førebyggjande helsearbeid.

Kva inneber ASK-prosjektet for skulekvardagen til dykkar son/dotter dersom dykkar son/dotter går på ein skule som skal gjennomføre dagleg fysisk aktivitet?

Det faglege innhaldet i ASK-modellen (den daglege timen med fysisk aktivitet) blir utvikla i samarbeid mellom barneskulane i Sogn og Fjordane og HiSF, og inkluderer i løpet av ei skuleveke:

- 2 dagar x 45 minutt kroppsøving (dette gjeld alle elevar, både prosjektgruppe og kontrollgruppe)
- 1 dag x 45 minutt fysisk aktivitet (mest mogleg fysisk aktivitet på borna sine premiss)
- 3 dagar x 30 minutt «Aktiv læring» (elevane er fysisk aktive utandørs og øver på fag (t.d. mattebingo)
- 5 dagar x 5 minutt fysisk aktivitet i fag (elevane er aktive 5 minuttar i klasserommet kvar dag)
- 5 dagar x 10 minutt fysisk aktivitet i «aktiv heimelekse» (elevane er aktive 10 minutt kvar dag heime)

Den daglege fysiske aktiviten er ikkje vurdert til å vere forbunden med risiko, og kan samanliknas med aktivitetar og metoder nytta i ein vanleg kroppsøvingstime.

Kva innber ASK-prosjektet for skulekvardagen til dykkar son/dotter dersom dykkar son/dotter ikkje går på ein skule som skal gjennomføre dagleg fysisk aktivitet?

For elevar ved skular som er kontrollgruppe, vil skuleåret gå som normalt.

Kva inneber testing i ASK-prosjektet for dykkar son/dotter?

Det vil, ved oppstart (august/sepember 2014) og avslutning (mai/juni 2015), bli gjennomført testar for å måle verknadar av ASK. Dette er derfor ein førespurnad til dykk som er foreldre eller føresette om ditt barn kan delta på ulike testar som målar verknadar av fysisk aktivitet på skuleprestasjon, skuletrivsel og helse i ASK-prosjektet.

Testane vert gjennomført i skuletida på dei lokale skulane eller på tilrettelagde testsenter i regi av HiSF. Tilhøva som blir undersøkt er alle knytt til skuleprestasjon, skuletrivsel og folkehelse. Dette inkluderer testar for kognisjon (testar som målar t.d. hukommelse og minne), ulike spørjeskjema, test av fysisk form og fysisk aktivitetsnivå, blodtrykk, motorikk, vekt og høgde. Det vil bli teke blodprøve. Foreldre/føresette blir spurde om å fylle ut eit spørjeskjema. Dersom ein elev sitt testresultatet visar avvikande medisinske verdiar vil skulehelsetenesta informeras og informasjonen til barn/foreldre vil ved desse tilfella komme frå skulehelsetenesta. Elevane i prosjektgruppa får fritak frå undervising slik at dei kan delta i testane. Dette er testar med låg eller ingen risiko for skader, og som er gjennomført og kvalitetsikra i fleire tilsvarande studiar. I tillegg til testane over, blir fire skular valt med på ei kvalitativ undersøking, som inneber intervju og observasjon. Viss dykkar son/dotter går i ein av desse skulane, vil han/ho få utdelt eit eige informasjonsskriv og samtykkjeerklæring for denne delen av studien.

Frivillig deltaking i testar

Det er frivillig å ta del i testane i ASK-prosjektet. Ein kan trekkje seg frå heile eller delar av testane kva tid som helst og utan å oppgje grunn, og utan at det får negative konsekvensar. De kan når som helst og utan å oppgje nokon grunn trekkje samtykke. Dette vil ikkje få konsekvensar for den vidare handsaminga av dykkar barn. Dersom foreldre/føresette eller dykkar son/dotter ynskjer å trekkje seg, vil innsamla data bli sletta.

Moglege føremoner og ulemper

Under alle testane bli det lagt vekt på barnet sitt beste, og personane som er ansvarleg for testane er sær medvitne om at barn er ei sårbar gruppe. Alle moglege førehandsreglar blir tekne for å unngå eventuelle situasjonar som kan opplevast som ukomfortable for borna. Til dømes vil alle blodprøvar bli tekne i trygge lokale av røynde bioingenjører. Me er medviten om at blodprøvetaking kan medføre psykisk påkjenningar for nokre av borna, og dersom barnet ditt ikkje ynskjer å ta blodprøven, men andre testar, er dette heilt i orden.

Kva skjer med informasjonen om dykkar barn?

Alle data som vert samla inn, både papirbasert og elektronisk, vert handsama i samsvar med krav til personvern og IKT-tryggleik nedfelt i helseforskningslova og personopplysningslova. Prøvene som ein tek og informasjonen som vert registrert om dykkar barn, skal berre nyttast i henhold til føremålet med studien. Alle skjema og data vert aidentifisert, det vil seie handsama utan namn og fødselsnummer eller andre direkte opplysningar som kan gjera at dei vert kopla til ditt barn. Identifiserbare opplysningar som knyter dykkar barn til opplysningane vert erstatta av ein kode. Lista som koplar kode og namn vert oppbevart på ein sikker måte åtskilt frå forskingsdataene, og berre prosjektleiinga har tilgang til namnelista og det er berre dei som kan finne attende til dykkar barn.

Kva skjer når prosjektet er avslutta?

Prosjektet vert avslutta 31.12.2016, men ASK ynskjer å oppbevare data for moglege framtidige oppfylgingsstudium. Datamaterialet vil 31.12.2016 bli anonymisert for forskarar i ASK, men namnelista over prosjektdeltakarar og koden som koplar dei til data vert lagra hjå ein autorisert tiltrudd tredjepart, i dette høvet Personvernombodet for forskning hjå Norsk samfunnsvitenskapelig datatjeneste. Det eksisterer i dag ikkje tilfredsstillande kunnskap vedrørande langtidsverknadar av skulebaserte fysiske aktivitetsintervensjonar, og det kan derfor bli aktuelt at dykkar barn blir spurt om å delta ved eit seinare høve. Dersom dette blir aktuelt tek me kontakt.

Resultata av prosjektet vert publisert i form av engelskspråklege artiklar i internasjonal faglitteratur. I tillegg vil resultata frå prosjektet bli formidla til det norske fagmiljøet i form av populærvitenskaplege artiklar og faglege føredrag. Me skal også skrive ein rapport frå prosjektet som er retta mot deltakarane og aktørar som har vore med på å legge til rette for gjennomføringa av prosjektet. Me understrekar at opplysningar som kjem fram i publikasjonar og føredrag ikkje kan førast tilbake til einskildpersonar.

Høgskulen i Sogn og Fjordane (HiSF) er ansvarleg for forskingsprosjektet, og vil gjennomføre all testing. Prosjektleiingar er førsteamanuensis Geir K. Resaland og professor Sigmund Alfred Anderssen. Prosjektet har vore gjennom ei grundig fagleg vurdering i Norges Forskningsråd som tildelte prosjektet 17,5 millionar kroner i oktober 2012 (prosjektnr. 221047). Norges Forskningsråd vurderte ASK-prosjektet til å ha svært høg kvalitet.

Dersom de aksepterer at dykkar barn tek del i testinga i ASK-prosjektet, skriv du under samtykkjeerklæringa på neste side. Om du seier ja til å vera med no, kan du seinare trekkje attende samtykkje utan at det påverkar handsaminga di elles. Dersom du seinare ynskjer å trekkje dykkar barn eller har spørsmål til studien, kan du kontakte Geir K. Resaland.

Dersom de på noko tidspunkt har spørsmål, ta gjerne kontakt på telefon eller e-post.

Venleg helsing

Førsteamanuensis Geir K. Resaland
Tlf. 57676097, Mob. 41621333
e-post gk@hisf.no

Professor Sigmund Alfred Anderssen
Tlf. Mob. 45279348
e-post s.a.anderssen@nih.no

Samtykkje til deltaking i ASK-studiet

Eg har lese informasjonsskrivet og aksepterer at mitt barn tek del i ASK-studiet

(Signert av foreldre til prosjektdeltakar, dato)

Eleven sitt førenamn og etternamn: (Skriv tydeleg, helst med blokkbokstavar)

.....

Foreldre/føresette sitt førenamn og etternamn: (Skriv tydeleg, helst med blokkbokstavar)

.....

Eg stadfestar at eg har gjeve informasjon om studiet

Signert, prosjektkoordinator Geir K. Resaland, dato

