DISSERTATION FROM THE
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Guro Pauck Bernhardsen

Pre- and postnatal factors related to cardiometabolic health and adiposity in children and adolescents

Does physical activity matter?

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Sammendrag på norsk

Innledning: Kardiovaskulære sykdommer er en ledende årsak til for tidlig død over hele verden, og er sterkt forbundet med overvekt og fedme. Pre- og postnatale faktorer, inkludert mors kroppsmasseindeks (KMI) før svangerskapet, fødselsvekt og vektøkning første leveår, er konsistent assosiert med kardiometabolske risikofaktorer og utvikling av overvekt og fedme hos barn. Økt kunnskap om mulige forebyggende strategier er således avgjørende, og fysisk aktivitet er trolig et viktig folkehelsetiltak. Imidlertid har få studier undersøkt om pre- og postnatale faktorer også påvirker fysisk aktivitet i barne- og ungdomsårene eller om det er en interaksjon mellom disse tidlige faktorene og fysisk aktivitet i utviklingen av kardiometabolsk helse og overvekt/fedme hos barn og ungdom.

Hensikt: Hovedhensiktene med denne avhandling var å undersøke **1)** om pre- og postnatale faktorer (mors KMI før svangerskap, fødselsvekt, vektøkning første leveår og motorisk utvikling) er assosiert med fysisk aktivitet hos barn og ungdom, og **2)** om det er en interaksjon mellom pre- og postnatale faktorer (mors KMI før svangerskap, fødselsvekt og vektøkning første leveår) og fysisk aktivitet i utviklingen av kardiometabolsk helse og mål på overvekt/fedme hos barn og ungdom.

Metode: Resultatene fra denne avhandlingen er basert på ulike forskningsdesign og deltakere. Forskningsspørsmål **1)** ble undersøkt ved en systematisk litteraturgjennomgang og meta-analyse, og data fra Den norske mor, far og barn- undersøkelsen (MoBa). MoBa er en populasjonsbasert fødselskohort hvor barna er fulgt opp jevnlig ved spørreskjema besvart av mor. Barna er også koblet til Medisinsk Fødselsregister. Totalt 48 672 barn med tilgjengelige data på fysisk aktivitet (besvart av mor) ved 7 -års alder ble inkludert i analysene. Forskningsspørsmål **2)** ble undersøkt med data fra en sub-kohort av MoBa, som inkluderte 445 barn med tilgjengelig data på fysisk aktivitet målt med akselerometer. Alle barna hadde data på KMI, mens 186 av barna også hadde målt kroppssammensetning ved Dual energy X-ray absorptiometry (DXA). Sub-kohorten ble undersøkt separat eller inkludert i sammenslåtte individuelle data fra 12 kohort- eller tverrsnittsstudier, som totalt inkluderte 9 100 barn og ungdommer.

Hovedresultat: 1) Den systematiske litteraturgjennomgangen og meta-analysen viste ingen lineær sammenheng mellom fødselsvekt og senere fysisk aktivitet hos barn og ungdom. Tre studier undersøkte sammenhengen mellom tidlig vektøkning og senere fysisk aktivitet, men resultatene var inkonsekvente. Vi fant to studier som indikerte en mulig sammenheng mellom tidligere motorisk utvikling og fysisk aktivitet hos barn og ungdom. Videre viste analyser at mors

KMI før svangerskapet og fødselsvekt er ikke-lineært forbundet med senere fysisk aktivitet hos gutter, hvor det var en positiv sammenheng under 21kg/m^2 og -1 z-skåre, og en svak negativ sammenheng over 21 kg/m^2 og -1 z-skåre for henholdsvis mors KMI under svangerskapet og standardisert fødselsvekt justert for svangerskapsuke. Videre observerte vi en svak positiv sammenheng mellom tidlig vektøkning og senere fysisk aktivitet hos gutter. Vi observerte ingen sammenheng mellom mors KMI før svangerskapet, fødselsvekt og vektøkning første leveår med senere fysisk aktivitet hos jenter. **2)** Økt høy-intensiv fysisk aktivitet modifiserte og svekket sammenhengen mellom mors KMI før svangerskapet og barnets KMI hos gutter, men ikke hos jenter. Fødselsvekt var ikke relatert til kroppssammensetningen hos barn, og det var ingen effekt modifikasjon av fysisk aktivitet. Videre observerte vi at fysisk aktivitet modifiserte og svekket sammenhengen mellom vektøkning første leveår og barnets fettmasse og fettprosent hos gutter, men ikke hos jenter. De fleste sammenhengene mellom lav fødselsvekt og kardiometabolske risikofaktorer ble ikke modifisert av moderat til høy fysisk aktivitet, bortsett fra sammenhengen mellom fødselsvekt og midjemål hos barn og high density lipoprotein (HDL)-kolesterol hos ungdom. Sensitivitetsanalyser viste at fysisk aktivitet med høy intensitet modifiserte sammenhengen mellom fødselsvekt og diastolisk blodtrykk hos barn og low density lipoprotein (LDL)-kolesterol og triglyserider hos ungdom.

Konklusjon: Pre- og postnatale faktorer kan være ikke-lineært assosiert med senere fysisk aktivitet hos gutter, men trolig ikke hos jenter. Den sterkeste sammenhengen synes å være på den lavere skalaen av mors KMI før svangerskapet og fødselsvekt, noe som indikerer at føtal underernæring kan føre til lavere fysisk aktivitetsnivå hos gutter. Videre kan en senere motorisk utvikling påvirke det fysiske aktivitetsnivået til barn og ungdom. Gutter ser også ut til å være mer sårbare for en høy KMI hos mor under svangerskapet og en rask vektøkning første leveår når det kommer til senere fettmasse og KMI i barndommen. Noen av disse sammenhengene ser imidlertid ut til å bli modifisert og svekket av et høyere fysisk aktivitetsnivå hos gutter. Fysisk aktivitet kan til en viss grad også svekke sammenhengen mellom en høy fødselsvekt og sentral fedme hos barn. Moderat til høy intensiv fysisk aktivitet ser imidlertid ikke ut til å konsistent modifisere sammenhengen mellom en lav fødselsvekt og kardiometabolsk helse hos barn og ungdom. Optimal pre- og postnatal utvikling og fysisk aktivitet i barne- or ungdomsårene er alle viktige i relasjon til kardiometabolsk helse og kroppssammensetning hos barn og ungdom.

Summary

Introduction: Cardiovascular diseases are a leading cause of premature mortality in all regions of the world, and they are highly linked to obesity. Pre- and postnatal factors, including maternal pre-pregnancy body mass index (BMI), birth weight and infant weight gain, have consistently been shown to be associated with higher cardiometabolic risk factors and greater adiposity in children and adolescents. Increased knowledge to establish safe and efficacious prevention strategies in these predisposed groups is thus urgent. An important public health strategy may be physical activity (PA); however, few studies have examined whether pre- and postnatal factors are also associated with or interact with PA in the development of cardiometabolic health and adiposity in children and adolescents.

Objectives: The main objectives are **1)** to examine whether pre- and postnatal factors (maternal pre-pregnancy BMI, birth weight, infant weight gain and motor development) are associated with PA in children and adolescents and **2)** to examine whether PA interacts with pre- and postnatal factors (maternal pre-pregnancy BMI, birth weight and infant weight gain) in the development of cardiometabolic health and adiposity in children and adolescents?

Participants and methods: This thesis is based on different study designs and comprises of different participants. The first research question was examined by a systematic review and meta-analysis and data from the Norwegian Mother, Father and Child cohort study (MoBa). The latter (MoBa) is a population-based birth cohort study in which the children are followed up regularly with maternal reported questionnaires and linked to the Medical Birth Registry of Norway (MBRN). For the present analyses 48 672 children were eligible for inclusion. The second research question was examined using data from a sub-cohort of the MoBa, including 445 children with available data on accelerometer-assessed PA. All participants had data on BMI, and 186 provided data on body composition (dual energy X-ray absorptiometry [DXA]). The sub-cohort was either examined separately or included in pooled individual data from 12 cohort- or cross-sectional studies including 9 100 children and adolescents.

Main results: 1) The systematic review and meta-analysis suggest no linear association between birth weight and later PA in children and adolescents. Three studies examined infant weight gain and later PA; they differ in methodology, and the results are inconsistent. Two studies suggest that earlier motor development is associated with PA and sport participation in children and adolescents. Moreover, analyses indicate that maternal pre-pregnancy BMI and birth weight are non-linearly associated with maternally reported leisure time PA (LTPA) in boys, in which the

association was positive below 21kg/m^2 and -1 z-score, and slightly inverse above 21kg/m^2 and -1 z-score for maternal pre-pregnancy BMI and birth weight for gestational age z-score, respectively. We further observed a weak positive association between infant weight gain and LTPA in boys. We found no associations between maternal pre-pregnancy BMI, birth weight and infant weight gain with LTPA in girls. **2)** A higher vigorous PA (VPA) attenuated the association between maternal pre-pregnancy BMI and BMI in boys, but not in girls. Furthermore, birth weight was unrelated to childhood body composition, and there was no effect modification by PA. Physical activity attenuated the associations between infant weight gain and childhood fat mass and percent fat in boys but not in girls. Most of the associations between birth weight and cardiometabolic risk factors were not modified by moderate-to-vigorous PA (MVPA), except between birth weight and waist circumference in children and high-density lipoprotein (HDL) cholesterol in adolescents. Sensitivity analyses suggest that some of the associations were modified by VPA: those between birth weight and diastolic blood pressure in children and between low-density lipoprotein (LDL) cholesterol and triglycerides in adolescents.

Conclusion: Pre- and postnatal factors may be non-linearly associated with later PA in boys but not in girls. The strongest influence appears to be at the lower end of the maternal pre-pregnancy BMI and birth weight continuum, indicating that fetal undernutrition may undesirably impact the PA level in boys. Furthermore, motor development may be inversely associated with PA in children and adolescents. Boys also appears to be more vulnerable to a high maternal pre-pregnancy BMI and infant weight gain on subsequent fat mass and BMI in childhood, and some of these associations may be modified and attenuated by PA in boys. In addition, PA may, to some degree, attenuate the association between a higher birth weight and abdominal adiposity in children, whereas MVPA does not appear to consistently modify the associations between a lower birth weight and either cardiometabolic risk factors or clustered cardiometabolic risk. Finally, optimal pre- and postnatal environments and subsequent PA are all important in relation to cardiometabolic health and adiposity in children and adolescents.

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Oslo, February 2020

Guro Pauck Bernhardsen

Abbreviations

ALSPAC – Avon Longitudinal Study of Parents and Children

ASK – Active Smarter Kids

BMI – Body mass index

DOHaD – Developmental origins of health and disease

DLW – Double labelled water

DXA – Dual-energy x-ray absorptiometry

EYHS – The European Youth Heart Study

FGR – Fetal growth restriction

GDM – Gestational diabetes mellitus

HDL – High density lipoprotein

HOMA - IR – Homeostatic model assessment - insulin resistance

IBDS – The Iowa Bone Development Study

ICAD – International Children Accelerometry Database

KISS – Kinder-Sportstudie

LDL – Low density lipoprotein

LGA – Large for gestational age

LTPA – Leisure time physical activity

MAR – Missing at random

MET – Metabolic equivalent of task

MetS – Metabolic syndrome

MI – Multiple imputation

MoBa – The Norwegian Mother, Father and Child cohort study

MVPA – Moderate to vigorous physical activity

PA – Physical activity

PANCS – Physical activity among Norwegian children study

PAEE – Physical activity energy expenditure

QA – Quality assessment

RMR – Resting metabolic rate

SGA – Small for gestational age

SPEEDY – The Sport, Physical activity and Eating behaviour: Environmental Determinants in Young people

TEE – Total energy expenditure

VPA – Vigorous physical activity

List of papers

This dissertation is based on the following research papers, which are referred to in the text by their Roman numerals:

I. Oglund GP, Hildebrand M, Ekelund U. *Are birth weight, early growth, and motor development determinants of physical activity in children and youth? A systematic review and meta-analysis.* Pediatr Exerc Sci. 2015;27(4):441-53.

II. Bernhardsen GP, Stensrud T, Nystad W, Ekelund U. *Pre- and postnatal factors and physical activity in childhood: The Norwegian Mother and Child Cohort Study.* Submitted

III. Bernhardsen GP, Stensrud T, Nystad W, Dalene KE, Kolle E, Ekelund U. *Early life risk factors for childhood obesity – Does physical activity modify the associations? The MoBa cohort study.* Scand J Med Sci Sports. 2019;29(10):1636-46.

IV. Bernhardsen GP, Stensrud T, Hansen BH, Steene-Johannesen H, Kolle E, Nystad W, Anderssen SA, Hallal PC, Janz KF, Kriemler S, Andersen LB, Northstone K, Resaland GK, Sardinha L, van Sluijs EMF, Ried-Larsen M, Ekelund U; On behalf of the International Children's Accelerometry Database (ICAD) Collaborators. *Birth weight cardiometabolic risk factors and effect modification of physical activity in children and adolescents: Pooled data from 12 international studies.* Submitted

Note: former name was Øglund (Paper I)

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Introduction

Noncommunicable diseases are the leading cause of health loss and deaths in all regions of the world (1, 2), with cardiovascular diseases alone accounting for one-third of all deaths globally (1). The current global health policy goals include a 25% reduction in premature mortality from noncommunicable diseases (3). Furthermore, obesity is highly linked to cardiovascular diseases (4) and is reaching epidemic proportions worldwide (5). Therefore, investigating in prevention strategies is of high importance.

Whilst the main focus for the prevention of non-communicable diseases and obesity is on individual health behaviors, including smoking, physical activity (PA), diet and alcohol (3, 6, 7), a growing body of literature recognizes that the prevention of noncommunicable diseases should start with maternal health (7-11). The developmental origins of health and disease (DOHaD) approach has emerged in the last three decades and suggests that poor developmental experiences in the pre- and postnatal period increase the risk of non-communicable diseases and obesity later in life (12). A low birth weight, used as a proxy measure for fetal growth restriction (FGR), is the most studied exposure in the early years of the DOHaD (12-14). However, since then, several other possible pre- and postnatal factors have been suggested to influence subsequent cardiovascular health and adiposity, including maternal pre-pregnancy body mass index (BMI) (15) and infant weight gain (16).

Increased PA is another important and widely recognized prevention strategy (17). Physical inactivity is estimated to cause 6–10% of the major non-communicable diseases and 9% of premature mortality worldwide (18), and it thus constitutes a significant economic burden via health-care expenditures and productivity losses (19). A recent harmonized meta-analysis has demonstrated a non-linear risk reduction in all-cause mortality across PA at any intensity in middle-aged and older people (20). The greatest risk reduction was observed at the lower end of the PA continuum; hence, the proposed public health message is "sit less and move more and more often" (20).

Childhood and adolescence are considered to be important periods in life to implement interventions in those at higher risk of developing cardiovascular diseases or obesity due to poor developmental experiences (8, 21). The present thesis is based on four papers that aimed to determine whether pre- and postnatal factors either are associated with PA or interact with PA in the development of cardiometabolic health and adiposity in children and adolescents.

More specifically, the two research questions to be answered are as follows:

1) Are pre- and postnatal factors (maternal pre-pregnancy BMI, birth weight, infant weight gain and motor development) associated with PA in children and adolescents?
2) Does PA modify the associations between pre- and postnatal factors (maternal pre-pregnancy BMI, birth weight and infant weight gain) and the development of cardiometabolic health and adiposity in children and adolescents?

Theoretical background

The developmental origins of health and disease

The first 1000 days of life – from conception to the second birthday – are considered a vulnerable period in life when the body's structure and physiology are developing. Appropriate nourishment during this period is increasingly recognized as having an impact not only on early growth and development, but also on the lifelong health of an individual (8). Three Lancet-papers by David Barker and colleagues (13, 14, 22) are deemed to serve as the greatest impetus for the beginning of the DOHaD-concept, which was formerly called the fetal origins of adult disease and is also referred to as "Barker's hypothesis" (23). Barker's first clue arose from a geographical study (22), in which areas in England and Wales with high infant mortality in the 1920s correlated with subsequent mortality from ischemic heart disease in the 1960s and 1970s. The authors suggested that poor living standards in childhood may affect the development of diseases in adulthood. This was former also observed in Norway, where counties with high infant mortality correlated with subsequent higher mortality from heart disease (24). The authors argued that these variations could not be explained by the living standard at follow-up, as the prosperity levels rose in all regions (22, 24). The association was replicated in a second study by Barker and colleagues (14) that included adult men born between 1911 and 1930 in Hertfordshire, England, in which birth weight and weight at the age of one had been registered by midwifes. Men with the lowest weight at birth and at one year old had higher mortality from ischemic heart disease (14). Results from the same cohort also revealed a higher prevalence of coronary heart disease (25) and a higher risk of developing type 2 diabetes (26) in men with a low birth weight, and higher mortality from cardiovascular diseases in women with a low birth weight (27). The third Lancet-paper was a review by Barker et al. (13) that summarized how fetal undernutrition at different stages of pregnancy could lead to metabolic abnormalities in adult life. The early hypothesis was "(…) that undernutrition in utero and during infancy permanently changes the body's structure, physiology and metabolism and leads to coronary heart disease and stroke in adult life" (12).

Many of the early studies linking low birth weight to later risk of cardiovascular diseases arose in a time when maternal obesity during pregnancy, gestational diabetes mellitus (GDM) and fetal macrosomia (birth weight ≥ 4.0 kg) were uncommon. As these factors increased in the population, the associations became more complex as fetal overnutrition was also demonstrated to influence later health in offspring, but possibly via different mechanisms (8, 28).

Both developmental under- and overnutrition may thus lead to increased risk of cardiovascular diseases and obesity later in life (29, 30). While many factors may lead to or are proxy measures of developmental under- and overnutrition, this thesis is limited to the pre- and postnatal factors, namely, maternal pre-pregnancy BMI, birth weight and infant weight gain.

Developmental undernutrition

Fetal growth restriction occurs when a fetus does not reach its intrauterine potential for growth and development (31, 32). The etiologies of FGR are multifactorial and include placental insufficiency (major contributor), maternal undernutrition, maternal diseases (e.g. hypertension and pre-eclampsia), multiple pregnancies, pregnancy complications, infections, toxic exposures and maternal drug use (mainly smoking) (31-34). Furthermore, FGR is difficult to define in practice (34, 35), and a low birth weight (<2.5 kg) is therefore used as a proxy measure of restricted fetal growth. The estimated worldwide prevalence of low birth weight is 14.6%, with the highest prevalence being in Southern Asia (26.4%) (36). Another more appropriate, yet still not optimal, proxy measure for FGR is small for gestational age (SGA), defined as infants below the 10^{th} centile of a gestational age- and sex-specific birth weight in a reference population (32, 34). Although FGR has considerable overlap with SGA, not all FGRs are SGAs and vice versa (34).

A large number of studies have provided support for the impact of a low birth weight on subsequent risk of diseases in adulthood, a low birth weight has specifically been associated with a subsequent increased risk of coronary heart disease (37-43), stroke (37, 40, 42), hypertension (44-47) and type 2 diabetes (46, 48-53). A meta-analysis including more than 36 000 deaths suggested a 6% reduction in all-cause mortality and a 12% reduction in mortality from cardiovascular diseases per kg higher birth weight (54). In addition, early signs of disease are apparent already in children and adolescents, in whom a lower birth weight is associated with higher cardiometabolic risk factors, including higher systolic- and diastolic blood pressure (55-60) and higher insulin levels (56-59, 61-63). Some studies suggest an association between lower birth weight and triglycerides (57, 64), whereas others do not (58, 59, 63). Most studies suggest no association between birth weight and subsequent high-density lipoprotein (HDL)- and low-density lipoprotein (LDL)- cholesterol (58, 59, 63, 65, 66) in childhood or adolescence, with some exceptions suggesting an unfavorable composition in those born with a lower birth weight (57, 64). Furthermore, a clustering of cardiometabolic risk factors is likely more important for future health than single risk factors. A clustered cardiometabolic risk score can be calculated by summarizing sex-specific z-scores for several risk factors, divided by the total number of risk

factors included. Few studies have examined the association between birth weight and a clustered cardiometabolic risk score. Chiavaroli et al. (66) observed a higher clustered cardiometabolic risk score in both SGA and large for gestational age (LGA) individuals, combining both BMI and cardiometabolic risk factors in the summary score.

A low maternal pre-pregnancy BMI, which may be a risk factor for FGR via maternal undernutrition, has been associated with increased risk of coronary heart disease (43) and mortality from cardiovascular events (67) in adult offspring, although in markedly less studies compared to a low birth weight.

Although most studies suggest a positive linear association between birth weight and later measures of adiposity (68-73), some studies have suggested a J-shaped or U -shaped relationship (69, 74). A lower birth weight may thus also lead to greater adiposity, and this is mostly evident in studies with assessment of fat mass or abdominal adiposity after adjustments for current body mass (74-77).

Possible mechanisms

A challenge to human cohort studies has been the elucidation of clear mechanisms behind the DOHaD approach. One of the initial hypotheses, proposed by Barker and his colleagues (12, 13), was that nutrient restrictions during a highly developmental period, such as fetal life, lead to adaptive responses in the fetus. Fetal life is a critical period in life when the body's system is plastic and sensitive to the environment, followed by more fixed periods that increases with age (12). The cardiovascular disease risk in undernourished fetuses is further amplified with an unhealthy lifestyle, that is, an increasing mismatch between the prenatal and postnatal environment (Figure 1) (8, 12). Some evidence for this hypothesis was observed in Jamaican children experiencing severe malnutrition, in which children born with a lower birth weight handled the malnutrition better than those born with higher birth weight (78).

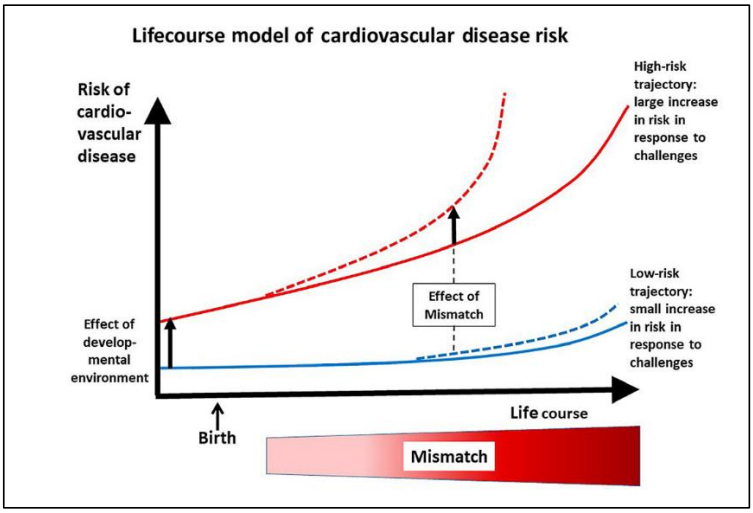

Figure 1: The risk of cardiovascular diseases is partly established during pre- and postnatal development. The trajectory of risk sets the response of the individual to health challenges, graded across the entire range in a population from low to high (blue to red solid lines). Amplification of risk occurs especially when there is a mismatch between the pre- and postnatal environment (dashed lines).
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In recent years, increasing evidence has also suggested that FGR is associated with direct changes in the cardiovascular system, in the form of cardiac remodeling, increased arterial stiffness and increased intima-media thickness, a marker of preclinical atherosclerosis (21, 60, 79, 80). Furthermore, reduced oxygen and nutrient availability in critical periods in fetal life may lead to asymmetric organ development, whereby there is reduced growth of less essential organs such as the liver, lungs and kidneys (81), in addition to reduced skeletal muscle growth (82).

More recently the DOHaD- concept has been developing into the field of epigenetics – the mechanisms by which genes interact with the environment to produce various phenotypic expression (83). Studies have demonstrated that a lower birth weight (84-87) and lower maternal pre-pregnancy BMI (88), are associated with differences in DNA methylation in neonatal blood and that some of these persist later in life (85, 87, 88). These findings support that changes in DNA methylation may be a potential mechanism linking early exposures to later health. Furthermore, recent studies have also suggested that the association between birth weight and adult cardiometabolic diseases are in part the result of shared genetic effects (89, 90).

Several other mechanisms have been suggested, many of which are proposed and examined using animal experiments (8, 21, 81). These are not further elaborated here.

Developmental overnutrition

The developmental overnutrition hypothesis proposes that an intrauterine environment that overfeeds a developing fetus sets the offspring on a path of greater adiposity across his or her life (28, 29). This hypothesis may also be expanded to the postnatal period (16). In two recent review articles, the pre- and postnatal factors with the strongest scientific evidence of a linkage to childhood adiposity are a high maternal pre-pregnancy BMI, a high birth weight and a rapid infant weight gain (30, 91).

Maternal pre-pregnancy BMI

Maternal pre-pregnancy BMI reflects the maternal BMI at the start of pregnancy (i.e. not influenced by amount of weight gain due to the pregnancy). The prevalence of overweight and obesity in women of reproductive age exceeds 30% in developed countries and is increasing in line with the global obesity epidemic (5).

Maternal pre-pregnancy obesity is associated with three times increased odds for childhood overweight or obesity (15). Evidence also supports that a higher maternal pre-pregnancy BMI across the whole spectrum, and not only at the extreme of obesity, is associated with greater adiposity (92-95) and an adverse body composition (93, 96, 97) in offspring. Some studies have also suggested that maternal pre-pregnancy obesity increases the risk of mortality from cardiovascular diseases in adult offspring (67, 98) and cardiometabolic risk factors (94, 99-101) in adult and adolescent offspring. However, these associations may be driven by offspring adiposity (94, 100, 101).

The challenge is to disentangle whether these associations reflect causal intrauterine mechanisms or are explained by mother-child genetics and shared postnatal lifestyles. Some studies have used a negative control design in which the association with maternal BMI is compared to the association with paternal BMI on the same outcome. The clue to the negative control design is that both the mother and father share the same contribution to genetic influences as well as similar lifestyles. The results from these studies are contradictory; some support a causal intrauterine effect of maternal BMI, that is, the association with maternal BMI is stronger than the association with paternal BMI (95, 102, 103), whereas others observed a similar magnitude of the associations between both maternal and paternal BMI and the offspring's adiposity (104-107). Lawlor et al. (103) observed that maternal BMI was more strongly associated with childhood adiposity than paternal BMI; however, after controlling for the fat mass and obesity (FTO) associated gene there was no longer an association between maternal BMI and offspring fat mass and the results give thus no support of an intrauterine effect. In contrast, two studies

observed that siblings born before and after a large weight loss in the mother, due to bariatric surgery, differed in obesity-status; the prevalence of overweight and obesity was higher in the children born before surgery than in those born after surgery (108, 109). The latter group of children also demonstrated a more favorable cardiometabolic risk profile (109). It is difficult to infer causality from observational studies only; therefore, numerous animal studies have been conducted, demonstrating that maternal obesity is causally linked to higher adiposity in offspring across many species (110). However, animal models may not perfectly reflect the biological processes in humans. It is thus still unclear whether a causal effect via intrauterine mechanisms exists or whether the higher risk of obesity is due to transmission of genotypes and lifestyle to the offspring. It is argued that the developmental overnutrition hypothesis may be limited to the offspring of mothers on the highest end of the BMI- scale (28).

High birth weight

High birth weight is another recognized early life risk factor for obesity (73). A high birth weight, also termed macrosomia, is often defined as a birth weight ≥4.0 kg (111, 112) and is represented in approximately 10% of all births (113). However, a more appropriate measure is LGA, since weight at birth is highly correlated with gestational age at birth. Large for gestational age is usually defined as weight above the 90th centile of a gestational age- and sex-specific birth weight in a reference population (111, 112, 114). Important risk factors for high birth weight are a higher maternal pre-pregnancy BMI, maternal pre-existing diabetes or GDM, and excessive gestational weight gain (111, 112). Moreover, a high birth weight is consistently associated with increased risk of obesity later in life (30, 69, 73, 115), and a meta-analysis suggests that a high birth weight (≥4.0 kg) is associated with twofold increased odds of obesity later in life compared to a normal birth weight (2.5–4.0 kg) (73). A higher birth weight is also associated with a subsequent higher fat mass (68, 70, 116-118) and fat-free mass (68, 70, 116, 118) in children and adolescents, whereas the influence on fat mass relative to total body mass is less clear (68, 70, 118).

Rapid infant weight gain

A rapid infant weight gain may be linked both to the developmental undernutrition and the developmental overnutrition hypothesis, as infants who have experienced growth restraint in utero tend to gain weight rapidly in the postnatal period – a so-called "catch up growth" (119). The accelerated postnatal growth is considered to play a major role in aggravating the risk of cardiovascular diseases and obesity later in life in FGR infants (81). An increase in z-score equal

to or larger than 0.67 between two time-points is commonly referred to as upward centile crossing and is defined as rapid infant weight gain, as 0.67 standard deviations (*SD*s) represents the difference between each displayed percentile line on standard infant growth charts (i.e., 2nd, 10th, 25th, 50th, 75th, 90th, and 98th percentile lines) (16, 120). Rapid infant weight gain is consistently associated with increased risk of overweight and obesity in children and adolescents (16, 115, 121), and it is thus considered an important postnatal risk factor for obesity (30, 122). A meta-analysis of 17 studies suggested a 3.66 higher odd of obesity in children and adolescents who experienced a rapid infant weight gain (16). Rapid infant weight gain is also consistently associated with higher fat mass (70, 123), percent body fat (70, 124) and fat-free mass (70, 123). Although FGR infants are at higher risk of a rapid infant weight gain, it appears that an increased risk of greater adiposity due to this weight gain is not limited to those with a low birth weight (16, 125). The underlying mechanisms for the association between rapid infant weight gain and subsequent development of obesity is not clear. It may be linked to the mechanisms proposed by the developmental overnutrition hypothesis (explained in the next section). Another proposed theory is that an undernourished prenatal environment leads to developmental responses to which the fetus anticipates it may be exposed to after birth, possibly resulting in a mismatch between the prenatally undernourished and postnatally nourished environments (Figure 1), hence leading to a rapid infant weight gain and increased risk of adult disease and obesity (81). This mismatch may put strain on the undernourished neonatal organs, for example the impaired liver function (81, 126).

Possible mechanisms

The developmental overnutrition hypothesis proposes that an excessive nutritional pre- and postnatal environment leads to lifelong risk of obesity. The evidence of potential underlying mechanisms on this association is still sparse, especially in human studies. One main hypothesis is that the fetus is exposed to high levels of glucose and free fatty acids via the placenta, whereby the developing fetus responds by producing insulin that, in addition to lowering the blood glucose, also increases the number of adipocytes and triglyceride deposition in them (28, 127, 128). Some evidence supports that maternal insulin resistance and glucose levels are important mediators on the association between maternal pre-pregnancy BMI and neonatal adiposity, whereas maternal plasma triglycerides do not mediate this relationship (129). Larger infants may further become more adipose adults because of tracking of body size throughout life (28). The number of adipocytes may be determined early in life, as they are observed to be constant in adulthood even after a large weight loss (130). Developmental overnutrition may further alter the

development of the hypothalamic-endocrine system due to high fetal and neonatal insulin, leptin or lipid levels, leading to increased appetite and altered satiety responses (28, 110). Results by Boone-Heinonen et al. (131) have suggested that both a high and low birth weight are associated with greater appetite, particularly for sweet foods, and lower satiety responsiveness in preschool-aged girls, but not boys. However, a former systematic review does not support an association between birth weight and subsequent energy intake and eating behavior (132). Van Deutekom et al. (133) observed that a rapid infant weight gain, but not birth weight, was associated with energy intake and diminished satiety response at 5 years.

Epigenetic modification is also suggested as a possible mediating mechanism in the developmental overnutrition hypothesis. Sharp et al. (88, 134) observed differences in DNA methylation in neonatal offspring depending on maternal pre-pregnancy BMI, where sites that were hypermethylated tended to be positively associated with adiposity (88). Additional use of paternal BMI as a negative control demonstrated that the effect of maternal obesity was stronger than that of paternal obesity on DNA methylation (88, 134). Nevertheless, the comparisons between underweight and normal-weight mothers identified more differently methylated sites than the comparisons of normal-weight to obese mothers, suggesting that maternal underweight may have a larger epigenetic effect on a fetus (88). In one of the studies, further causal inference strategies suggested that the effect of maternal pre-pregnancy BMI on neonatal blood DNA methylation via a causal intrauterine effect was observed only at eight sites (134). A higher birth weight has also been suggested to be associated with differences in DNA methylation (84, 87), including a meta-analysis comprising of 24 birth cohorts (85).

Physical activity in children and adolescents

Definitions and basic principles of physical activity

Physical activity is defined as "any bodily movement produced by the skeletal muscles that results in energy expenditure" (135). It is a multidimensional behavior and can be quantified according to duration (continuance in time), intensity (e.g. energy expenditure per time unit) and frequency (number of occurrences). Duration, intensity and frequency make up the total amount of PA-induced energy expenditure (PAEE). In turn, PA can be categorized based on mode (types of activities, e.g. running and cycling) and domain (the context of the PA, e.g. occupational PA, leisure time PA [LTPA] and sports) (136).

Multiples of energy expenditure above the resting metabolic rate (RMR), referred to as metabolic equivalent of task (MET) values, are frequently used to describe the energy costs of physical

activities. For adults, the traditionally accepted value for 1 MET is an oxygen uptake equivalent to 3.5 $ml \cdot kg^{-1} \cdot min^{-1}$ or 1 $kcal \cdot kg^{-1} \cdot min^{-1}$ (136, 137). Furthermore, 1.5–2.9 METs, 3.0–5.9 METs and METs >6.0 correspond to light, moderate and vigorous intensities respectively (137). The RMR of children is greater per kg body mass than adults, and it declines gradually with increasing age. The energy expenditure relative to body mass of physical activities simultaneously decreases with age (138, 139). Therefore, choosing one MET value to apply across all age- groups may be challenging, and MET- values calculated from an estimated RMR in youths are suggested as both a more appropriate and a feasible method in children and adolescents (138, 139).

Sedentary behavior is defined as "any waking behavior characterized by an energy expenditure ≤1.5 METs, while in a sitting, reclining or lying posture" (140, 141). Sedentary time is referred to as the time (e.g. minutes per day) spent in sedentary behaviors in all contexts (e.g. at school or at home) (140). The term sedentary has been confused with the term physical inactivity; however physical inactivity is defined as "an insufficient PA level to meet present PA recommendations" (141). One may thus be sedentary for a large part of the day, but still meet the current recommended PA level.

Physical activity recommendations in children and adolescents

The primary aim of PA recommendations is to provide policy makers, health care professionals and employees in the education sector with guidance on the relationship between PA and enhanced growth, development and health, to be used in public health promotion (142-144). Over the past decades, the amount of research on PA and health in children and adolescents has grown considerably and provided new evidence in relation to the PA recommendations. Despite this, the recommendations for children and adolescents have been relatively stable over the past two decades (144, 145), and quite similar between countries (144, 146). The Norwegian recommendations from 2014 currently states that 1) children and adolescents should perform at least 60 min of moderate to vigorous PA (MVPA) daily. At least three times per week PA of vigorous intensity, which increases muscle and bone strength, should be implemented; 2) PA in excess of 60 min per day offers additional health benefits, and 3) sedentary behaviors should be reduced (142).

The proportions of children and adolescents adhering to the recommended PA level depend on the interpretation of the guidelines. Cooper et al. (147) pooled data from eight countries in the International Children's Accelerometry Database (ICAD) and examined the proportion of children and adolescents accumulating ≥60 min of MVPA on *every* measured day, and they observed that small proportion – only 9% of the boys and 2% of the girls – met the PA

guidelines. In the Norwegian sample, the proportion was higher, albeit still modest – ~30 % of the boys and ~13% of the girls met the recommended PA level (147). In a nationally representative sample of Norwegian 9- and 15-year-olds, the proportions accumulating to ≥60 min of MVPA on *average per day* during the measurement period were 69% and 86% for 9-year-old girls and boys respectively and 42% and 57% for 15-year-old girls and boys respectively (148). The proportion meeting the recommended PA level will also depend on the assessment method and definition of MVPA, which are further discussed in the next section.

Assessments of physical activity

In epidemiological PA research, it is crucial to use valid and reliable assessment methods of PA. The selected method must also generally be suitable and feasible in large-scale studies (149, 150).

Children's PA patterns differ substantially from those of adults; children often shift between the different intensities. A direct observation of children's PA patterns suggests that the vast majority (95%) of high-intensity events lasted no longer than 15 sec (151). This has important implications for the assessment of free-living PA levels in children. We may expect the PA patterns of adolescents to gradually become more similar to those of adults, with longer durations of bouts spent sedentary or at different intensities of PA.

Numerous PA assessment methods exist, with accompanying advantages and disadvantages. We can roughly say that the cost of an assessment method is inversely related to its accuracy (149), and important considerations must be taken into account before decisions can be made regarding measurement methods. The different measurement methods can broadly be categorized into measures of energy expenditure (e.g. double labelled water [DLW] and indirect calorimetry), device-measured PA (e.g. motion sensors and heart rate sensors) or self-reported PA (e.g. diaries and questionnaires) (149, 150).

In free-living PA, the DLW technique is considered the "gold standard" of total energy expenditure (TEE) measurements (152). In brief, the principle of the method is to consume a dose of water labeled with the stable isotypes of ^{2}H and ^{18}O; ^{2}H is eliminated from the body as water, whereas ^{18}O is eliminated as both water and carbon dioxide (CO_2; end product of metabolism that is excreted via the lungs). The difference between the two elimination rates is therefore a measure of carbon dioxide production, and accordingly energy production (152). A person's PAEE can be extracted from the TEE measured by DLW (152, 153) and the method thus provides an accurate measure of PAEE over a defined period, but gives no information on the frequency, duration, intensity, mode or domain of PA. Furthermore, the method has

additional disadvantages that make it inappropriate for use in large-scale epidemiological research, including the high costs of stable isotypes and the dependency on individual assessments of RMR to provide accurate PAEE estimates.

Self-reports via questionnaires and, to an increasing extent, device-measured PA via accelerometers are widely used in large-scale epidemiological studies in children and adolescents. They are further elaborated below.

Self-reported physical activity – questionnaires

Physical activity has historically been assessed via self-reported measurement tools, which have contributed substantively to the understanding of the link between PA and the development of diseases (154). These tools include questionnaires, interviews, diaries and logs (149, 154, 155). Questionnaires typically record information on the types, frequency and duration of PA at moderate and vigorous intensities over a defined time period (156). The questionnaire-method has the lowest investigator and respondent burden, and it is thus a highly feasible and cost-effective method for assessing PA in large-scale studies (157). However, the method is dependent on respondent's ability to accurately recall their PA level, which may be particularly problematic for children especially in the lowest age-groups (155, 157). In addition to this, the intermittent activity pattern in children makes it even more problematic to accurately recall and report their PA level via subjective instruments. To consider the recall-issue, proxy reports have been used as an alternative method, in which children's activity level is reported by their parents or teacher. Nevertheless, this method is still problematic due to the intermittent activity pattern, and because neither the parents nor teachers follow the child throughout the day (155, 157). The validity of both proxy-reported and self-reported PA questionnaires in children is hence generally considered to be low (158, 159).

Device-measured physical activity – accelerometry

To overcome some of the drawbacks of self-reports, an increasingly proportion of studies include device-measured PA (154), and accelerometers are now considered to be the method of choice even in large-scale epidemiological studies (160-162). In addition to accelerometers, devices for measuring PA also include pedometers, heart-rate monitors and multi-sensor systems (154); however, they are not further elaborated on here.

Accelerometers are small and wearable devices that record acceleration (change in velocity over time, m/s^2) in gravitational units (g, $1g=9.81m/s^2$) in one to three planes (154, 163). The sampling rates are typically 40–100Hz (154). The recorded acceleration is therefore movement of

the body segments (frequency and amplitude) to which the monitor is attached (163). Captured accelerations are then processed to a lower resolution (epoch) and usually expressed as a unitless intensity metric and brand-specific "activity counts" (154, 164). The average number of registered counts per minute (cpm) is often calculated to estimate a participant's overall PA level over a defined time period. Furthermore, counts per unit of time (epochs) are used to assess minutes spent within user-defined count thresholds, or cut-points, corresponding to sedentary, light, moderate and vigorous intensity (154, 163).

Although accelerometers have several advantages over self-reports, they are also prone to misclassification of PA. They generally underestimate non-ambulatory activities (e.g. bicycling) and swimming due to removal of the monitor during water-based activities. Furthermore, the monitor cannot distinguish between for example walking with or without carrying heavy bags, or walking uphill or downhill, in which the former yields additional costs in the form of energy expenditure (154). In children, the use of long sampling intervals (epochs) may lead to underestimation of activities at the highest intensities due to the typically short duration spent at these intensities. A number of different accelerometer brands are available (164), and they recommend different attachment sites (e.g. waist or wrist) and operate with different brand-specific activity counts. Furthermore, even for monitors of the same brand, there is little consensus on how to process accelerometer data (e.g. the accelerometer cut-points for definition of the different intensities). The PA data are consequently not uniformly comparable across the different monitors and studies. A widely used accelerometer is Actigraph, which has been previously validated in free-living conditions among children (164, 165).

Physical activity and cardiometabolic risk factors in children and adolescents

Cardiovascular diseases develop gradually and they rarely manifest in childhood or adolescence; nevertheless, even at young ages adverse cardiometabolic risk profiles are observed in typically adults' high-risk groups, including children with obesity (166, 167), a low birth weight (57, 59) and a low PA level (168, 169). Cardiometabolic risk factors generally include systolic- and diastolic blood pressure, insulin resistance, LDL cholesterol, HDL cholesterol, triglycerides and measures of adiposity.

Systolic blood pressure is the maximum arterial pressure and occurs during peak ventricular ejection, whereas diastolic blood pressure is the minimum arterial pressure and occurs just before ventricular ejection begins. Since diastole lasts about twice as long as systole the average pressure in the cardiac cycle, mean arterial pressure *(MAP),* is calculated as systolic blood pressure+(diastolic blood pressure*2)/3. Blood pressure is determined by cardiac output and

total peripheral resistance (170). A high blood pressure (hypertension) is consistently associated with increased risk of cardiovascular diseases in adulthood (171).

Insulin is a peptide hormone (cannot freely cross the plasma membrane) secreted by the beta-cells in pancreas, and it is the major controller of human metabolism (170). Insulin stimulates the uptake and storage of glucose (stored as glycogen), amino acids (stored as proteins) and fatty acids (stored as triglycerides) into mainly muscle cells, adipocytes and liver cells (170, 172). Insulin resistance occurs when targeted cells are hyporesponsive to insulin. Insulin resistance is an important factor in the early development of type 2 diabetes, and the condition is further aggravated by defects in the beta-cells affecting their ability to secrete insulin in response to a rise in plasma glucose concentration (170). Homeostatic model assessment (HOMA-IR) is a method for assessing insulin resistance from fasting plasma insulin and glucose concentration. The physiological basis for the HOMA-model is the relationship between fasting insulin and glucose concentrations, which is determined and maintained by a feedback loop (173). The model was first described in 1985, with the following widely used equation: (fasting insulin(mU/l)*fasting glucose(mmol/l))/22.5 (174). An updated non-linear and computer-based model (HOMA2-IR) has recently been suggested as a more appropriate method (173, 175).

An important lipid that, unlike triglycerides and fatty acids, does not serve as metabolic fuel is cholesterol. It has many important functions in the body, for example in cell membranes; however, it can also cause problems. In particular, high concentrations of cholesterol in plasma enhance the development of atherosclerosis (170). Cholesterol is transported in the blood as part of various forms of water-soluble lipoproteins, including LDL and HDL. The former delivers cholesterol to cells throughout the body and is positively associated with development of cardiovascular diseases (170, 176). In contrast, the latter removes excess cholesterol from blood and tissue and is inversely associated with cardiovascular diseases (170, 176).

Triglycerides consist of glycerol and three fatty acids (saturated or unsaturated) and are the most common lipids in the body. Triglycerides are often simply referred to as fat, and can be metabolized to provide energy (170). Although elevated triglyceride levels are associated with cardiovascular diseases, the extent to which triglycerides have a direct effect on the development of those diseases is debated (177). While some argue that triglycerides are independently associated with risk of cardiovascular diseases (178), high triglyceride levels may also influence the development of cardiovascular diseases via their effect on insulin resistance (179) and an unfavorable cholesterol composition (177, 178).

A clustering of cardiometabolic risk factors is likely more important for future health than single risk factors. In adults, a clustering of cardiometabolic risk factors is known as the metabolic syndrome (MetS). Although several definition criteria exist (180-182), the definitions commonly include elevated abdominal adiposity, fasting glucose/insulin resistance, blood pressure and dyslipidemia (i.e. high triglycerides or low HDL cholesterol). Several attempts have been made to define MetS in children and adolescents (183-185); however, the use of thresholds and a dichotomized definition (MetS – yes/no) is argued to be an inadequate method at younger ages when cardiovascular diseases are not yet manifested (186). Therefore, a continuous clustered cardiometabolic risk score is suggested as a more suitable measure for children and adolescents (186, 187). Several compositions of risk factors have been applied in the pediatric population, in which have demonstrated high comparability (186).

Childhood obesity is associated with several adverse health outcomes, including hyperlipidemia, hyperinsulinemia, hypertension and early atherosclerosis (188), and it is further a strong predictor of adult obesity, with accompanying risks of cardiovascular diseases and mortality (189, 190). The fact that the proportion of overweight and obese children has increased substantially over the last four decades is thus of great concern (5). A widely used method to assess adiposity and to define weight status, specifically underweight, normal-weight, overweight and obesity, is BMI, expressed in kilogram (kg) per meter squared (m^2). The BMI in childhood changes substantially with age, and a single cut-point to define weight status is clearly not appropriate in the pediatric population (191). Therefore, age- and sex-specific cut-points have been developed, with the two most common approaches being those suggested by the International Obesity Task Force (IOTF) (191, 192) and the World Health Organization (193). Abdominal adiposity is a strong predictor for elevated cardiometabolic risk factors, also independently of BMI (194, 195). Abdominal adiposity is frequently measured as waist circumference in children and adolescents (195). Although BMI and waist circumference are considered valuable and feasible measures of adiposity and abdominal adiposity in groups of children and adolescents (196, 197), a limitation is their inability to differentiate between fat mass and fat-free mass. Several methods for assessment of body composition exist, with skinfold thickness, dual-energy X-ray absorptiometry (DXA), air displacement plethysmography (ADP) and bioelectric impedance analysis (BIA) being the most feasible and appropriate methods in pediatric research (198).

The association between PA and cardiometabolic health has been substantially examined in cross-sectional studies (199), and especially high intensity PA, namely MVPA, and vigorous PA (VPA), demonstrate consistent and robust associations with a more favorable cardiometabolic risk profile in children and adolescents (199-201). More specifically, in cross sectional analyses,

device-measured PA been associated with lower systolic- and diastolic blood pressure (168, 169, 200), lower insulin levels (168, 169, 200, 201), lower triglycerides (168, 169, 200, 201), higher HDL cholesterol (168, 200), lower total cholesterol (169), lower waist circumference (168, 169, 200, 201) and lower clustered cardiometabolic risk score (169, 200, 201). The association between PA and LDL cholesterol is less studied, and the association is less clear compared to the other lipids (202, 203). Although the evidence is still sparse, the associations between higher PA and lower cardiometabolic risk factors are also demonstrated in prospective studies (167, 204-206), and a recent systematic review and meta-analysis over prospective studies has concluded that a consistent inverse association exists between MVPA and clustered cardiometabolic risk in children and adolescents (207).

The association between PA and adiposity may be more complex. In cross-sectional analyses, the association between PA and the different measures of adiposity is strong and consistent (168, 169, 208-212), and a recent systematic review suggests that children and adolescents with obesity tend to be well below the recommended level for PA (208). Physical activity is hence considered to play a major role in the prevention of excess adiposity in children and adolescents (7, 213). Despite some inconsistencies (214-216), prospective observational studies have also demonstrated that time spent in MVPA is inversely associated with adiposity (205, 217-220). On the other hand, prospective observational studies have also found that adiposity may lead to lower PA (214, 221), including a mendelian randomization that supports a causal link between adiposity and lower PA (222). Thus, there might be a bi-directional relationship between adiposity and PA.

Pre- and postnatal factors and physical activity in children and adolescents

As I have demonstrated over the previous sections, pre- and postnatal factors and low levels of PA are widely recognized as being associated with the development of diseases and risk of obesity. However, noticeably fewer studies have examined if, and how, these risk factors may be related in the development of disease. In particular, the mechanisms of developmental over- and undernutrition and subsequent greater risk of adult diseases and obesity are still unclear, and whether PA in childhood and adolescence is either on the causal pathway or interacts with the development of later diseases and adiposity is unknown.

Pre- and postnatal factors and association with physical activity

Studies in rodents have suggested that impaired prenatal nutrition leads to lower birth weight and subsequent reduced activity in offspring (223, 224), of which was further exacerbated by a postnatal hypercaloric nutrition (223). In contrast, Miles et al. (225) demonstrated that prenatally undernourished rats displayed a greater preference for wheel running over lever pressing for food. In humans, a very low birth weight due to pre-term birth has been suggested to be associated with lower PA later in life (226, 227), although not consistently in all studies (228, 229), and the differences in PA levels between those born pre-term and at full-term are argued to be small (230). Nevertheless, a low birth weight due to pre-term birth or animal models may not be representative for FGR.

In a large meta-analysis, including 13 cohort studies, both a low and high birth weight were associated with lower self-reported LTPA in adolescents and adults (14–74 years) (231). In contrast, a study by Tikanmaki et al.(232) suggested no quadratic, nor linear, association between birth weight z-scores and PA in 16-year-olds. Previous studies have observed either no linear relationship (233-239) or no association between categories of birth weight and PA in children and/or adolescents (240, 241) or adults (242). Some of these studies have used only two categories of birth weight (241, 242), which leads to a substantial loss of power and precludes the detection of any non-linear relationship (243). Gopinath et al. (244) observed that adolescents in the highest compared to the lowest birth weight quartile spent more time in self-reported PA. Similarly, two studies reported that a low birth weight was associated with lower odds of participating in self-reported LTPA in adults (245) and children (girls only) (246), compared to higher categories of birth weight. Similarly, Salonen et al. (247) suggested that weight and length at birth were positively associated with self-reported LTPA in 57- to 70-year-old men and women.

Few studies have examined the association between maternal pre-pregnancy BMI with subsequent PA in offspring. Two studies observed no linear association between maternal pre-pregnancy BMI in children and adolescents (235) or in adults (242). Data from Mintjens et al. (248) suggested no association between maternal pre-pregnancy overweight (>25 kg/m^2) or normal-weight (<25 kg/m^2) and PA levels in offspring. However, by dichotomizing maternal BMI children whose mothers were underweight are characterized as similar to those whose mothers were normal-weight. In a secondary analysis from that study, maternal pre-pregnancy BMI modeled as a continuous variable was inversely associated with MVPA (248). Furthermore, no association was found between categories of maternal pre-pregnancy BMI and a subsequent inactive lifestyle in Brazilian adolescents (240). Tikanmaki et al. (232) observed a quadratic

association between maternal pre-pregnancy BMI and self-reported PA in adolescents. However, when maternal pre-pregnancy BMI was modeled as a categorical variable, only adolescents whose mothers were obese before pregnancy were less physically active than those whose mothers were normal-weight. This is probably explained by loss of information and power when the continuous variable is modeled as a categorical variable (243, 249).

In three studies examining the association between infant weight gain and subsequent PA there was no association between quartiles of weight gain from 0–1 year and self-reported PA in 10–12-year-olds (240), nor a linear association between infant weight gain and device-measured PA in children (238) and adolescents (250).

Categorization of continuously distributed exposures is highly dependent on the choice of cut-points, in addition to the assumed homogeneity of association within groups, leading to inaccurate estimations and a substantial loss of power (243, 249). Furthermore, it is likely that the pre- and postnatal factors are non-linearly associated with PA as both developmental under- and overnutrition are linked to the subsequent development of cardiovascular diseases and obesity (37, 73, 251); however, this has rarely been examined without categorization of the exposure variable (232).

Salonen et al. (247) observed that the inverse association between birth weight and LTPA in adults became non-significant after inclusion of adult lean body mass, indicating that muscle mass may be a possible mediator. Additional studies have demonstrated an association between a low birth weight and a lower lean body mass (118, 252, 253), muscle strength (254-257), muscle quality (258, 259) and cardiorespiratory fitness (CRF) (253, 254, 260-262). All these factors could possibly be on a causal pathway between FGR and lower PA or alternatively a consequence of a low PA level. Moreover, a higher infant weight gain is also associated with lower adult muscle strength (254); however, in contrast, it has also been observed to be positively associated with CRF (263).

Another possible mechanism of the conceivable association between pre- and postnatal factors and PA in children and adolescents is the effect of these factors via higher adiposity. That is, a higher maternal pre-pregnancy BMI, a high birth weight and rapid infant weight gain might lead to lower PA due to the bi-directional association between adiposity and PA. Children with higher adiposity could refrain from engaging in PA at high intensities and thus enter a vicious circle of inactivity and increased adiposity.

Pre- and postnatal factors and interaction with physical activity in relation to cardiometabolic health and adiposity

The term "fetal programming" is frequently used within the DOHaD-approach. However, it is arguable that this term might be misleading because it implies that the development of disease is definite from the onset, whereas an impaired pre- and postnatal environment is more likely to add to the risk of other risk factors later in life. Pre- and postnatal factors may hence cause subtle physiological changes that increase one's susceptibility to disease, which may not be detected or lead to a disease without a second "hit" later in life, for example an inactive lifestyle (8, 21, 264). Childhood and adolescence are further considered important periods in life for intervening as the body's system is still sensitive to the environment (8, 21). Therefore, the question arises as to whether the associations between pre- and postnatal factors and the development of cardiometabolic risk factors and adiposity are conditioned on PA levels in children and adolescents. However, this has rarely been investigated, and with contradictory results.

In two experimental studies, Mortensen et al. (265, 266) examined the responses of bed rest and exercise on insulin resistance and insulin signaling in adults with a low birth weight compared to a control group with a normal birth weight. After a period of bed rest (nine days) the low birth weight group exhibited a decrease in insulin signaling, but no differences in insulin resistance, compared to no effect of bed rest on the control group (265). This may, to some degree, suggest that adults with a low birth weight respond differently to a period of bed rest, and the risk of developing type 2 diabetes is thus amplified in low birth weight subjects when they are sedentary. Furthermore, low birth weight individuals responded more favorably to increased PA (266), which may indicate that the risk of disease development in this group is mitigated in those who are physically active. Similar findings were also demonstrated in young adults, where an eight-week exercise program eliminated the observed differences between high and low birth weight groups for total cholesterol and LDL cholesterol (267).

Two observational studies examined whether device-measured PA modifies the association between birth weight and insulin resistance (HOMA-IR) in European children and adolescents (268, 269), with contradictory results. In a study by Ridgway et al. (268), PA appeared not to interact in the association between birth weight and HOMA-IR, whereas in a similar study by Ortega et al. (269), an observed significant interaction suggested that the association between birth weight and HOMA-IR was attenuated in the most active adolescents. In adults, the joint association between birth weight (median split) and self-reported PA (median split), demonstrated that the risk of clustering of two or more cardiometabolic risk factors was greatest in the combined low birth weight and low PA group (270). Similar results have been observed in

middle-aged and elderly people (271, 272): the combined low PA and low birth weight group displayed greater odds for MetS (271) and type 2 diabetes (272). However, combining the risk of two risk factors in a joint association does not alone indicate whether there is an additivity of effect – that is, whether the risk of the combination of a low birth weight and low PA are larger than their independent effect added together, or whether adding PA attenuates the effect of a lower birth weight (273). Laaksonen et al. (271) further found that the increased risk observed in those with a low birth weight was absent in men who were more fit or more physically active, whereas this was not evident in the two other studies (270, 272). Laaksonen et al. (271) and Eriksson et al. (272) further observed an interaction on the multiplicative scale (271, 272), of which is not comparable with examining an interaction on the additive scale (268, 269).

A paucity of studies have examined the effect modification of PA on the association between pre- and postnatal factors and subsequent greater adiposity. One study has suggested that device-measured PA does not modify the association between birth weight and both fat mass index (fat mass/m^2) and waist circumference in 9- and 15-year-olds (268). Furthermore, joint association analyses revealed that children with a high birth weight (>4.0 kg) but who were physically active (MVPA < 60 min/day) still had higher odds for obesity and high body fat, compared to children with a normal birth weight and a similar activity level (274). In contrast, others have suggested an effect modification by self-reported MVPA on the risk of obesity in girls with a high birth weight, but not in boys (275). Kolle et al. (276) examined the associations between weight gain in infancy (0–2 years) and childhood (2–4 years) with subsequent fat mass in 30-year-olds and they observed that only the association between weight gain in childhood and fat mass index was attenuated by device-measured MVPA. No effect modification of MVPA was observed on the association between infant weight gain and fat mass index.

Infant motor development

During the first year of life movement capabilities change dramatically and an infant reaches several developmental motor milestones, such as sitting alone, crawling, standing unaided and eventually walking (277). A lower birth weight (278, 279) and higher infant adiposity (280) have been linked to delayed motor development. Furthermore, earlier infant motor development, measured as age at first standing or walking unaided, has been positively associated with adult muscle strength (254, 257), muscle endurance (254) and aerobic fitness (254).

Stodden et al. (281) argue that the PA level in early childhood is driven by the development of motor skills. An earlier infant motor development may hence promote PA, which further

improves motor skills. The association is thus likely to be bi-directional (281), and the question arises as to whether infants who develop their motor skills later are less physically active during childhood. Cross-sectional studies have repeatedly demonstrated an association between motor skills (e.g. run, jump, throw and catch) and PA in children and adolescents (282-287). Furthermore, a few prospective studies have also demonstrated that motor skills in childhood predict greater PA in adolescence (288, 289) and adulthood (290). However, few studies have examined the association between infant motor development and subsequent PA in children and adolescents.

Ridgway et al. (291) suggested an association between a lower age at reaching developmental milestones and greater self-reported sport participation at age 14 years. A possible weak relationship was also demonstrated by Mattocks et al. (235), of which motor coordination at 6 months was associated with overall device-measured PA in 11- to 12-year-olds. This is in contrast to a study by Wijtzes et al. (241) in which no association was observed between infant motor development and subsequent device-measured PA in 2-year-olds, although this study may be limited by a smaller sample size.

Theoretical framework

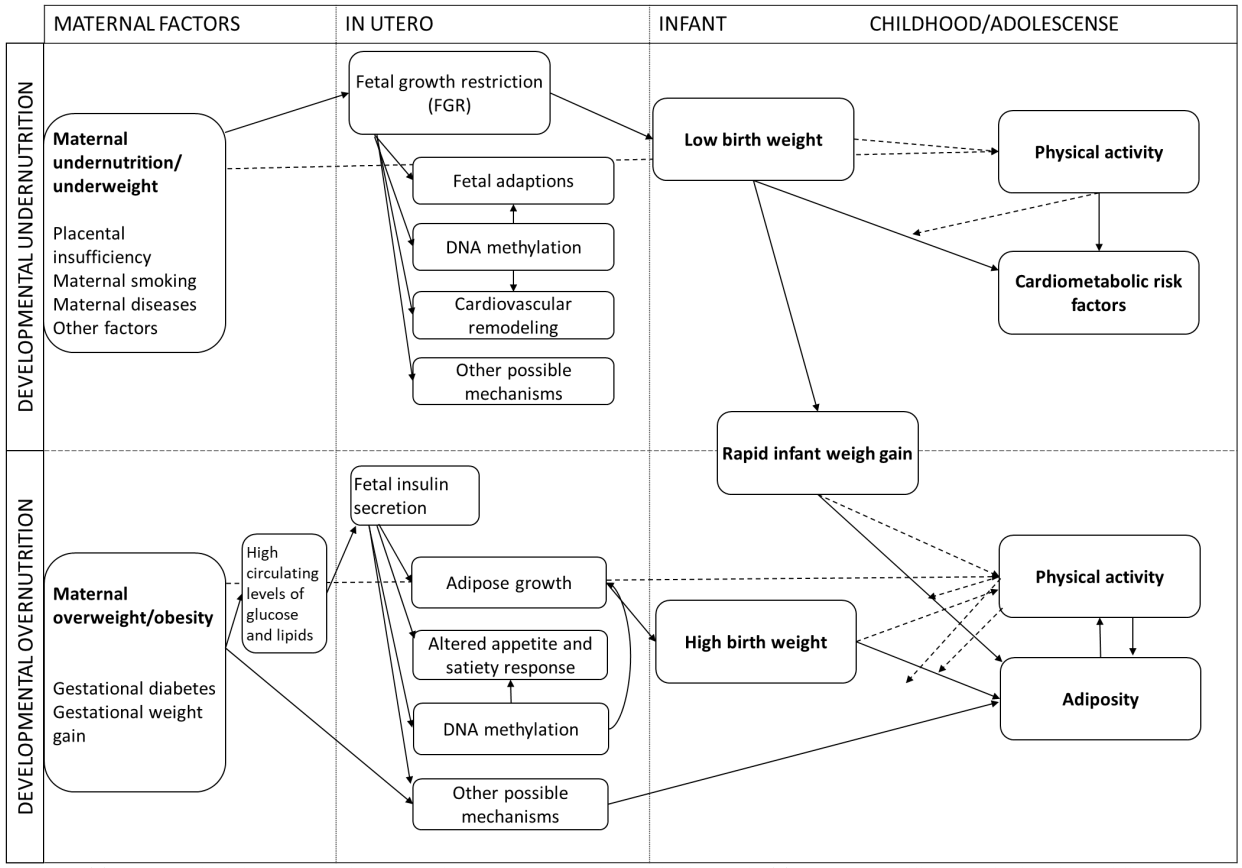

Figure 2: The theoretical framework for the main research questions of this thesis. The pathways illustrated with dashed lines represent the research questions. A dashed line with an arrow pointed towards a line illustrates a potential interaction. The included variables of this thesis are highlighted in bold. The figure is explanatory of the focus of this thesis and does not aim to show all possible relationships or mechanisms.

Need for new information and theoretical framework

The theoretical framework of this thesis and the main research questions are presented in Figure 2.

Maternal pre-pregnancy BMI, birth weight and infant weight gain are considered risk factors for greater adiposity and elevated cardiometabolic risk factors in children and adolescents. While PA may mitigate the increased risk in pre-disposed children and adolescents, few studies have examined whether pre- and postnatal factors are also associated with PA or interact with PA in the development of diseases and greater adiposity. This information may provide important knowledge in the establishment of safe and efficacious prevention strategies for those predisposed to later adverse health effects due to their early environment.

Aims of the thesis

I. To examine the associations between pre- and postnatal factors (birth weight, early growth and motor development) and PA in children and adolescents through a systematic review and meta-analysis of the current available evidence **(Paper I).**

II. To examine the associations between pre- and postnatal factors (maternal pre-pregnancy BMI, birth weight and infant weight gain) and LTPA in 7-year-old Norwegian children, and to examine whether the possible associations are non-linear or mediated by a child's BMI at age 3 years **(Paper II).**

III. To examine whether MVPA or VPA in childhood modifies the associations between pre- and postnatal factors (maternal pre-pregnancy BMI, birth weight and infant weight gain) and precisely measured body composition and BMI in 9- to 12-year-old Norwegian boys and girls **(Paper III).**

IV. To examine whether MVPA modifies the associations between birth weight and several cardiometabolic risk factors and a clustered cardiometabolic risk score in a diverse sample of children and adolescents **(Paper IV).**

Methods

Study designs and participants

The four papers included in the present thesis have different study designs and comprise of different participants. In short, **Paper I** is a systematic review and meta-analysis, **Paper II** uses data from the MoBa, **Paper III** uses data from a sub-cohort of the MoBa, and **Paper IV** consists of pooled data from 12 international studies.

Paper I

To review the current evidence of the association between birth weight, infant growth and motor development on subsequent PA in children and adolescents, we performed a systematic literature search. The search protocol was published in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42014014243).

Search strategy

Two researchers undertook a systematic search in PubMed, SPORTDiscus, PsychINFO, Embase and Web of Science in September 2014, using the keywords listed in Table 1. Manual searches of personal literature databases were performed for any additional studies that met the inclusion criteria. All identified articles underwent a forward- and backward-tracking process. The forward-tracking process was performed in Web of Science.

Objective criteria

We sought to identify all studies examining the association between the pre- and postnatal factors (birth weight, early growth and early motor development) and subsequent PA in children and adolescents (aged ≤ 18 years). Early growth included both growth in weight and height up to age 6 years (292). Moreover, early motor development was defined as motor development up to 2 years of age since this period is characterized by achieving fundamental developmental milestones. Studies were included if they measured total PA, MVPA (e.g., min/day), VPA (e.g., min/day), or LTPA (e.g., sport participation) or if they measured whether participants met the recommended PA level. All measures of PA were included (e.g. device-measured or self-reports). In addition, articles had to meet the following criteria: they (i) were written in English, Swedish or Norwegian; (ii) were published between 01/01/2000 and 31/08/2014; (iii) were longitudinal

observational studies; (iv) examined the general, healthy population; and (v) were published as journal articles, reports or dissertations.

Table 1: Complete search strategy Paper I

	Included search words
#1	("Physical activity" OR "Physical activities" OR "Physically active" OR "Physical exercise" OR "Exercise" OR "Motor activity")
#2	("Children" OR "Child" OR "Youth" OR "Youths" OR "Adult child" OR "Adult children" OR "Adolescent" OR "Adolescents" OR "Teenager" OR "Teenagers" OR "Teen" OR "Teens")
#3	("Birth weight" OR "neonatal weight" OR "newborn weight" OR "postnatal weight")
#4	("Weight gain" OR "Weight gains" OR "Growth" OR "Growths" OR "Growth trajectory" OR "Growth trajectories" OR "Body weight changes" OR "Body weight change" OR "Body weight gain" OR "Body weight gains" OR "Postnatal weight gain" OR "Postnatal weight gains" OR "Catch-up growth" OR "Catch-up growths")
#5	("Child development" OR "Infant development" OR "Motor development" OR "Motor milestones" OR "Motor milestone" OR "Motor skills" OR "Motor skill" OR "Motor coordination" OR "Postnatal development")
Factor	Combination of search words
Birth weight	#1 AND #2 AND #3
Early growth	#1 AND #2 AND #4
Motor development	#1 AND #2 AND #5

Study Selection

All identified articles in the searches were imported into Reference Manager (version 12, Thomson Reuters, San Francisco, CA, USA), and duplicates were removed. The titles of all retrieved articles were reviewed by one researcher and if there were any doubts, the articles were included in the next phase. The abstracts for all articles selected in the title review phase were reviewed by two independent researchers, and all eligible abstracts, in addition to abstracts that provided insufficient data were retrieved for full-text evaluation. Full-text copies were obtained through the library of the Norwegian School of Sport Sciences and reviewed for inclusion by two researchers independently. Any discrepancies between the reviewers were discussed and if necessary, solved with a third reviewer. After the full-text review phase all included articles were divided into three groups:

1) studies presenting data on the association between birth weight and PA,

2) studies presenting data on the association between early growth and PA and

3) studies presenting data on the association between early motor development and PA.

If a study included several of the possible determinants examined, it was included in all relevant groups.

Data Extraction

Data from the included studies were extracted independently by two reviewers, and any disagreements between the two reviewers were discussed with a third reviewer. The following information was extracted from the studies: study characteristics (i.e., title, author, year, study design, country, number of participants, subject characteristics, age at baseline measure and age at follow-up); pre- and postnatal factor (birth weight, infant growth or infant motor development); PA assessment method; amount of PA; measure of PA (e.g. MVPA or overall PA); statistics; main results and results stratified by subgroups if provided in the article (e.g., sex and age groups). Reviewers were not blinded to the authors or journals when extracting data.

Quality assessments of included articles

Two researchers independently assessed the methodological quality of the included studies using the "Standard quality assessment criteria for evaluating primary research papers from a variety of fields" (293) checklist. All included studies were observational studies, and we therefore removed items that were irrelevant for those studies (random allocation and blinding of investigators and participants). The final quality assessment (QA) included 11 criteria that were scored according to fulfillment: "yes" (2), "partial" (1) or "no" (0). We calculated a methodological quality score for each included study by summarizing the scores on each item (number of "yes"*2) + (number of "partial"*1) and divided this score by the total possible sum of scores. The 11 included criteria are listed in Table 2. Any disagreements between the two researches were discussed with a third researcher, and we did not exclude any articles based on the QA.

Table 2: Included items from the "Standard quality assessment criteria for evaluating primary research papers from a variety of fields" (293), and proportion of studies scoring "yes" on each item (Paper I).

#	Criteria	% "yes"
1	Is the question or objective sufficiently described?	100%
2	Is the design evident and appropriate to answer study question?	100%
3	Is the method of subject selection described and appropriate?	45%
4	Are the subject's (and comparison group's, if applicable) characteristics sufficiently described?	63%
5	Are the outcome and (if applicable) exposure measure(s) well defined and robust to measurement or misclassification bias? Are the Means Of assessment reported?	63%
6	Is the sample size appropriate?	63%
7	Is the analysis described and appropriate?	73%
8	Is some estimate of variance (e.g., confidence intervals, standard errors) reported for the main results/outcomes (i.e., those directly addressing the study question/ objective upon which the conclusions are based)?	63%
9	Is the study controlled for confounding	73%
10	Are the results reported in sufficient detail?	100%
11	Do the results support the conclusions?	100%

Paper II

To examine the associations between PA level in childhood and the three pre- and postnatal factors –maternal pre-pregnancy BMI, birth weight and infant weight gain – we used data from the MoBa.

The MoBa is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (294). All women attending a routine ultrasound examination at 17–20 weeks of gestation at a Norwegian maternity unit (50 units out of 52 participated) between 1999 and 2008 were invited to participate. The women consented to participation in 41% of the pregnancies. The total cohort includes 114 500 children, 95 200 mothers and 75 200 fathers. The current study is based on version 10 of the quality-assured data files released for research in June 2017.

For the current study, we included children aged 7 years with available data on LTPA. Due to a different prenatal environment, we excluded children from multiple births, and due to associated health implications, we excluded children born extremely or very preterm (<32 completed weeks of gestation). Mothers could participate with more than one child, and the total study sample comprised of 48 672 children from 37 261 mothers (Figure 3). The LTPA questionnaire was included in the second version of the 7-year questionnaire, and our analyses therefore include children born in the period 2002 to 2009.

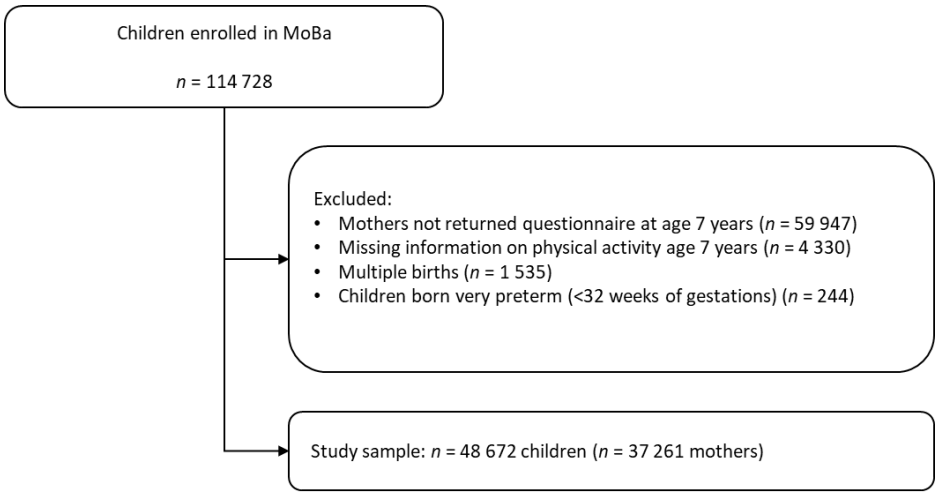

Figure 3: Study population flow chart (Paper II)

Paper III

To examine whether PA modifies the associations between maternal pre-pregnancy BMI, birth weight and infant weight gain with subsequent body composition and BMI in childhood, we used data from a sub-cohort of the MoBa.

The sub-cohort comprised of 1 603 participants born between 2002 and 2004, living within a one-hour radius of one of four test centers in Norway. The participants were invited to undergo additional testing, including anthropometric, body composition and device-measured PA measurements. The tests were conducted between 2013 and 2015, in Oslo, Bergen, Stavanger and Fredrikstad. A total of 470 children agreed to participate (participation rate 29.3%), 445 of whom provided complete PA data (Figure 4). A DXA scan was only available at the test center located in Oslo, and body composition measurements were thus only obtained from 186 participants. Therefore, the number of participants included in the different analyses differs depending on the outcome measure.

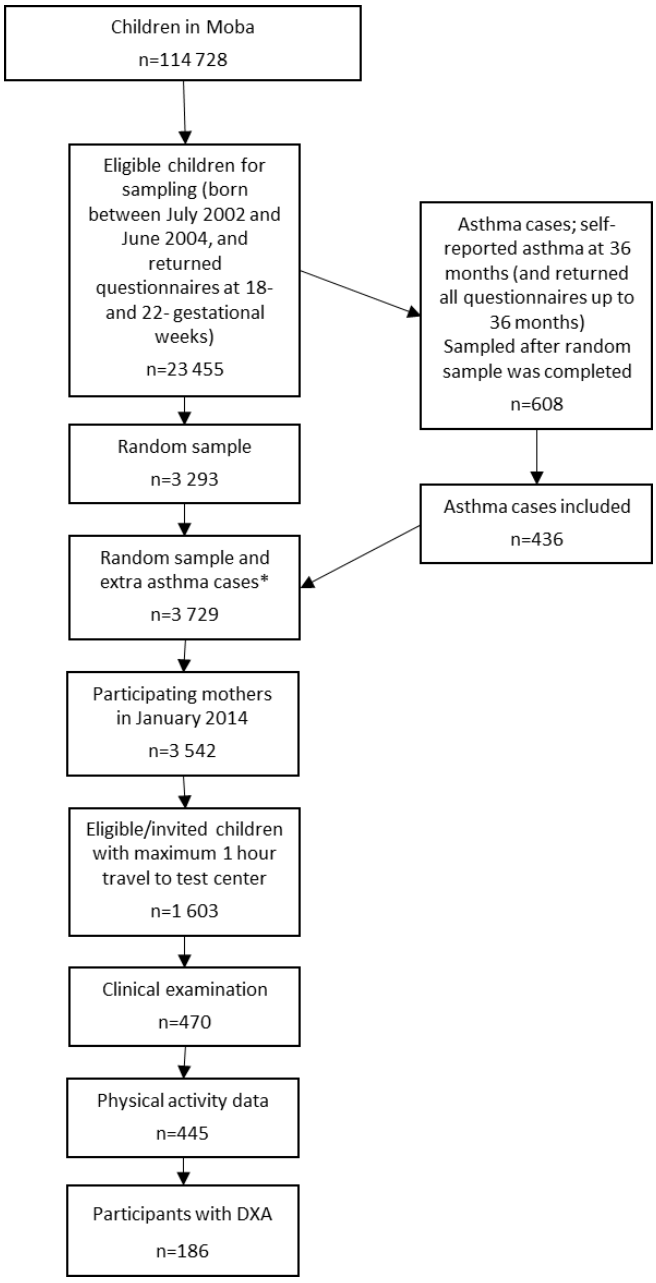

Figure 4: Flow-chart of study participants (Paper III)
DXA- Dual-energy X-ray absorptiometry
*Among the eligible children (*n* = 23 455), a random sample was drawn (*n* = 3 293), and extra asthma cases (*n* = 608) were sampled thereafter.

Paper IV

To examine whether PA modified the associations between birth weight and cardiometabolic risk factors in children and adolescents, we used pooled individual data from nine studies included in ICAD (295), the sub-cohort of the MoBa-study (294), the Physical Activity among Norwegian Children Study (PANCS) (296, 297) and Active Smarter Kids (ASK) (298). The analyses included only participants for whom data were available regarding birth weight, PA (≥3 valid days) and at least one cardiometabolic risk factor (=3 534 participants removed). The total study sample comprised of 9 100 children and adolescents. Table 3 lists the number of participants and simple descriptive statistics of participants from each study included in the pooled analyses.

ICAD (295) consists of device-measured PA, anthropometrics and health data collected in children and adolescents from 20 studies worldwide. Detailed descriptions of the aims, design, recruitment of studies, and protocols of the ICAD project have been provided elsewhere (295), and the harmonization documents are available at the ICAD website (http://www.mrc-epid.cam.ac.uk/research/studies/icad/data-harmonisation/). For the present analyses we used data from nine ICAD-studies (ICAD 2.0). The included studies are the Avon Longitudinal Study of Parents and Children (ALSPAC) (299, 300), the European Youth Heart Study (EYHS) of which includes four studies from Norway, Portugal, Estonia and Denmark (301), the Iowa Bone Development Study (IBDS) (302), the Pelotas birth cohort study (303), the Kinder-Sportstudie (KISS) (304) and the Sport, Physical Activity and Eating Behaviour: Environmental Determinants in Young People Study (SPEEDY) (305). Three studies are prospective birth-cohort studies (299, 302, 303, 306) and six are cross-sectional studies with retrospectively reported birth weight (301, 304, 305). In longitudinal studies, data from the first wave of PA assessments in which each person participated were included, unless later waves of data collection comprised a wider array of cardiometabolic risk factors (299, 302, 305, 306). The participants were recruited either because they were born at a certain hospital or in a certain area in a specific period (299, 302, 303, 306), through randomly selected schools (301) or through schools willing to participate within a defined area (304, 305). More information about the population and recruitment method in each study is available elsewhere (299, 301-306).

The participants from the sub-cohort of the MoBa (294), included in **Paper III,** were also included in these pooled analyses. Of the 1 603 10–12-year-olds invited to participate; 430 children were included in the present analyses.

The PANCS 1 study included a national representative sample of Norwegian 9- and 15-year-olds (296, 297). In total 2 299 agreed to participate, and the participation rate was 89% and 74% for 9- and 15- year-olds, respectively.

The ASK study is a school-based cluster randomized controlled trial carried out in 2014/15, situated in the western part of Norway (298). Sixty schools were approached and 57 of them (1129 children) agreed to participate (recruitment success of 95% of schools, 94% of children). For the present analyses, we included the baseline data on PA and cardiometabolic risk factors in 857 children.

Table 3: Study characteristics of the 12 pooled studies included in Paper IV

Study	Country, city/area	Year	n (% boys)	Age, years	Available cardiometabolic risk factors
ALSPAC	UK, Avon	2006–2008	2110 (45.1%)	15.4 (15.3–15.6)	SBP, DBP, LDL, HDL, TG, HOMA-IR, WC
Denmark EYHS	Denmark,Odense	1997–2010	1438 (44.0%)	10.2 (9.6–15.5)	SBP, DBP, LDL, HDL, TG, HOMA-IR, WC
Estonia EYHS	Estonia, Tartu	1998–1999	568(44.2%)	10.2 (9.5–15.4)	SBP, DBP, LDL, HDL, TG, HOMA-IR, WC
IBDS	US, Iowa	2003–2005	431 (48.0%)	11.0 (10.9–11.3)	WC
Norway EYHS	Norway, Oslo	1999–2000	236 (50.8%)	9.7 (9.4–10.0)	SBP, DBP, LDL, HDL, TG, WC
Pelotas	Brazil, Pelotas	2006–2007	426 (52.8%)	13.3 (13.1–13.6)	SBP, DBP, WC
Portugal EYHS	Portugal,Madeira	1999–2000	590 (51.5%)	10.0 (9.6–15.4)	SBP, DBP, LDL, HDL, TG, HOMA-IR, WC
SPEEDY	UK, Norfolk	2011	358 (45.5%)	14.3 (14.0–14.5)	SBP, DBP, WC
KISS	Switzerland[a]	2005–2006	306 (45.8%)	10.4 (7.1–11.2)	SBP, DBP, LDL, HDL, TG, HOMA-IR, WC
MoBa	Norway[b]	2013–2015	430 (54.4%)	11.0 (10.3–11.3)	SBP, DBP, WC
ASK	Norway[c]	2014	857 (51.6%)	10.2 (10.0–10.5)	SBP, DBP, LDL, HDL, TG, HOMA-IR, WC
PANCS	Norway[d]	2005–2006	1350 (49.9%)	9.8 (9.5–15.3)	SBP, DBP, LDL, HDL, TG, HOMA-IR, WC

Data are expressed as median (25–75 percentile) for age, number of participants (*n*) and percent boys (%). DBP – diastolic blood pressure; HDL – high-density lipoprotein cholesterol; HOMA-IR – homeostasis model assessment (HOMA2); LDL – low-density lipoprotein cholesterol; SBP – systolic blood pressure; TG – triglycerides; WC – waist circumference

[a] Two provinces in Switzerland

[b] Four cities in Norway (Oslo, Fredrikstad, Stavanger and Bergen)

[c] Sogn and Fjordane county

[d] Representative sample from all regions in Norway

Measurements

Exposures

The participants in the MoBa and the sub-cohort included in **Paper II** and **Paper III** are followed up regularly with maternally reported questionnaires and linked to the Medical Birth registry of Norway (MBRN). The MBRN is a national health registry containing information about all births in Norway. The mothers reported their height and pre-pregnancy weight in gestational week 18. We calculated maternal pre-pregnancy BMI by dividing weight by height squared (kg/m^2), and we obtained birth weight and gestational age (weeks) at birth from the MBRN. Gestational age was estimated by ultrasound; however, in a few cases (<2% in **Paper II** and <1% in **Paper III**), gestational age from ultrasound was not available, and this age was consequently based on the first day of the last menstrual period. The mothers used information from their child's health record, where weight and length are measured by nurses, and reported their child's weight at 1 year via a questionnaire. We calculated infant weight gain as a change in sex-specific z-scores from birth to 1 year using the mean and *SD* from the total MoBa population.

In **Paper IV**, birth weight was either measured at birth (294, 299, 302, 303, 306) or retrospectively parentally reported (296-298, 301, 304, 305).

We standardized birth weight by calculating sex- and gestational age-specific z-scores, using mean and *SD* from the total MoBa population in **Paper II** and **Paper III.** In **Paper IV**, birth weight is expressed in kg.

Physical activity

In **Paper I** and **Paper II,** PA is the outcome, whereas in **Paper III** and **Paper IV,** PA is included in the model as a possible effect modifier.

In **Paper II**, LTPA at age 7 years was reported by the mother via a questionnaire. The questionnaire comprised of two questions; the mother reported the number of times (frequency) and hours per week her child participated in MVPA ("...the child becomes short of breath or sweaty") outside of school hours. In the questionnaire, hours per week were categorized into "1–2 hours per week," "3–4 hours per week," "5–7 hours per week," "8–10 hours per week" and "11 hours or more per week" during both summer and winter. We recoded these categories to 1.5, 3.5, 6, 9 and 11 hours per week respectively, and we calculated the average for summer and winter combined.

To test the construct validity of the LTPA questionnaire, we compared the questions to accelerometer-assessed PA in an independent convenient sample of 82 mother-and-child pairs. The children wore an Actigraph accelerometer (Actigraph GT3X+; LLC, Pensacola, Florida, USA), and the protocol and data processing methods are provided in Table 4. Awareness of wearing the monitor may have influenced the participants' PA levels. Measures of day-to-day variability in PA levels in children and adolescents after attachment of the monitor revealed that the first day of measurement was the most active day (307). To eliminate this reactivity bias, we set the monitors to start recording at 06:00 the day after the participants received the monitors. The mothers received and answered the LTPA questionnaire twice by e-mail – the first time approximately one week after the children finished using the accelerometer and the second time 14 days after they returned the first questionnaire. Of the 82 participants included, 77 (53% girls) completed three or more days of activity monitoring and answered the questionnaire. The mothers and children's mean ages (*SD*s) were 40.4 (4.3) years and 7.9 (0.7) years respectively, and the mean (*SD*) BMI in the children was 16.3 (1.5) m/kg^2. The mothers reported, on average (*SD*), children's participation in LTPA 4.5 (1.8) and 6.0 (2.4) times and hours per week respectively. On average (*SD*), the mothers answered the first questionnaire 14.4 (6.5) days after their child finished wearing the accelerometer, and the second questionnaire 19.5 (7.0) days after the first questionnaire. The partial Pearson correlation coefficients, adjusting for child's sex and BMI (kg/m^2), between accelerometer-assessed LTPA and the questionnaire were $r = 0.32$ ($p = 0.0056$) and $r = 0.09$ ($p = 0.46$) for frequency and hours per week respectively. Moreover, the partial Pearson correlation coefficients, using the same adjustments, between the first and second questionnaire were $r = 0.69$ ($p = 0.000$) and $r = 0.69$ ($p = 0.000$) for frequency and hours per week respectively. The absolute agreement, measured with intraclass correlation coefficients (ICCs), between the first and second questionnaire were ICC = 0.71 ($p = 0.000$) and ICC = 0.69 ($p = 0.000$) for frequency and hours per week respectively. The results of this validation study suggest that the question about the frequency of LTPA participation per week may be useful for ranking children according to level of LTPA, and this question was thus used as the outcome measure of PA in **Paper II**.

In **Paper III**, we measured PA using Actigraph accelerometers (Actigraph GT3X+; LLC, Pensacola, Florida, USA), and the protocol and data processing method are provided in Table 4. The rationale for including all participants with at least one valid day was the small study sample and the fact that we wanted to include as many participants as possible. Furthermore, 98% of the participants provided three or more valid days of activity recordings, and there was no difference in MVPA and VPA between these children and those who provided less than three valid days.

In **Paper IV,** PA was measured using uniaxial Actigraph- (model GT1M and 7164) (295-297) and triaxial Actigraph (model GT3X+; LLC, Pensacola, Florida, USA) (294, 298) accelerometers. For data harmonization purposes, all data were reintegrated into a uniaxial format and 60-sec epochs. All studies provided raw Actigraph data files, and the data were further reanalyzed in a standardized way to ensure comparability across studies. Protocol and data processing methods are provided in Table 4.

Time (minutes) per day spent in the intensity specific categories of PA was derived by summing all epochs falling within the thresholds presented in Table 4 for each valid day. The cut-points used in the validation study in **Paper II** and in the main analyses in **Paper III** and **Paper IV** correspond to the cut-points suggested by Evenson et al. (308). These cut-points are widely used and recommended to estimate PA intensities in children and adolescents (309).

Table 4: Protocol and data-processing methods in Paper II–Paper IV using Actigraph accelerometer to measure PA

	Validation study (Paper II)	Paper III	Paper IV
Actigraph model	Actigraph GT3X+	Actigraph GT3X+	Actigraph 7164, GT1M and GT3X+
Data processing software	ActiLife (version 6.13.3)	ActiLife (version 6.13.3)	Kinesoft (version 3.3.20 and 3.3.80)
Valid day definition	Minimum 480 min wear time / day	Minimum 480 min wear time / day	Minimum 480 min wear time / day
Minimum number of valid days	Minimum 3 valid days	Minimum 1 valid day	Minimum 3 valid days
Epoch length	10 sec	10 sec	60 sec
Non-wear time definition	≥20 min of consecutive zero counts	≥20 min of consecutive zero counts	≥60 min of consecutive zeros counts, with an allowance of two min of nonzero interruptions
PA measure	MVPA (min/day) after school hours (removed activity between 08:00 and 13:00)	MVPA (min/day) and VPA (min/day)	MVPA (min/day). VPA (min/day) for sensitivity analyses

Intensity cut-points	MVPA ≥ 2 296 cpm	MVPA ≥ 2 296 cpm VPA ≥ 4 012 cpm	MVPA ≥ 2 296 cpm VPA ≥ 4 012 cpm
Overnight activity	Overnight activity (00:00–05:59) removed	Overnight activity (00:00–05:59) removed	Overnight activity (00:00–05:59) removed, or days with more than 18 hours wear time were set to missing.
Protocol	The monitor was attached around the waist (right hip) using an elastic band. The children wore the monitor for seven consecutive days, removing it only when sleeping or during water-based activities. We set the monitors to start recording at 06:00 the day after the participants received the monitors.	The monitor was attached around the waist (right hip) using an elastic band. The children wore the monitor for seven consecutive days, removing it only when sleeping or during water-based activities. We set the monitors to start recording at 06:00 the day after the participants received the monitors.	The monitor was attached around the waist (right hip) using an elastic band. The children and adolescents wore the monitor for four[a] or seven consecutive days, removing it only when sleeping or during water-based activities.

[a]PANCS
Cpm – counts per minute; MVPA – moderate to vigorous physical activity; PA – physical activity; VPA – vigorous physical activity

Adiposity

In **Paper II**, a secondary aim was to examine whether the possible associations between the exposures and LTPA were mediated by BMI at age 3 years. Weight and height at age 3 years were maternally reported via a questionnaire, in which the mothers extracted the information from the child's health record where weight and height were measured by nurses.

Trained personnel performed anthropometric measurements in **Paper III** and **Paper IV**. The participants wore light clothing during body weight and height measurements, which were taken using a mechanical scale and a stadiometer respectively.

We calculated BMI by dividing weight by height squared (kg/m2) (**PaperII–PaperIV**). For descriptive statistics (**Paper III**), we defined childhood underweight, overweight and obesity using the IOTF criteria, whereby "underweight" corresponds to an adult BMI value ≤18.5

kg/m^2, "overweight" corresponds to an adult BMI value ≥25 kg/m^2, and "obesity" corresponds to an adult BMI value ≥30 kg/m^2 (191, 192).

Trained personnel measured fat mass (kg), fat-free mass (kg) and percent body fat (in %) with DXA using a Lunar iDXA (GE Healthcare Lunar, Madison, Wisconsin, USA) (enCORE Pediatric whole-body analysis Software Version 14.10.022) (**Paper III**); DXA is a two-dimensional imaging technique that measures body composition by X-ray with two diverse energies. Different tissues attenuate the X-ray differently, thereby allowing for distinction of, for example, lean body mass and fat mass (310). Furthermore, DXA provides an accurate measure of total body fat and lean body mass (198, 310). The participants underwent a whole-body scan, wore light clothes and removed all loose metal items prior to scanning. The test personnel calibrated the scanner daily according to the Lunar iDXA enCORE manual.

Test personnel measured waist circumference midway between the lower rib and the iliac crest (294, 296, 297, 299, 301-306), or 2 cm above the level of the umbilicus (298) at end of gentle expiration (**Paper IV**).

Cardiometabolic risk factors

In **Paper IV,** 11 studies provided data on systolic and diastolic blood pressure (Table 3) (294, 296-299, 301, 303-306). Blood pressure was measured repeatedly in a resting condition using automated blood pressure monitors, and the mean of repeated measures (two or three) was calculated. Eight studies (Table 3) provided data on LDL cholesterol, HDL cholesterol and triglycerides (296-299, 301, 304, 306). In one study (301), fasting blood samples were drawn from capillary blood. Fasting glucose and insulin levels were available from seven studies (Table 3) (296-299, 301, 304, 306). We calculated insulin resistance using the updated HOMA2 calculator (175). All blood samples were collected while participants were in a fasting state.

Clustered risk scores with different combinations of cardiometabolic risk factors are comparable (186), and we therefore used the available variables and calculated a clustered cardiometabolic risk score by summarizing age-group specific standardized values of MAP, triglycerides, LDL/HDL ratio and HOMA-IR, divided by 4 (number of variables) (**Paper IV**).

Socioeconomic status

Parental education was treated as a proxy measure for socioeconomic status and was included in the models as a possible confounder. The parent's education level was combined into one variable reflecting the highest education level by either the mother or the father (**Paper III** and **Paper IV**) or included in the model separately (**Paper II**).

In **Paper II** and **Paper III,** we obtained information about completed and ongoing maternal and paternal education via a maternal-reported questionnaire in gestational weeks 17–20 (<high school / college or university 1–4 years/>4 years of college or university). If ongoing education was reported, this education level was used instead of completed education (7.6% and 5.6% of the mothers and fathers reported ongoing education respectively).

To harmonize the parents' education level across all included studies in **Paper IV**, a dichotomous variable was created dividing the maternal and paternal education level into 1) up to and completion of compulsory education and 2) any post-compulsory education.

Other confounding factors and covariates

We obtained maternal age at time of delivery (years), maternal parity at time of delivery (0/1/2/3/≥4) and maternal smoking during pregnancy (yes/no) from the MBRN **(Paper II)**. In addition, we obtained data regarding breastfeeding from birth to 4 months (exclusive/partial/none) via the maternally reported questionnaire at child's age 6 months (**Paper II**).

Statistics

The descriptive statistics of participants are presented as mean and *SD*, median and 25th and 75th percentile and number of participants and proportions, depending on the data. We tested for differences between boys and girls (**Paper II** and **Paper III**) or children and adolescents (**Paper IV**) using independent samples *t*-tests, the Mann-Whitney two-sample test and chi-squared statistics.

We performed all analyses using Stata/SE – version 13.1 (**Paper I**), version 14.2 (**Paper III** and **Paper IV**) and version 16.0 (**Paper II**). The two-sided statistical level was set to $p < 0.05$ for all analyses, including interaction effects in **Paper III**, or $p < 0.10$ for interaction effects in **Paper IV**.

Paper I

The results from the studies included in the systematic review are summarized in a narrative synthesis. We performed a meta-analysis on the association between birth weight (kg) and device-measured overall PA (cpm), using a random-effects model with unstandardized regression coefficients and 95% confidence intervals (CIs). We contacted the corresponding authors if we were not able to obtain the required information from the articles. To examine the degree of heterogeneity between studies, we used Cochrane's Q and the I^2 index. The Q test assesses

whether variation between the effect estimates is likely because of chance alone, whereas the I^2 statistic quantifies the amount of variation between studies that cannot be attributed to chance (311). We performed a sensitivity analysis by excluding one study at a time from the model to assess the impact of a specific study on the overall conclusion.

Performing a meta-analysis on the associations between infant growth, motor development and PA was not appropriate due to few and heterogeneous studies.

Paper II

A formal interaction test revealed that some of the associations in **Paper II** may differ between boys and girls, and we therefore stratified all analyses by sex.

To examine possible non-linear associations, we visually assessed the dose-response relationships between the exposures and LTPA in the adjusted models (without possible mediators) using fractional polynomials, and we estimated the approximate number and placement of knots with restricted cubic and linear splines. We tested multiple placements of knots and compared the fits by Akaike information criterions (AICs). In cases were the best fits were non-linear, we tested deviation from the linear model by a likelihood ratio test. The models with the best fit included linear splines (maternal pre-pregnancy BMI and birth weight [boys]) and linear (birth weight [girls] and infant weight gain) models. We used multilevel linear regression with or without linear splines, including the mother as the random factor to take into account the dependencies between siblings. We examined each model for normal distribution of residuals and homoscedasticity. Furthermore, all models were adjusted for maternal age, maternal parity, maternal education, paternal education and maternal smoking during pregnancy and child's age at completion of the PA questionnaire. When birth weight was modeled, we further adjusted for maternal pre-pregnancy BMI (linear splines), and when infant weight gain was modeled, we included maternal pre-pregnancy BMI (linear splines), birth weight (linear splines or linear depending on sex) and breastfeeding as possible confounders.

Maternal pre-pregnancy BMI, birth weight and infant weight gain are affected by one another (15, 312). We therefore tested for interactions between the exposures (maternal pre-pregnancy BMI*birth weight and birth weight*infant weight gain) by including product terms in the model. If no interaction occurred, then we further examined whether birth weight and infant weight gain were mediators on a possible association between maternal pre-pregnancy BMI and LTPA, and whether infant weight gain was a mediator on the possible association between birth weight and LTPA, by evaluating the controlled direct effect (313, 314). We further included child's BMI

at age 3 years in the model to assess the controlled direct effect in a similar manner. Child's BMI was included in the model with all the other possible mediators due to the strong confounding assumptions necessary in mediation analyses (313, 314). There was no interaction between any of the exposures and child's BMI ($p > 0.05$). We did not test for mediation if no exposure-outcome association was observed.

We graphically illustrated the predicted LTPA with a 95% CI across the exposures.

The number of participants with missing data on one or more of the exposures and covariates was 45%, for both boys and girls, in which increased to 60% when BMI was included as a possible mediator. We replaced missing values using multiple imputation (MI) by chained equations (predictive mean matching, logistic regression and ordered logistic regression). We imputed a total of 20 datasets separately for boys and girls, based on all variables in the models in addition to auxiliary variables. More information about the imputation method, imputation model, number of missing values for each variable, and complete case analyses is provided in Appendix 1.

Paper III

We used multiple linear regression to examine the associations between the exposures (maternal pre-pregnancy BMI, birth weight and infant weight gain) and both childhood body composition and BMI. We examined for linearity between independent and dependent variables and each model for normal distribution of residuals and homoscedasticity. We included a sex interaction term as previous studies have observed sex-dependent associations (275, 315). The formal interaction tests demonstrated that certain associations may differ between boys and girls ($p < 0.05$), and we thus stratified all analyses by sex. We adjusted each model for parental education. When BMI was modeled as the outcome, we additionally adjusted for current age, whereas models including body composition (i.e. fat mass, percent body fat and fat-free mass) as the outcome measure were additionally adjusted for current height. Furthermore, other possible covariates were included depending on the exposure. For example, when maternal pre-pregnancy BMI and infant weight gain were modeled as the exposures, we additionally adjusted the analyses for birth weight. Similarly, the models including birth weight as the main exposure were adjusted for maternal pre-pregnancy BMI. To test whether MVPA or VPA modified the associations, we included the interaction terms "exposure*MVPA" or "exposure*VPA" into separate models – a significant interaction indicates an additive interaction. In the case of a significant interaction, we graphically displayed the predicted values of the outcome variable (calculated from the adjusted regression models with the interaction terms), at given values of the exposure of interest and the

25th, 50th and 75th percentiles of MVPA and VPA. In addition, we stratified the participants using a median split in MVPA and VPA, and we examined the magnitude of the associations in the models without the interaction term.

The numbers of participants with missing values for one or more variables were 50 (20.7%) and 37 (18.2%) for boys and girls respectively. We replaced missing values on exposures and covariates using MI by chained equations (predictive mean matching and ordered logistic regression). We imputed a total of 20 datasets separately for boys and girls, based on all variables in the full models in addition to auxiliary variables. More information about the imputation method, imputation model, number of missing values for each variable and complete case analyses is provided in Appendix 2.

Paper IV

In **Paper IV**, the participants' age distribution revealed two clusters around age 9–10 and 15–16 years. We therefore performed a median split, dividing the participants into children (≤11.6 years old) and adolescents (>11.6 years old) for all the analyses.

We used multilevel linear regression, including study as a random factor (12 studies), to examine the associations between birth weight, MVPA and the cardiometabolic outcomes. We adjusted all models for highest parental education, age and sex. When systolic- and diastolic blood pressure were modeled as the outcome, we adjusted for childhood height and excluded age from the model due to risk of collinearity. In Model 2, we further adjusted analyses for waist circumference. To examine whether MVPA modified the associations between birth weight and the cardiometabolic outcomes, we included the interaction term (birth weight * MVPA) in the models – a significant interaction indicates an additive interaction. We tested all models for the assumptions of linear regression (linearity between exposure and outcome, normal distribution of residuals and homoscedasticity). For the models including HOMA-IR and triglycerides, a slightly skewed distribution of the residuals was found. However, due to the large sample size and sensitivity analyses with and without log-transformed variables demonstrating similar results, we kept the variables not transformed in the models for ease of interpretation of the effect estimates. Furthermore, we used robust standard error estimates due to signs of heteroscedasticity in some of the models. A formal interaction test revealed no evidence of an interaction with sex on any of the associations. We conducted sensitivity analyses using VPA as the effect modifier, as well as sensitivity analyses where we excluded all participants with birth weight < 1.5 kg – that is, participants most likely to be born prematurely (n = 66).

For illustrative purposes, we graphically displayed unstandardized regression coefficients with 95% CIs from the final adjusted models (without the interaction term) across low or high MVPA (median split).

In case of a significant interaction, we graphically illustrated the predicted values of the outcome variable, based on the final adjusted models with the interaction term, across values of birth weight and the 25th, 50th and 75th percentiles of MVPA/VPA. Regardless of an interaction, we also graphically illustrated the predicted values of the clustered cardiometabolic risk score in a similar manner.

Three percent (n = 116) and 19% (n = 875) of the children and adolescents, respectively, had missing data on one or more of the included covariates. We replaced missing values using MI by chained equations. We then imputed a total of 20 datasets separately for children and adolescents. More information about the imputation method, imputation model, number of missing values for each variable and complete case analyses is provided in Appendix 3.

Ethics

The establishment of the MoBa and initial data collection was based on a license from the Norwegian Data Protection Agency and approval from the Regional Committee for Medical Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act, and the sub-cohort of the MoBa was additionally approved by The Regional Committee for Medical Research Ethics (REC South East). Furthermore, written informed consent was obtained from the children's parents prior to all measurements.

Each collaborator in the ICAD consulted his or her research board to ensure that sufficient ethical approval had been obtained. Written informed consent was obtained from each child's parent prior to all testing in ICAD, PANCS and ASK, and the study protocols were approved by the Regional Committee for Medical Research Ethics.

Results

Paper I

In the initial search we identified 15 481 publications, 11 868 of which remained after removal of duplicates. The identified publications were manually screened based on title and thereafter abstract. The screening process resulted in 41 publications that we retrieved for full-text review. In total, 11 publications met our search criteria and were included in the present review (Figure 5).

Study Details

Study characteristics for the 11 included publications are provided in Table 5. Nine studies were prospective cohort studies (235, 236, 239-241, 250, 291, 316, 317), while one study was a cross-sectional study with retrospective data collection of the exposure (244). The publication by Ridgway et al. (233) included a meta-analysis of results from four studies (EYHS, Roots, Speedy, Pelotas); one of these studies was a prospective cohort study (Pelotas), while the others used retrospectively reported exposures. Results on birth weight and PA from three (EYHS, Roots, Speedy) of the four studies included in the meta-analysis have not been published in original articles (233), whereas results from one of the included studies (Pelotas) have been published in another article using a slightly different outcome measure of PA (250).

The sample size ranged from 44 to 7736 participants across the studies, and ages ranged from 1.5 to 18 years at follow-up. The studies included populations from Europe (233, 235, 236, 241, 291, 317), Australia (244), India (239), Brazil (233, 240, 250) and Jamaica (316). Three publications included data from the Pelotas Birth Cohort (233, 240, 250). The studies used different exclusion criteria, namely, children from multiple births (235, 236, 239), birth weight < 1.5 kg (233), home births (239, 240, 250), a gestational age of less than 36 weeks (291), children with severe hearing or sight problems (291), mothers age at birth > 40 years (316), maternal diabetes (239) and >32-week gestation at recruitment (239). The included studies had a quality score between 0.73– and 0.95 (possible range 0–1) (Table 5).

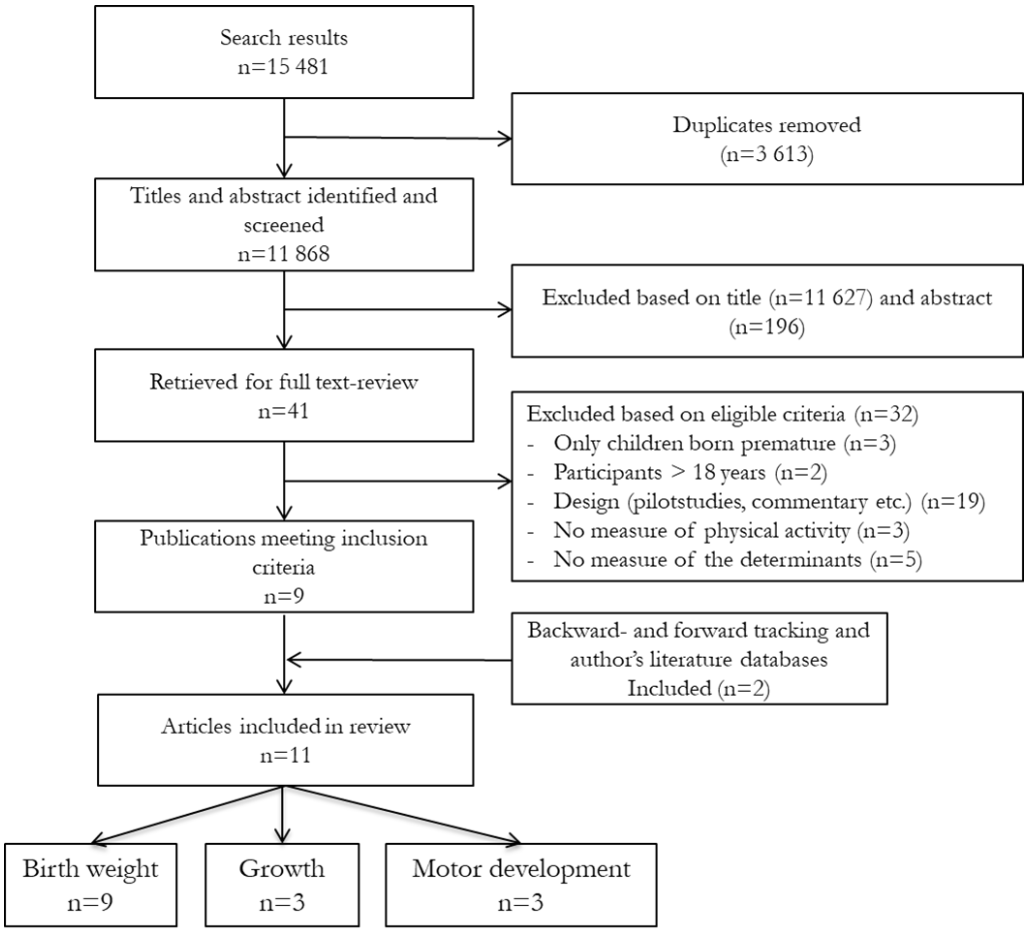

Figure 5 Flow-chart of study selection for the systematic review (Paper I).

Table 5: Characteristics and results from the included studies in the systematic review (Paper I)

Birth weight								
First author and publication year	Country	Age (years[a]) (Baseline/ follow-up)	*n* (% girls)	BW assessment	PA assessment	Statistical analyses and covariates	Main results	QA
Campbell, C.P. 2010 (316)	Jamaica	0/13.2(0.9)	284 (56)	Measured, continuous	Actical accelerometer, total PA (cpm), %counts>200, PAEE	Partial correlation. Age and sex	No association between BW and PA	0.73
Gopinath, B. 2013 (244)	Australia	12/12, 17–18	1 794 (50) 752 (53)	Reported, continuous (z-scores) and categorized: <2 000, 2 001–2 499, 2 500–4 000 and >4 000 g or quartiles	Self-reported participation in sports (hours/week)	Multiple linear reg. Age, sex, GA, ethnicity, SES, BMI, and passive smoking exposure	12-year-olds: higher quartiles of birth weight associated with higher participation in sports (p for trend 0.02). 1 z-score increase in BW was associated with a 15-min/week increase in PA, $p = 0.05$). 17- to 18-year-olds: No association between BW and PA	0.91
Hallal, P. C. 2006 (240)	Brazil	0/10–12	4 450 (51)	Measured, categorized: <2 500 g, 2 500–3 499 g and ≥3 500 g	Self-report-interview. Inactive lifestyle (yes/no), defined as <300 min of PA/week	Poisson reg (Wald's test). Sex, SES, pre-pregnancy BMI and birth order	No association between BW and PA	0.73

Hallal, P. C. 2012 (250)	Brazil	0/13.3	457 (48)	Measured, continuous (conditional residuals)	Actigraph accelerometer (GT1M), total PA (counts/day).	Multiple linear reg. Sex, GA, SES, maternal BMI, maternal smoking during pregnancy and length/height	No association between BW and PA	0.86
Kehoe, S.H. 2012 (239)	India	0/7.8(1.1)	415 (51)	Measured, continuous (kg).	Actigraph accelerometer (GT1M or 7164), total PA (cpm), counts/day, MVPA (%/day ≥2292–4008 cpm.	Multiple linear reg. Age, Sex, GA, SES, and %BF	No association between BW and PA	0.95
Mattocks, C. 2008 (235)	England	0/11.8(0.2)	5451 (52)	Measured, continuous (100g)	Actigraph accelerometer (7164), total PA (cpm)	Multiple linear reg. Age, sex, SES and GA	No association between BW and PA	0.95
Pearce, M. S 2012 (236)	England	0/8–10	482 (52)	Measured, continuous (z-scores)	Actigraph accelerometer (GT1M), total PA (cpm) or MVPA (%/day >3200 cpm	Multiple linear reg. Age, sex and BMI	No association between BW and PA	0.77

Ridgway, C.L. 2011 (233)		0–15/10–15		Continuous (kg)	Accelerometers–total PA (cpm) and time spent in MVPA (min/day >2000cpm)	Multiple linear reg. Age, sex, SES and BMI	Meta-analysis: No association between BW and PA	0.95
	1:DK,N,P,E E, 2: UK 3: UK, 4: Brazil	1: 9,15 / 12.0 (2.9), 2: 13–15 / 14.5 (0.5), 3: 9–10 / 10.2 (0.3), 4: 0 / 13.3 (0.3)	1: 1240 (53), 2: 811 (56), 3: 1647 (56), 4: 472 (48)	1–3: Reported 4: Measured	1:Actigraph,7164 2: Actiheart 3–4: Actigraph,GT1M		1–3: No association 4: BW was associated with total PA (cpm) (B=-33.39, 95% CI= -61.18, -5.60), but not with MVPA. The association between BW and total PA was no longer significant after further adjustment for GA.	
Wijtzes, A.I. 2013 (241)	Netherlands	0/2.1(0.1)	347 (48)	Measured at birth, categorized: < 2 500 g and ≥ 2 500 g	Actigraph accelerometer, 7164, total PA (cpm) and MVPA (min/day >2460 cpm)	Multiple linear reg. Age, sex, SES, maternal BMI, breastfeeding status, number of siblings, daycare attendance and season	No association between BW and PA	0.86

Infant weigh gain (growth)								
First author and publication year	Country	Age (years[a]) (Baseline/ follow-up)	*n* analyzed (% girls)	Growth assessment	PA assessment	Statistical analyses and covariates	Main results	QA
Eriksson, B 2012 (317)	Sweden	12 w/1.5 (0.04)	44 (48)	Change in %BF from 12 weeks to 1.5 years, measured with ADP.	Doubly labeled water, PAL	Correlation, none	Change in %BF from 12 weeks to 1.5 years was inversely correlated with PAL at 1.5 years (r=-0.38, p = 0.0105).	0.77
Hallal, P. C 2006 (240)	Brazil	0,1,4/10-12	4450 (51)	Weight gain (kg), categorized quartiles 0–1 year, 1–4 years.	Self-report–interview. Inactive lifestyle (yes/no), defined as <300 min of PA/week	Poisson reg (Wald's test). Sex, SES, pre-pregnancy BMI and birth order	No association between weight gain from 0–1 year or 1–4 years with PA	0.73
Hallal, P. C. 2012(250)	Brazil	0-4/13.3(0.3)	457 (48)	Body weight, length/height, continuous (conditional residuals)	Actigraph accelerometer (GT1M), total PA (counts/day)	Multiple linear reg. Sex, GA, SES, maternal BMI, maternal smoking during pregnancy, prior weight and length/height	Conditional weight at 1 month, 3 months, 6 months, 1 year and 4 years were not associated with PA Conditional length/height at 3 months (B = -18.0, 95% CI = -33.0, -2.9) and 1 year (B = -23.4, 95% CI = -39.7, -7.4) were inversely associated with PA.	0.86

Motor development								
First author and publication year	Country	Age (years[a]) (Baseline/ follow-up)	*n* analyzed (% girls)	Motor development assessment	PA assessment	Statistical analyses and covariates	Main results	
Mattocks, C. 2008(235)	England	0.5/11.8(0.2)	5 451 (52)	Parent report, continuous (χ-score)	Actigraph accelerometer (AM7164)	Multiple linear reg. Age, sex and SES	Motor coordination at 6 months was associated with PA (cpm) (*B* = 5.77, 95% CI = 0.25, 11.29). When stratified by sex, motor coordination was associated with total PA in girls (*B* = 11.63, 95% CI = 4.86, 18.40), but not in boys (*B* = -1.55, 95% CI= -9.57, 6.45)	0.91
Ridgway, C.L. 2009(291)	Finland	1/14	7736	Parent-report, continuous- age (months) walking and standing unaided	Self-report, questionnaire, participation in sports	Multiple linear reg. Sex, GA, birth season, SES, BW and current BMI.	Age at walking with support was inversely associated with PA (*B*=-0.04, 95%CI= -0.09, 0.00). Age at standing unaided was not associated with PA.	0.91

Wijtzes, A. I. 2013(241)	Netherlands	1/2.1(0.1)	347 (48)	Parent-report, dichotomized, delayed (yes/no).	Actigraph accelerometer, 7164, total PA (cpm) or MVPA (min/day >2460 cpm)	Multiple linear reg. Age, Sex, BW, SES, maternal BMI, breastfeeding status, number of siblings, daycare attendance, season.	No association between delayed motor development and PA	0.86

[a] unless otherwise stated (w = weeks, m = months). Abbreviations: ADP – whole-body air displacement plethysmography; BMI – body mass index; BW – birth weight; cpm – counts per minute; DK – Denmark; EE – Estonia; GA – gestational age; MVPA – moderate to vigorous physical activity; N – Norway; P – Portugal; PA – physical activity; PAEE – physical activity energy expenditure; PAL – physical activity level; Reg. – regression; SES – socioeconomic status; QA – quality assessment; %BF – percentage of body fat

Birth weight

We identified nine studies examining the association between birth weight and PA in children or adolescents (233, 235, 236, 239-241, 244, 250, 316) (Figure 5), and the main results are provided in Table 5. None of the studies with device-measured PA observed an association between birth weight and PA (233, 235, 236, 239, 241, 250, 316). Of the two studies with self-reported PA, one study observed an association between birth weight and participation in sports in 12-year-olds; however, this was not observed at follow-up at age 17–18 years (244). The second study found a weak and significant difference between birth weight groups for self-reported median PA in 10- to 12-year-olds, with those having a higher birth weight being more active (240).

We were able to obtain unstandardized regression coefficients with 95% CIs from eight studies, in which the four studies from the previous meta-analysis by Ridgway et al. (233) were included separately in the meta-analysis. The required information was available in the original publications of six studies (233, 235, 239). We contacted the corresponding authors of publications that did not provided the necessary data, and we hence received data from two additional studies (241, 316). The results from Hallal et al. (250) were not included in the meta-analysis, as these data were included in the article by Ridgway et al. (233).

The meta-analysis suggested no association between birth weight and overall PA (cpm) (Figure 6). The results were unchanged in sensitivity analyses when removing one study at a time (data not shown).

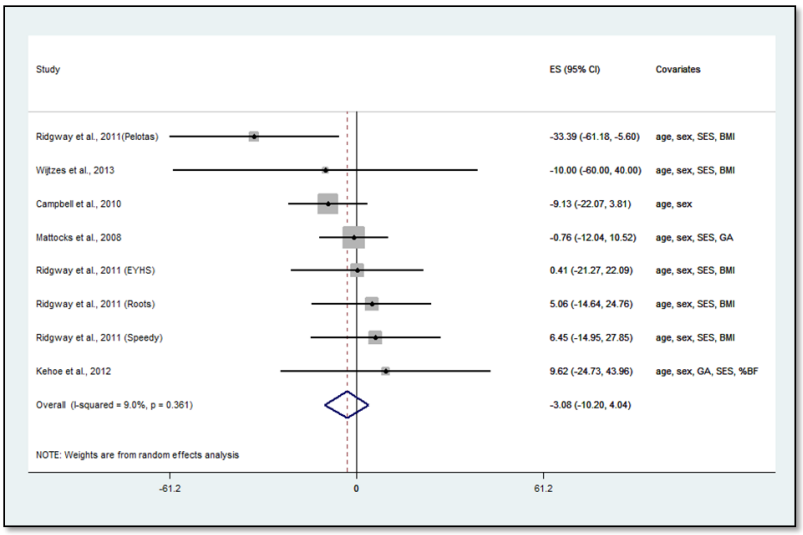

Figure 6: Random effects meta-analysis and forest-plot of the association between birth weight (kg) and overall PA (cpm) in children and adolescents (Paper I).

Infant weight gain

We retrieved three studies examining the association between infant weight gain and subsequent PA (240, 250, 317) (Figure 5), and the main results are provided in Table 5. Change in percent body fat from age 12 weeks to 1.5 years was inversely associated with the PA level measured with DLW at age 1.5 years (317). In the study by Hallal et al. (250), conditional weight up to four years, calculated as the deviation from the preceding growth interval in weight predicted by weight at birth and any prior weights, was not associated with subsequent PA. This was confirmed in another study from the same cohort, where weight gain from 0–4, 1–4 and 4–11 years were unrelated to self-reported physical inactivity, defined as participating in less than 300 min of recreational and transport-related PA per week (240).

Furthermore, in the study by Hallal et al. (250), conditional length/height at age 3 months and 1 year were associated with lower total PA, measured with accelerometers in 13-year-olds.

Motor development

We retrieved three studies examining the association between infant motor development and subsequent PA in childhood and adolescence (235, 241, 291) (Figure 5), and the main results are provided in Table 5. Older age at walking with support, but not age at standing unaided, was associated with a lower frequency of self-reported weekly sport participation in 14-year-olds (291), while maternally reported motor development at 6 months was positively associated with device-measured PA (cpm) in children aged 11-12 years (235). A further sex- stratified analysis revealed that this association was significant in girls, but not in boys. Moreover, a delayed gross motor development at age 1 (gross motor scale of the Minnesota Infant Development Inventory) was not associated with device-measured MVPA in 2-year-olds (241).

Paper II

Table 6 provides the descriptive characteristics of study participants included in **Paper II**. On average, boys had a higher weight at birth and 1 year and were more physically active by the age of 7 years compared to girls. The mothers were highly educated – 74% reported education from college or university – and the majority were normal-weight at the onset of pregnancy and primiparous.

Table 6: Descriptive characteristics of study participants in Paper II stratified by sex. Mean (*SD*) for continuous variables and frequency (%) for categorical variables unless otherwise stated.

Variable	Boys *n* = 24 823	Girls *n* = 23 849
Maternal characteristics		
Maternal pre-pregnancy BMI (kg/m^2)	23.9 (4.1)	23.9 (4.1)
Maternal pre-pregnancy weight status (cat)		
Underweight, *n*(%)	702 (2.9%)	635 (2.7%)
Normal weight, *n*(%)	16 108 (67.1%)	15 549 (67.4%)
Overweight, *n*(%)	5 164 (21.5%)	4 937 (21.4%)
Obese, *n*(%)	2 024 (8.4%)	1 951 (8.5%)
Maternal age[a] (years)	30.6 (4.4)	30.6 (4.4)
Maternal parity[a] (cat)		
Primiparous, *n*(%)	11 335 (45.7%)	10 815 (45.3%)
1, *n*(%)	8 792 (35.4%)	8 558 (35.9%)
2, *n*(%)	3 700 (14.9%)	3 534 (14.8%)
≥3, *n*(%)	996 (4.0%)	942 (3.9%)
Maternal education[b] (cat)		
<High school, *n*(%)	1 076 (4.5%)	1 033 (4.4%)
High school, *n*(%)	5 156 (21.4%)	5 014 (21.6%)
College/university 1–4 years, *n*(%)	10 983 (45.6%)	10 354 (44.6%)
College/university >4 years, *n*(%)	6 879 (28.5%)	6 796 (29.3%)
Paternal education[b] (cat)		
< High school, *n*(%)	1 887 (8.1%)	1 866 (8.4%)
High school, *n*(%)	7 943 (34.2%)	7 482 (33.6%)
College/university 1–4 years, *n*(%)	7 011 (30.2%)	6 783 (30.4%)
College/university >4 years, *n*(%)	6 361 (27.4%)	6 162 (27.6%)
Maternal smoking in pregnancy (cat)		
No, *n*(%)	18 902 (91.1%)	18 089 (91.2%)
Yes, *n*(%)	1 849 (8.9%)	1 748 (8.8%)
Characteristics of child aged 0–3 years		
Child birth weight (g)	3 672 (532)	3 551 (509)*
Child gestational age at birth (weeks)[c]	40 (39–41)	40 (39–41)*
Breastfeeding 0–4 months (cat)		*
Exclusive, *n*(%)	12 798 (59.4%)	13 050 (63.0%)
Partial, *n*(%)	8 488 (39.4%)	7 435 (35.9%)
None, *n*(%)	275 (1.3%)	240 (1.2%)
Child weight at 1 year (kg)	10.3 (1.1)	9.6 (1.0)*
Child BMI at 3 years (kg/m^2)	16.2 (1.5)	16.0 (1.5)*
Characteristics of child aged 7 years		
Child age at follow-up	7.1(0.16)	7.1(0.16)
Child LTPA (frequency/week)	4.3 (2.3)	3.7 (2.1)*
Child BMI at 7 years (kg/m^2)	15.8 (1.8)	15.8 (2.0)

*$p < 0.05$ for difference between boys and girls; [a] At time of delivery, [b] Highest completed or ongoing education in pregnancy weeks 17–20, [c] median (25th–75th percentile)

Maternal pre-pregnancy BMI

Figure 7 provides the associations between maternal pre-pregnancy BMI and LTPA separately for boys (A) and girls (B), and the unstandardized regression coefficients with 95% CIs for the linear splines below or above maternal pre-pregnancy BMI at 21 kg/m^2 and 20 kg/m^2 for boys and girls respectively. For boys, the association was positive below the maternal pre-pregnancy

BMI of 21kg/m^2, that is a lower maternal pre-pregnancy BMI was associated with lower participation in LTPA in childhood. For maternal pre-pregnancy BMI above 21 kg/m^2, there was an inverse association. Furthermore, no association was found between maternal pre-pregnancy BMI and childhood LTPA in girls.

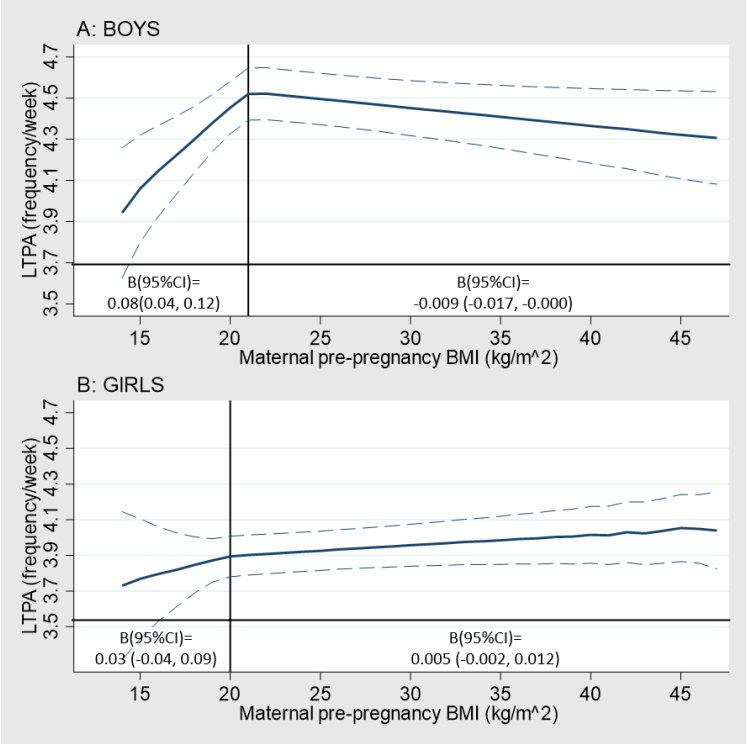

Figure 7: Predicted LTPA with a 95% CI in childhood across maternal pre-pregnancy BMI and unstandardized regression coefficients (95% CI), from multilevel linear model, including linear splines, in boys (A) and girls (B) (Paper II). Deviation from linearity (likelihood ratio test); boys $p > 0.001$, girls $p = 0.135$. Analyses adjusted for maternal age, parity, maternal education, paternal education, maternal smoking during pregnancy and child's age at follow-up. BMI – body mass index; LTPA – leisure time physical activity (frequency/week).

Birth weight

Birth weight *z*-scores, standardized for gestational age and sex, displayed a positive association with LTPA in boys with a birth weight *z*-score below or equal to -1, whereas the association was inverse for boys with a birth weight *z*-score above -1 (Figure 8). We observed no association between birth weight *z*-scores and LTPA in girls (Figure 8).

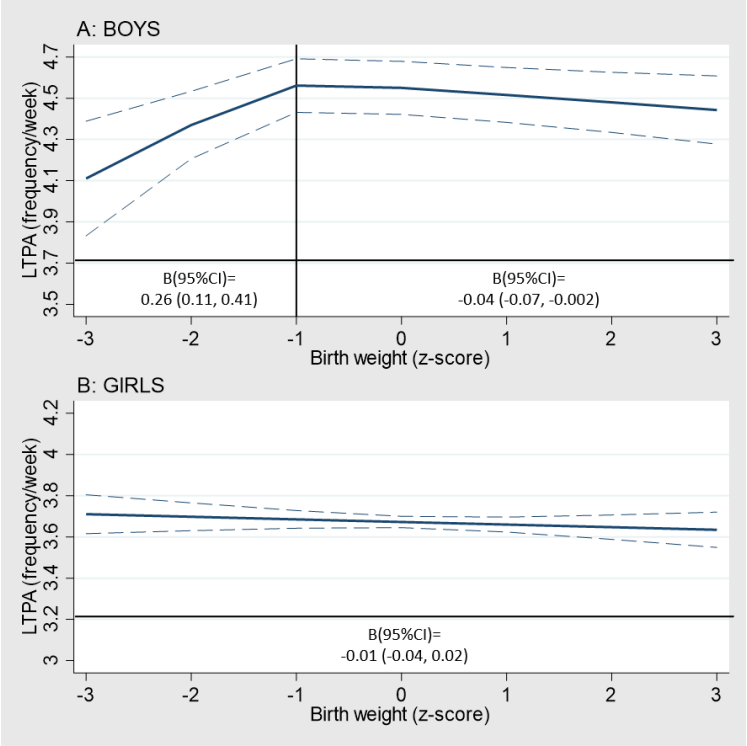

Figure 8: Predicted LTPA with a 95% CI in childhood across birth weight for gestational age z-scores and unstandardized regression coefficients (95% CI) from multilevel linear model, including linear splines (A) or linear model (B), for boys (A) and girls (B) (Paper II). Deviation from linearity (likelihood ratio test); boys $p < 0.001$. Analyses adjusted for maternal pre-pregnancy BMI, maternal age, parity, maternal education, paternal education, maternal smoking during pregnancy and child's age at follow-up. BMI – body mass index; LTPA – leisure time physical activity (frequency/week).

Infant weight gain

A positive linear association between infant weight gain and subsequent LTPA was observed in boys, but not in girls (Figure 9).

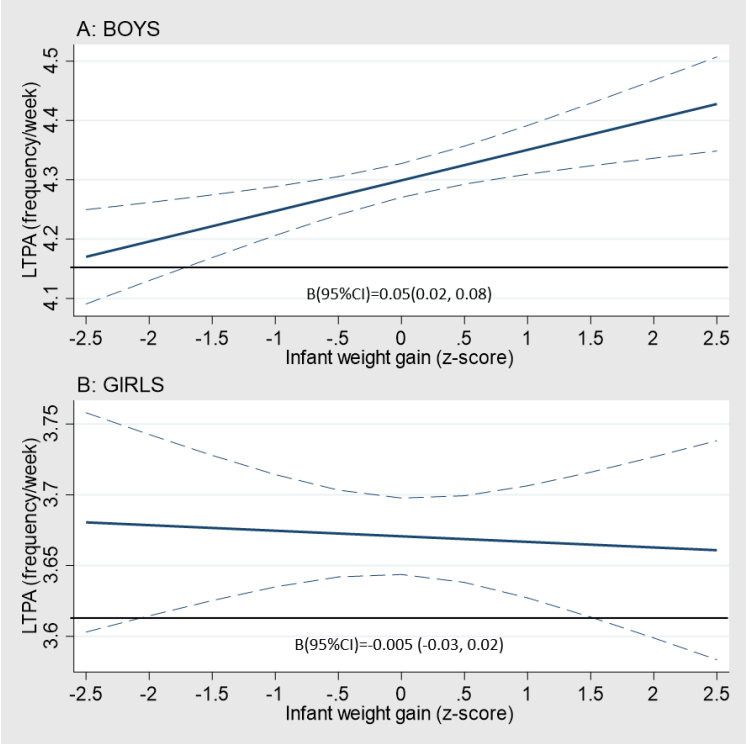

Figure 9: Predicted LTPA with a 95% CI in childhood across infant weight gain (change in z-scores from birth to 1 year) and unstandardized regression coefficients (95% CI), from multilevel linear model, for boys (A) and girls (B) (Paper II). Analyses adjusted for birth weight z-score, maternal pre-pregnancy BMI, maternal age, parity, maternal education, paternal education, maternal smoking during pregnancy, breastfeeding from 0–4 months and child's age at follow-up. BMI – body mass index; LTPA – leisure time physical activity (frequency/week).

Possible interactions and mediators

No interaction was observed between maternal pre-pregnancy BMI and birth weight on the association with LTPA in childhood (p = 0.349–0.659 and p = 0.074–0.270) for boys and girls respectively. We further observed a significant interaction between birth weight and infant weight gain on the association with LTPA above (p = 0.033) but not below (p = 0.113) a birth weight z-score of -1 in boys. No interaction was observed in girls (p = 0.279). From the regression model including the interaction term birth weight (splines) * infant weight gain, we graphically illustrated the interaction in boys (Figure 10) by depicting the predicted LTPA across birth weight z-scores and a slow (z-score = -0.67), normal (z-score = 0) and rapid (z-score = 0.67) infant weight gain. The association was slightly positive in those with a rapid infant weight

gain and slightly inverse in those with a slow infant weight gain above a birth weight z-score of -1.

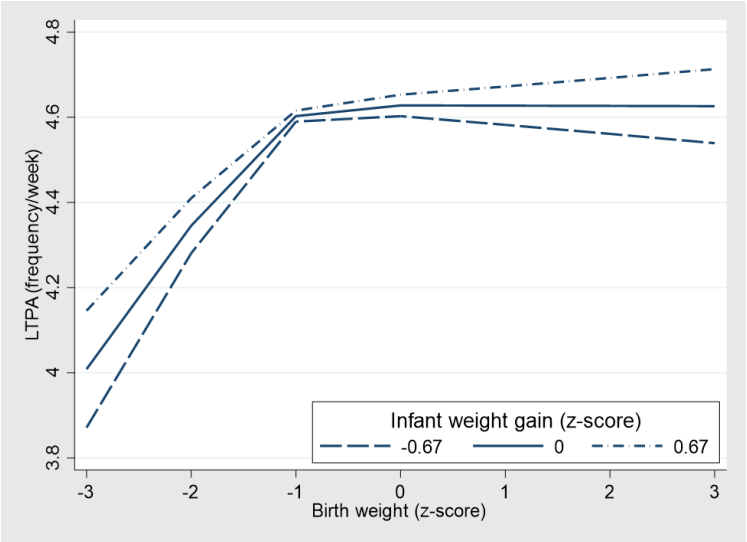

Figure 10: Predicted LTPA with a 95% CI in childhood across birth weight and infant weight gain at a change in z-score from 0–1 year at -0.67, 0 and 0.67. Predicted values from multilevel linear model including interaction term (birth weight * infant weight gain) (Paper II). Analyses adjusted for birth weight z-score, maternal pre-pregnancy BMI, maternal age, parity, maternal education, paternal education, maternal smoking during pregnancy, breastfeeding from 0–4 months and child's age at follow-up. BMI – body mass index; LTPA – leisure time physical activity (frequency/week).

The association between maternal pre-pregnancy BMI and LTPA in boys was not mediated by birth weight (splines) or infant weight gain – controlled direct effect: ≤21 kg/m^2: *B*(95% CI) = 0.08(0.03, 0.12); >21 kg/m^2: *B*(95% CI) = (-0.008(-0.017, 0.000), nor was child's BMI at 3 years – controlled direct effect: ≤21 kg/m^2: *B*(95% CI) = 0.08 (0.03, 0.12); >21 kg/m^2: *B*(95% CI) = -0.008(-0.017, 0.000). Figure 1 in Appendix 4 illustrates the interaction between birth weight and infant weight gain on LTPA in boys, with and without adjustments for BMI at age 3 years. The figure suggests that these associations were not mediated by BMI at that age.

The results using MI did not differ greatly from the complete case analyses (Appendix 1).

Paper III

Table 7 summarizes the characteristics of the total study sample and our sub-group with available DXA measurements included in **Paper III**. On average, participants wore the accelerometer for 6.5 (*SD* 1.34) days and for 786 (*SD* 55) min/d. Boys spent significantly more time in MVPA and VPA than the girls.

Table 7: Characteristics of the study participants in Paper III at birth and follow-up (9 to 12-year-olds). All values are mean (*SD*) unless otherwise specified.

	All participants		Participants with DXA	
	Boys (*n* = 242)	Girls (*n* = 203)	Boys (*n* = 98)	Girls (*n* = 88)
Age (years)	10.9(0.66)	10.9(0.66)	10.9(0.63)	11.0(0.63)
Birth weight (kg)	3.70(0.62)*	3.58(0.54)*	3.76(0.62)*	3.54(0.58)*
Gestational age (weeks)	39.5(1.96)	39.5(1.52)	39.8(1.84)	39.5(1.84)
Weight at 1 year (kg)	10.30(1.01)*	9.59(0.99)*	10.43(1.07)*	9.56(1.04)*
Maternal pre-pregnancy BMI (kg/m²)	23.9(4.3)	23.8(4.1)	23.7(4.1)	24.0(3.9)
Parental education [1], *n*(%)				
<High school	6(2.5%)	4(2.0%)	2 (2.1%)	3 (3.5%)
High school	50(20.9%)	48(24.0%)	18(18.7%)	13 (15.1%)
College/university 1–4years	95(39.7%)	80 (40.0%)	40 (41.7%)	36 (41.9%)
College/university >4years	88(36.8%)	68 (34.0%)	36 (37.5%)	34 (39.5%)
Weight (kg)	39.2(7.3)	39.1(7.7)	39.2(6.9)	40.0(8.4)
Height (m)	1.47(0.07)	1.48(0.08)	1.48(0.06)	1.49(0.08)
Fat mass (kg)	NA	NA	10.0(4.19)*	11.5(4.6)*
Fat-free mass (kg)	NA	NA	29.4(3.56)	28.6(4.84)
Percent body fat(%)	NA	NA	24.7(6.15)*	28.1(5.76)*
BMI (kg/m²)	17.9(2.47)	17.7(2.30)	17.8(2.46)	17.9(2.33)
Underweight (yes), *n*(%)	18(7.4%)	18(8.9%)	9(9.2%)	4(4.5%)
Normal weight (yes), *n*(%)	189(78.1%)	161(79.3%)	76(77.5%)	72(81.8%)
Overweight/obesity (yes), *n*(%)	35(14.5%)	24(11.8%)	13(13.3%)	12(13.6%)
Obesity (yes), *n*(%)	5(2.1%)	1(0.5%)	3(3.1%)	1(1.14%)
SED (min/day)	496(59.0)	506(57.3)	501(61.6)	508(55.6)
MVPA (min/day)	74(26.5)*	58(19.0)*	75(26.9)*	59(17.4)*
VPA (min/day)	29(14.6)*	21(10.3)*	30(15.7)*	21(8.7)*

*$p < 0.05$ for difference between boys and girls.

[1] the education level of the parent with the highest completed or ongoing education (mother or father)

BMI – body mass index (weight/height²); MVPA – moderate to vigorous physical activity; NA – not available; SED – sedentary time; VPA – vigorous physical activity

Maternal pre-pregnancy BMI

A higher maternal pre-pregnancy BMI was associated with higher fat mass, fat-free mass, percent body fat and BMI in boys (Table 8), whereas no significant associations were found in girls (Table 9). The associations with subsequent BMI were further weaker in girls than boys. There was no evidence that any of these associations differed according to time spent in MVPA or VPA in girls. However, the test for interaction demonstrated that in boys, the association

between maternal pre-pregnancy BMI and childhood BMI was modified by time spent in VPA, indicating that higher levels of VPA attenuated the association.

Figure 11 illustrates the predicted values of the boys' BMI at given values of maternal pre-pregnancy BMI and the 25th, 50th and 75th percentiles of VPA. The association between maternal pre-pregnancy BMI and childhood BMI was stronger (*B* = 0.32, 95% CI = 0.22, 0.41) in the participants below the median VPA (<28 min per day), compared with those above (*B* = 0.22, 95% CI = 0.12, 0.31).

Table 8: Unstandardized regression coefficients, with 95% CIs, for the associations between MVPA, VPA and pre- and postnatal factors with body composition measures and BMI in 9 to 12-year-old boys, and interaction between the pre- and postnatal factors and MVPA/VPA (in separate models) (Paper III).

	Fat mass (kg)	Fat-free mass(kg)	Percent body fat (%)	BMI (kg/m²)
	n = 98	*n* = 98	*n* = 98	*n* = 242
MVPA (min/day) [a]	-0.03(-0.06,-0.00)	-0.01(-0.03, 0.02)	-0.05(-0.09, 0.00)	-0.01(-0.03, -0.00)
VPA (min/day) [a]	-0.05(-0.11,-0.00)	-0.01(-0.05, 0.03)	-0.09(-0.16, -0.01)	-0.03(-0.06, -0.01)
Maternal pre-pregnancy BMI (kg/m²)[b]	0.45(0.28, 0.63)	0.14(0.02, 0.25)	0.64(0.36, 0.93)	0.28(0.22, 0.35)
* MVPA (interaction term)	-0.007(-0.02, 0.00)	-0.005(-0.01, 0.00)	-0.008(-0.02, 0.01)	-0.001(-0.00, 0.00)
* VPA (interaction term)	-0.010(-0.02, 0.00)	-0.006 (-0.02, 0.00)	-0.014(-0.04, 0.01)	-0.005(-0.01, -0.00)
Birth weight (z-score)[cd]	0.24(-0.45, 0.93)	0.07(-0.37, 0.51)	0.34(-0.76, 1.44)	0.13(-0.14, 0.40)
* MVPA (interaction term)	0.010(-0.01, 0.03)	0.000(-0.01, 0.01)	0.031(-0.00, 0.06)	0.000(-0.01, 0.01)
* VPA (interaction term)	0.012 (-0.02, 0.05)	0.004(-0.02, 0.03)	0.039(-0.01, 0.09)	0.001(-0.01, 0.01)
Infant weight gain (z-score)[bc]	1.45 (0.59, 2.31)	0.77(0.26, 1.28)	2.09(0.74, 3.43)	0.75(0.38, 1.11)
* MVPA (interaction term)	-0.026(-0.05,-0.01)	-0.003(-0.01, 0.01)	-0.035(-0.06,-0.00)	0.000(-0.01, 0.01)
* VPA (interaction term)	-0.068(-0.10,-0.02)	-0.005(-0.03, 0.02)	-0.085(-0.14,-0.03)	-0.002(-0.02, 0.02)

BMI – body mass index; MVPA – moderate to vigorous physical activity; VPA – vigorous physical activity. [a] Adjusted for highest parental education and current age. [b] Adjusted for highest parental education, birth weight and current height (for body composition outcomes only) and current age (for BMI outcome only). [c] Adjusted for highest parental education, maternal pre-pregnancy BMI and current height (for body composition outcomes only) and current age (for BMI outcome only). [d] Sex- and gestational age-specific z-scores [e] Change in sex-specific z-scores from birth to 1 year.

Birth weight

The gestational age- and sex-specific birth weight z-scores were not associated with fat mass, fat-free mass or percent body fat in boys or girls (Tables 8 and 9). We observed a positive association between birth weight and BMI in childhood in girls (Table 9). Moreover, including

the interaction terms birth weight * MVPA and birth weight * VPA into the models revealed no evidence of effect modification by PA (Table 8 and 9).

Table 9: Unstandardized regression coefficients, with 95%CI, for the associations between MVPA, VPA and pre- and postnatal factors with body composition measures and BMI in 9 to 12-year-old girls, and interaction between pre- and postnatal factors and MVPA/VPA (in separate models) (Paper III).

	Fat mass (kg)	Fat-free mass(kg)	Percent body fat (%)	BMI (kg/m²)
	n = 88	*n* = 88	*n* = 88	*n* = 203
MVPA (min/day) [a]	-0.03 (-0.08, 0.03)	-0.01(-0.06, 0.05)	-0.02(-0.09, 0.05)	-0.00 (-0.02, 0.01)
VPA (min/day) [a]	-0.04(-0.15, 0.07)	-0.00(-0.11,0.11)	-0.04(-0.18, 0.10)	-0.01(-0.04, 0.02)
Maternal pre-pregnancy BMI (kg/m²)[b]	0.20(-0.04, 0.45)	0.07 (-0.05,0.20)	0.25(-0.10, 0.61)	0.10(0.02, 0.18)
* MVPA (interaction term)	-0.003(-0.02, 0.01)	-0.003(-0.01, 0.01)	0.001(-0.02, 0.02)	-0.000(-0.00, 0.00)
* VPA (interaction term)	-0.006(-0.03, 0.02)	-0.003(-0.02, 0.01)	-0.000(-0.04, 0.04)	-0.003(-0.01, 0.00)
Birth weight (z-score)[cd]	0.25 (-0.58, 1.09)	0.39 (-0.05, 0.84)	0.21(-1.00, 1.41)	0.34(0.05, 0.64)
* MVPA (interaction term)	0.017(-0.04, 0.07)	0.015(-0.01,0.04)	0.036(-0.04, 0.11)	0.000(-0.01, 0.02)
* VPA (interaction term)	-0.001 (-0.11, 0.11)	0.033(-0.03, 0.09)	0.024(-0.14, 0.19)	-0.005(-0.04, 0.03)
Infant weight gain (z-score)[be]	0.04 (-1.24, 1.33)	-0.16(-0.75, 0.44)	0.28(-1.38, 1.94)	0.37(-0.06, 0.81)
* MVPA (interaction term)	-0.021(-0.08, 0.04)	0.002(-0.02, 0.03)	-0.041(-0.12, 0.03)	0.003(-0.02, 0.02)
* VPA (interaction term)	-0.025(-0.17,0.12)	0.005(-0.06, 0.07)	-0.072(-0.25, 0.10)	0.013(-0.03, 0.05)

BMI – body mass index; MVPA – moderate to vigorous physical activity; VPA – vigorous physical activity. [a] Adjusted for highest parental education and current age. [b] Adjusted for highest parental education, birth weight and current height (for body composition outcomes only) and current age (for BMI outcome only) .[c] Adjusted for highest parental education, maternal pre-pregnancy BMI and current height (for body composition outcomes only) and current age (for BMI outcome only). [d] Sex- and gestational age-specific z-scores. [e] Change in sex-specific z-scores from birth to 1 year.

Infant weight gain

Change in weight z-scores from birth to 1 year was positively associated with the different components of body composition and BMI in boys (Table 8). We did not observe any associations between infant weight gain and adiposity measures in girls (Table 9). Furthermore, MVPA and VPA interact with the associations between infant weight gain and fat mass, and infant weight gain and percent body fat in boys.

Figure 12 illustrates the predicted values of fat mass and percent body< fat across infant weight gain z-scores and the 25th, 50th and 75th percentiles of MVPA and VPA in boys.

In median split analyses, the association between infant weight gain and fat mass was stronger in the low MVPA group (*B* = 2.32, 95% CI = 0.50, 4.17) compared with the high (*B* = 1.00, 95% CI = 0.10, 1.91) MVPA group (high MVPA >73.6 min/day). The association with percent body fat in those below the median for MVPA was *B* = 3.35(95% CI = 0.55, 6.14) compared with those above the median: *B* = 1.41(95% CI = -0.06, 2.87).

The results from the complete case analyses are provided Appendix 2. The effect estimates are similar, but some confidence intervals are wider, in the complete case analyses.

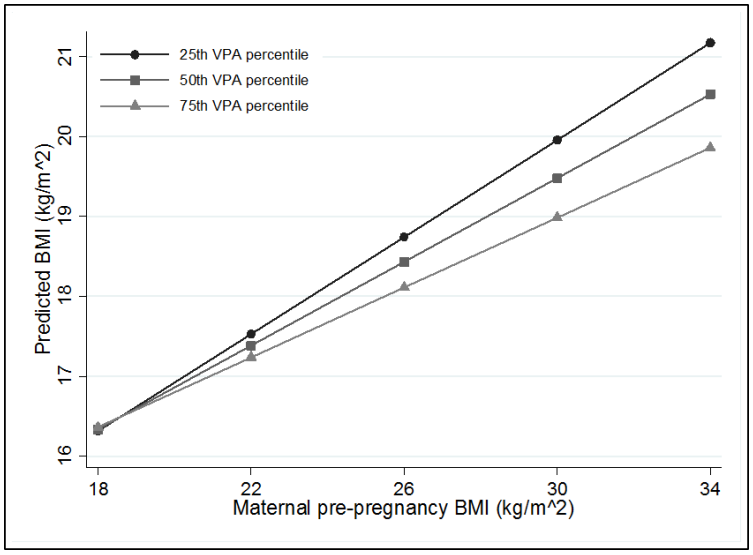

Figure 11: Predicted childhood BMI across values of maternal pre-pregnancy BMI and the 25th, 50th and 75th percentiles of VPA, in 9- to 12-year-old boys. Predicted values calculated from multiple regression model with interaction term (maternal pre-pregnancy BMI * VPA) (Paper III). 25th VPA percentile = 19.7 min/day, 50th VPA percentile = 28.3 min/day, 75th VPA percentile = 37.2 min/day. Adjusted for birth weight, parental education and age. BMI – body mass index; VPA – vigorous physical activity.

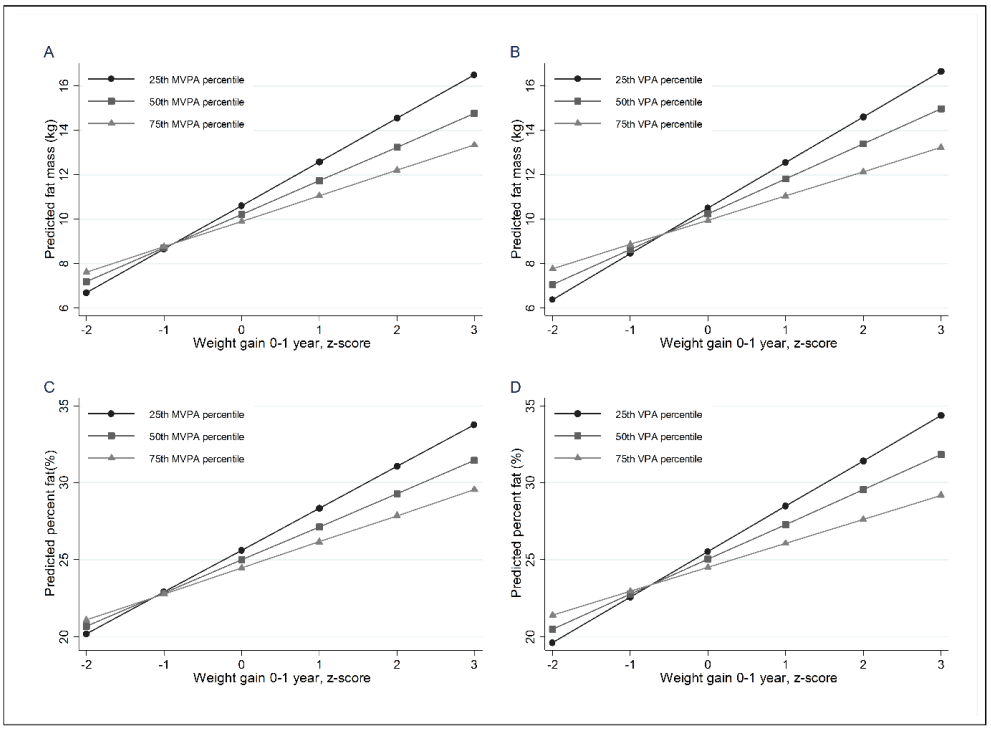

Figure 12: Predicted childhood fat mass (A and B) and percent body fat (C and D) across values of infant weight gain and the 25th, 50th and 75th percentiles of MVPA (A and C) and VPA (B and D), in 9- to 12-year-old boys. Predicted values calculated from multiple regression models with interaction terms (infant weight gain * MVPA/VPA) (Paper III). 25th MVPA percentile = 55.3 min/day, 50th MVPA percentile = 73.8 min/day, 75th MVPA percentile = 88.8 min/day. 25th VPA percentile = 19.7 min/day, 50th VPA percentile = 28.3 min/day, 75th VPA percentile = 37.2 min/day. Adjusted for birth weight, height and parental education. MVPA – moderate to vigorous physical activity; VPA – vigorous physical activity.

Paper IV

Table 10 provides the descriptive characteristics of the study sample in **Paper IV.** On average, the participants wore the accelerometer for 4.9 (*SD*=1.3) and 5.3 (*SD* = 1.4) days, with an average of 792 (*SD* = 69.0) and 814 (*SD* = 89.7) min per day, for children and adolescents respectively.

Table 10: Descriptive characteristics (mean and *SD* unless otherwise stated) of study participants in Paper IV and study availability, stratified by age group.

	CHILDREN		ADOLESCENTS	
	Studies[a]	Mean (SD)	Studies[a]	Mean (SD)
n(%boys)[b]	2–5, 7, 9–12	4560 (49.9%)	1–4, 6–10, 12	4540 (45.6%)
Age (years) [b]	2–5, 7, 9–12	9.9 (9.5–10.4)	1–4, 6–10, 12	15.4(15.1–15.6)
BMI (kg/m^2)	2–5, 7, 9–12	17.8 (3.0)	1–4, 6–10, 12	21.0 (3.5)*
>compulsory education,% [bc]	2– 5, 7, 9–12	84.1%	1–4, 6–10, 12	76.2%*
Birth weight (kg)	2–5, 7, 9–12	3.51 (0.60)	1–4, 6–10, 12	3.39 (0.57)*
MVPA (min/day)	2–5, 7, 9–12	62.0 (31.8)	1–4, 6–10, 12	44.7 (26.5)*
VPA (min/day)[b]	2–5, 7, 9–12	14.4 (7.7– 24.5)	1–4, 6–10, 12	10.5 (4.5–20.3)*
SBP (mmHg)	2–3, 5, 7, 9–12	102.8 (8.7)	1–3, 6–10, 12	116.5 (12.6) *
DBP (mmHg)	2– 3, 5, 7, 9–12	62.3 (8.2)	1–3, 6–10, 12	66.4 (8.9)*
LDL cholesterol (mmol/l)	2–3, 5,7,9, 11–12	2.48 (0.66)	1–3, 7, 9, 12	2.17 (0.60)*
HDL cholesterol (mmol/l)	2–3, 5,7, 9,11–12	1.61 (0.36)	1–3, 7, 9, 12	1.35 (0.31)*
Triglycerides (mmol/l) [b]	2–3,5,7, 9, 11–12	0.64 (0.49– 0.85)	1–3, 7, 9, 12	0.74 (0.58–0.97) *
HOMA-IR (score)[b]	2–3, 7, 9, 11–12	0.7 (0.5– 1.0)	1–3, 7, 9, 12	1.1 (0.8–1.5)*
Waist circumference (cm)	2–5, 7, 9–12	62.5 (8.7)	1–4, 6–10, 12	73.2 (8.9)*

DBP– Diastolic blood pressure; HDL– High-density lipoprotein; HOMA– IR– Homeostasis Model Assessment (HOMA2); LDL– Low-density lipoprotein; MVPA –Moderate to vigorous physical activity; SBP– Systolic blood pressure; VPA– Vigorous physical activity .[a]Studies: 1– ALSPAC, 2– Denmark EYHS, 3– Estionia EYHS, 4– IBDS, 5– Norway EYHS, 6– Pelotas, 7– Portugal EYHS, 8– SPEEDY, 9– KISS, 10– MoBa, 11– ASK, 12– PANCS. [b] Age, VPA, triglycerides and HOMA– IR expressed as median (25th–75th percentile). Number of participants (%), and % >compulsory education. [c]Percent (%) of which one or both parents have completed any post- compulsory education. *p<0.05 for difference between children and adolescents.

Based on the results, MVPA was associated with lower cardiometabolic risk factors, except for systolic blood pressure in children and waist circumference in adolescents (Table 11).

Table 11: Association (unstandardized regression coefficients and 95% CIs) between birth weight, MVPA and cardiometabolic risk factors in children and adolescents, and interaction between birth weight and MVPA (Paper IV).

	CHILDREN			ADOLESCENTS		
	n	*B*(95%CI)	*p*-value	n	B(95%CI)	*p*-value
SBP (mmHg)	4120			4491		
Model 1[a]						
Birth weight (kg)		- 1.10(- 1.50, - 0.70)			- 1.78 (- 2.52, - 1.04)	
Model 2[b]						
MVPA (min/day)		- 0.01 (- 0.03,0.00)			- 0.02 (- 0.03,- 0.01)	
Birth weight (kg)		- 1.30 (- 1.67, - 0.94)			- 1.98 (- 2.66, - 1.30)	
Birth weight * MVPA		0.005(- 0.007, 0.017)	0.440		- 0.005 (- 0.032,0.021)	0.685
DBP (mmHg)	4119			4491		
Model 1 [a]						
Birth weight (kg)		- 0.66 (- 0.80, - 0.42)			- 0.32 (- 0.61, - 0.04)	
Model 2 [b]						
MVPA (min/day)		- 0.01 (- 0.03,- 0.00)			- 0.01 (- 0.02,- 0.00)	
Birth weight (kg)		- 0.74 (- 0.99, - 0.48)			- 0.36 (- 0.65, - 0.08)	
Birth weight * MVPA		- 0.004(– 0.011, 0.002)	0.168		-0.002 (-0.023,0.021)	0.924
LDL cholesterol (mmol/l)	3225			2868		
Model 1 [a]						
Birth weight (kg)		0.03(-0.00, 0.06)			-0.000 (-0.04, 0.04)	
Model 2 [b]						
MVPA (min/day)		-0.001(-0.002,-0.001)			-0.001(-0.002,-0.000)	
Birth weight (kg)		0.01 (-0.01, 0.03)			-0.01 (-0.05, 0.03)	
Birth weight * MVPA		0.000(-0.001, 0.001)	0.915		-0.000(-0.001,0.000)	0.202
HDL cholesterol (mmol/l)	3230			2868		
Model 1 [a]						
Birth weight (kg)		-0.02 (-0.05, 0.01)			-0.02 (-0.03, 0.00)	
Model 2 [b]						
MVPA (min/day)		0.001 (0.000,0.002)			0.001 (0.000,0.001)	
Birth weight (kg)		0.001 (-0.028, 0.030)			-0.004 (-0.019,0.012)	
Birth weight * MVPA		-0.000(-0.001, 0.001)	0.978		-0.001(-0.001,-0.000)	0.040
Triglycerides (mmol/l)	3207			2866		
Model 1 [a]						
Birth weight (kg)		-0.01 (-0.03, 0.01)			0.003 (-0.007, 0.012)	
Model 2 [b]						
MVPA (min/day)		-0.001(-0.002,-0.000)			-0.001(-0.002,-0.000)	
Birth weight (kg)		-0.03 (-0.05, -0.02)			-0.01 (-0.02, -0.00)	
Birth weight * MVPA		-0.000 (-0.001,0.001)	0.921		0.000 (-0.000, 0.000)	0.839
HOMA– IR (score)	3109			2859		
Model 1 [a]						
Birth weight (kg)		-0.01 (-0.05, 0.03)			0.01 (-0.03, 0.05)	
Model 2 [b]						
MVPA (min/day)		-0.002(-0.003,-0.001)			-0.002(-0.003,-0.001)	
Birth weight (kg)		-0.07 (-0.11, -0.03)			-0.02 (-0.06, 0.00)	
Birth weight * MVPA		0.000 (-0.000, 0.001)	0.689		-0.000 (-0.001,0.001)	0.941

Waist Circumference (cm)	4536			4129		
Model 1 [a]						
MVPA (min/day)		-0.03(-0.05,-0.02)			-0.01(-0.03,0.00)	
Birth weight (kg)		1.90 (1.57, 2.23)			1.55 (0.96, 2.15)	
Birth weight * MVPA		-0.010(-0.018,-0.003)	0.005		-0.001 (-0.017,0.015)	0.896
Clustered risk score	3079			2839		
Model 1 [a]						
Birth weight (kg)		-0.008 (-0.06, 0.04)			-0.003 (-0.04, 0.03)	
Model 2 [b]						
MVPA (min/day)		-0.003(-0.005,-0.002)			-0.003(-0.003,-0.002)	
Birth weight (kg)		-0.08 (-0.12, -0.04)			-0.05 (-0.07, -0.02)	
Birth weight * MVPA		-0.000 (-0.001,0.001)	0.774		0.000 (-0.001, 0.001)	0.948

DBP – diastolic blood pressure; HDL – high-density lipoprotein; HOMA-IR – homeostasis model assessment (HOMA2–IR); LDL – low-density lipoprotein; MVPA – moderate to vigorous physical activity; SBP – systolic blood pressure. Separate models for MVPA and birth weight (Model 2). When interaction term (birth weight * MVPA) is examined, both MVPA and birth weight are also included in the model. [a]Model 1: Adjusted for highest parental education, sex and age. SBP and DBP adjusted for height instead of age. [b]Model 2: Adjusted for Model 1 and waist circumference. [c] Clustered cardiometabolic risk score calculated by summing standardized values for mean arterial blood pressure (MAP), triglycerides, LDL/HDL ratio and HOMA-IR, divided by 4 (number of variables).

A lower birth weight was associated with higher systolic- and diastolic blood pressure, an association which became stronger in magnitude after the inclusion of waist circumference in the model (Table 11). Birth weight was not associated with LDL- or HDL cholesterol, whereas a lower birth weight was associated with higher triglyceride levels, HOMA–IR (children only) and clustered cardiometabolic risk score following adjustments for waist circumference (Table 11). A higher birth weight was associated with a higher waist circumference. Furthermore, introducing the interaction term (birth weight * MVPA) into the model suggested effect modification by MVPA on the associations between birth weight and waist circumference in children and HDL cholesterol in adolescents (Table 11). Figure 13 graphically illustrates the unstandardized regression coefficients and 95% CIs across low and high MVPA (median split) in children (A) and adolescents (B). For waist circumference in children, the association appeared attenuated in the high MVPA group.

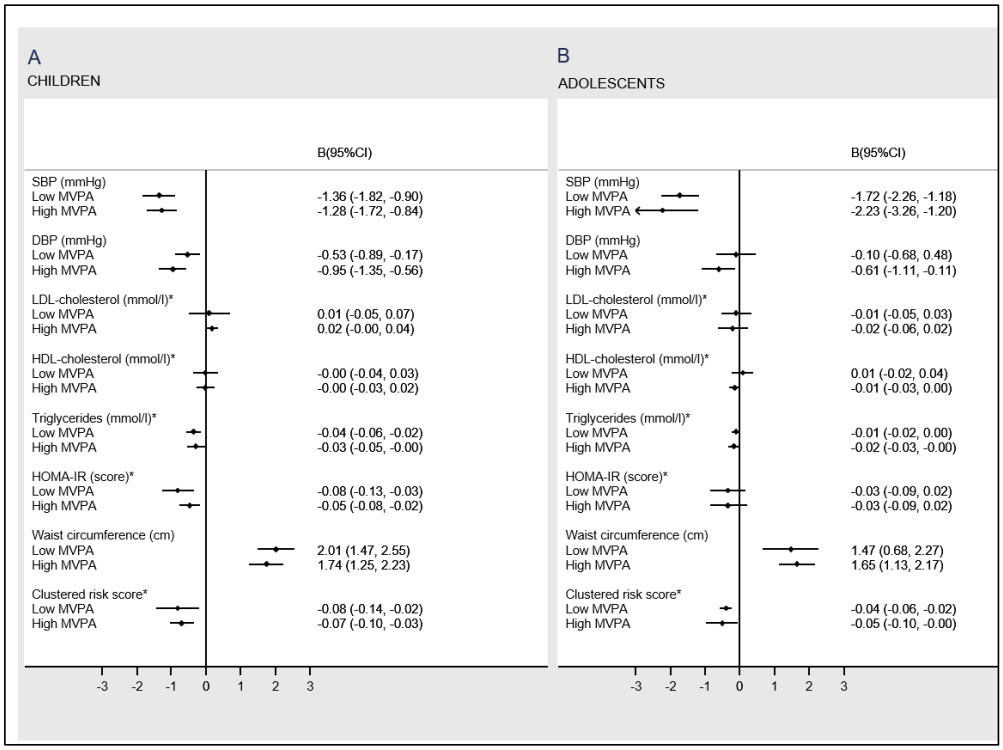

Figure 13: Forest plot of associations between birth weight and cardiometabolic risk factors (unstandardized regression coefficients with 95% CI) by median split in MVPA for children (**A**) and adolescents (**B**) (Paper IV). Adjusted for highest parental education, waist circumference (when not outcome), sex and age. SBP and DBP adjusted for height instead of age. *For illustrative purposes, the plots (not the provided *B*-values and confidence intervals) are multiplied by 10. Children: low MVPA ≤ 58 min/day, high MVPA > 58 min/day. Adolescents: low MVPA ≤ 40 min/day, high MVPA > 40 min/day.

Waist circumference increased by higher birth weight in the 25th, 50th and 75th percentiles of MVPA; however, the increase was slightly steeper in the 25th percentile compared to the 75th percentile of MVPA (Figure 14A). Figure 14B suggests that at the 75th percentile of MVPA the association between birth weight and HDL cholesterol was inverse, whereas it was positive at the 25th percentile of MVPA.

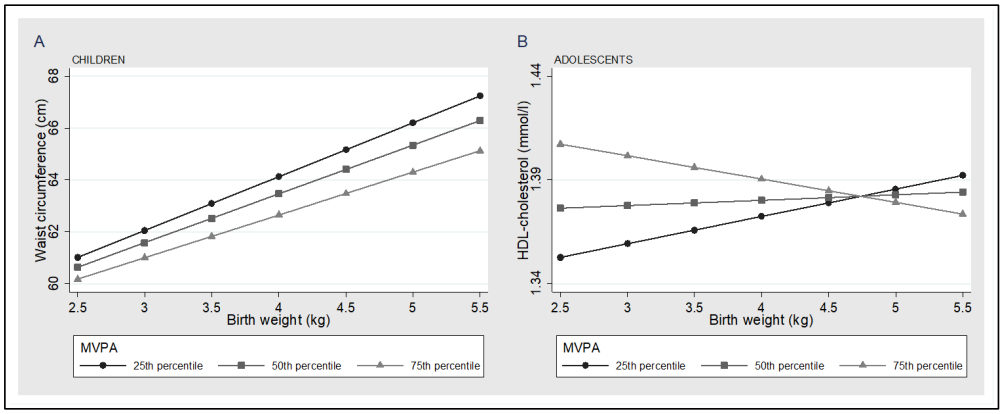

Figure 14: Predicted values of cardiometabolic outcomes (**A**: waist circumference, **B:** HDL cholesterol) across birth weight and the 25th, 50th and 75th percentiles of MVPA in children **(A)** and adolescents **(B)** from regression models with significant interaction between birth weight and MVPA ($p < 0.1$) (Paper IV). Adjusted for highest parental education, sex, age and waist circumference (when not the outcome). HDL – high-density lipoprotein; MVPA – moderate to vigorous physical activity. MVPA children: 25th percentile = 39.6 min/day, 50th percentile = 57.7 min/day, 75th percentile = 80.0 min/day. MVPA adolescents: 25th percentile = 25.3 min/day, 50th percentile = 39.8 min/day, 75th percentile = 58.7 min/day.

Sensitivity analyses suggested that VPA modified the association between birth weight and diastolic blood pressure in children and between birth weight and both LDL cholesterol and triglycerides in adolescents. These associations are illustrated across the 25th, 50th and 75th percentiles of VPA in Figure 15 A–C.

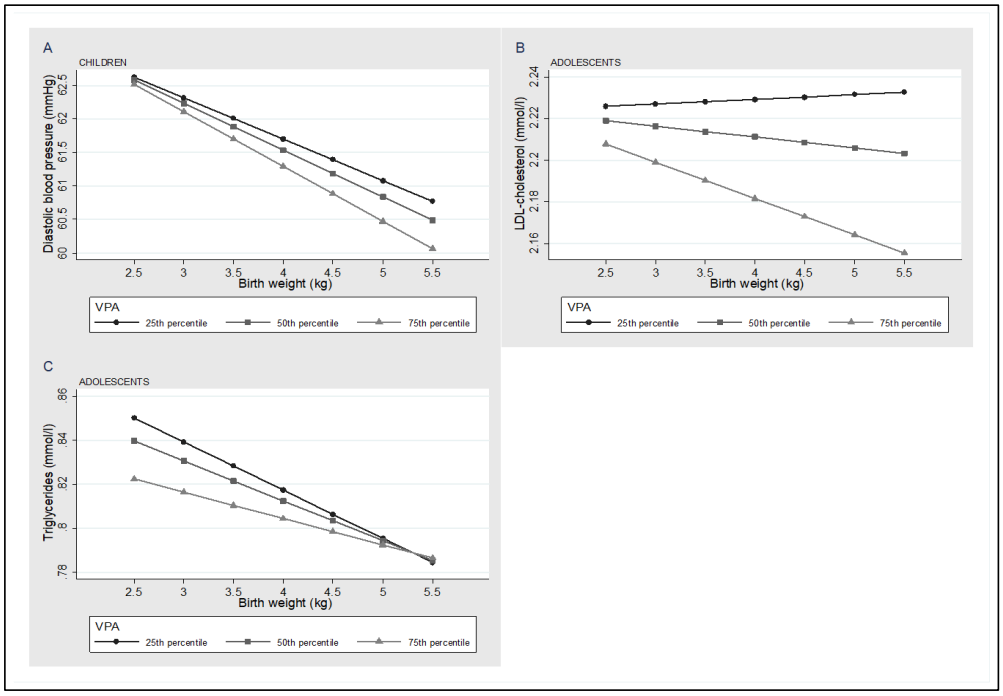

Figure 15: Predicted values of cardiometabolic outcomes (A: diastolic blood pressure, B: LDL cholesterol, C: triglycerides) across birth weight and the 25th, 50th and 75th percentiles of VPA in children (A) and adolescents (B, C) from regression models with significant interaction between birth weight and VPA ($p < 0.1$) (Paper IV). Adjusted for highest parental education, sex, age, (height for diastolic blood pressure) and waist circumference (when not the outcome). HDL – high-density lipoprotein; LDL – low density lipoprotein; MVPA – moderate to vigorous physical activity; VPA – vigorous physical activity. VPA children: 25th percentile = 7.7 min/day, 50th percentile =14.4 min/day, 75th percentile = 24.5min/day. VPA adolescents: 25th percentile = 4.5 min/day, 50th percentile = 10.5 min/day, 75th percentile = 20.3 min/day.

Although the diastolic blood pressure was consistently lower at the 75th percentile compared to the 25th percentile of VPA the association between birth weight and diastolic blood pressure was somewhat stronger in magnitude at the 75th percentile (Figure 15A). Figure 15B illustrates that the association between birth weight and LDL cholesterol in adolescents appeared to be inverse at the 75th percentile, and slightly positive at the 25th percentile of VPA. A somewhat steeper inverse association was observed at the 25th percentile of VPA, compared to 75th percentile, on the association between birth weight and triglycerides in adolescents (Figure 15C).

Figure 16 illustrates the inverse association between birth weight and the clustered cardiometabolic risk score. The magnitude of the associations was similar across levels of MVPA.

Results from sensitivity analyses excluding participants with birth weight < 1.5 kg did not differ from the results including the full birth weight spectrum (data not shown).

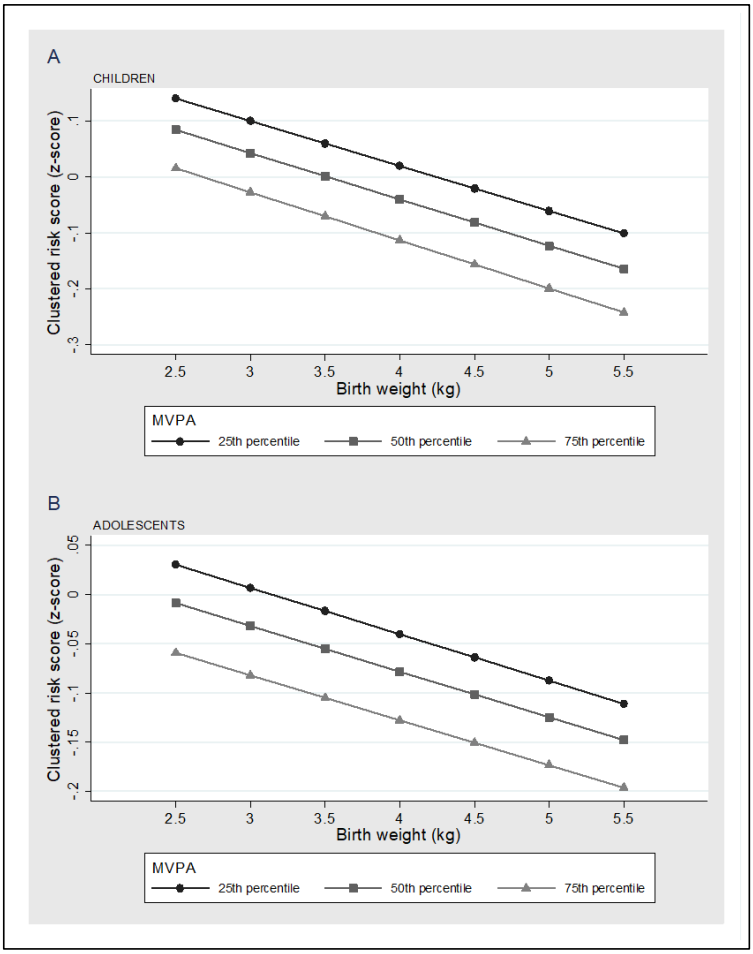

Figure 16: Predicted clustered cardiometabolic risk score across birth weight and 25th, 50th and 75th percentiles of MVPA from regression model with interaction term (birth weight * MVPA) in children (A) and adolescents (B), *p*-value for interaction between birth weight and MVPA; children $p = 0.774$, adolescents $p = 0.948$) (Paper IV). Adjusted for highest parental education, waist circumference, sex and age. Clustered cardiometabolic risk score calculated by summing standardized values for mean arterial blood pressure (MAP), triglycerides, LDL/HDL ratio and HOMA-IR, divided by 4 (number of variables). MVPA – moderate to vigorous physical activity. Children MVPA: 25th percentile = 39.6 min/day, 50th percentile = 57.7 min/day, 75th percentile = 80.0 min/day. Adolescents: 25th percentile = 25.3 min/day, 50th percentile = 39.8 min/day, 75th percentile = 58.7 min/day.

The complete case analyses (Appendix 3) did not differ from the results using MI on missing values, except for a non-significant interaction of MVPA and birth weight on the association with HDL cholesterol in adolescents.

Discussion

This thesis aimed to examine the following two research questions: 1) Are pre-and postnatal factors (maternal pre-pregnancy BMI, birth weight, infant weight gain and motor development) associated with PA in children and adolescents, and 2) Does PA interact with the associations between pre- and postnatal factors (maternal pre-pregnancy BMI, birth weight and infant weight gain) in the development of cardiometabolic health and adiposity in children and adolescents?

Are pre- and postnatal factors associated with physical activity?

Our results indicate that some pre- and postnatal factors may be associated with later PA in children and adolescents. However, maternal pre- pregnancy BMI, birth weight, infant weight gain may influence PA differently in boys and girls and some of the factors are possibly non-linearly associated with PA.

The results suggest that both a low- and a high maternal pre-pregnancy BMI may influence maternally reported LTPA in 7-year-old boys, but not girls. Furthermore, the positive association at the lower end of the maternal pre-pregnancy BMI scale appears to be substantially stronger than the inverse association observed at the higher end of the scale, indicating that a possible effect of a low maternal pre-pregnancy BMI on offspring LTPA may be more detrimental than a high maternal pre-pregnancy BMI. Similar to our results, Tikanmaki et al. (232) observed a quadratic association between maternal pre-pregnancy BMI and self-reported PA in adolescent offspring. The association was observed in both girls and boys, although it was stronger in boys (232). Furthermore, a few studies have examined the linear association between maternal pre-pregnancy BMI and later PA in offspring, and they suggest no association (235, 242), with one exception suggesting an inverse association between maternal pre-pregnancy BMI and device-measured PA in childhood (248). The focus has traditionally been on the linear association or the detrimental effect of mothers being overweight or obese on both PA (235, 242, 248) and health outcomes (67, 252, 318, 319) in offspring. Our results suggest that maternal pre-pregnancy underweight may have a stronger impact on subsequent LTPA, at least in boys, and that studies examining the linear association or dichotomized maternal BMI into normal weight and overweight/obese may have masked a possible non-linear association.

None of the studies included in the systematic review and the meta-analysis, nor studies published after the literature search, support the existence of a linear relationship between birth weight and PA (233-239, 250, 316) (**Paper I**). However, our results suggest that there might be a

non-linear relationship, but only in boys (**Paper II**). We observed that 7-year-old boys born with either a low- or high birth weight may be less physically active than children born closer to the average birth weight for their gestational age (**Paper II**). Similar to when maternal pre-pregnancy BMI was modeled the exposure, the strength of the association was stronger in magnitude at the lower end of the birth weight continuum than at the higher end. A low maternal pre-pregnancy BMI and a low birth weight are respectively a risk factor and a proxy measure for fetal undernutrition, and they may therefore reflect the same physiological mechanisms associated with the development of disease and possibly also lower PA. Nevertheless, mutual adjustments and interaction analysis suggest that these factors may independently be associated with later PA in boys. Alternatively, the birth weight for gestational age z-score may not be an adequate measure to capture all infants who have FGR due to lower maternal pre-pregnancy BMI, as probably not all FGR infants are small for their gestational age.

An inverse U-shaped association has previously been demonstrated using categories of birth weight in a large meta-analysis including more than 40 000 adolescents and adults from 13 Nordic cohort studies (231). In contrast, Tikanmaki et al. (232) observed neither a non-linear, nor a linear, association between birth weight and self-reported PA in adolescents, girls and boys combined. Moreover, in studies using categories of birth weight, the results are inconsistent. Three of the nine studies included in the systematic review reported on categories of birth weight (**Paper I**) (241, 244, 320). Hallal et al. (240) suggested a small difference between these categories and self-reported PA in crude analysis, with those in the higher birth weight category being more active. Gopinath et al. (244) observed that those in the higher birth weight-quartiles reported greater participation in sports at age 12 years, compared to the lowest quartile. This association did not persist at follow-up five years later. Wijtzes et al. (241) found no association between low birth weight (< 2.5kg) and device-measured PA at age 2 years; however, this study may have been limited by few participants in the low birth weight group (n=9). Additional studies, published after the literature search or comprising older age groups, suggest a lower PA level in those born with a low birth weight, compared to higher categories of birth weight (245-247), or no difference (242). Contrary to our results, one study observed an association in girls only (246). The inconsistent results across studies may be due to large differences in methods used; for example, different categorizations of birth weight or the use of data-driven quartiles may impact the results. Furthermore, linear models may mask a possible non-linear association. Our results, in addition to others (246), indicate that sex differences might exist, and they highlight the need for sex-stratified analyses.

Few studies have examined whether infant weight gain influences subsequent PA in childhood or adolescence (**Paper I**). Crude analysis suggests that change in percent body fat from 12 weeks to 1.5 years is inversely associated with PAEE at 1.5 years (317). No association was observed between quartiles of weight gain from 0–1 year and self-reported PA in 10–12-year-olds (240), nor was a linear association found between infant weight gain and device-measured PA in children (238) and adolescents (250). In **Paper II**, we observed a weak positive association between infant weigh gain and LTPA in boys, but not in girls. Smaller sample sizes may explain the discrepancy with our findings (238, 240, 250), although some studies included more precise assessments of PA (238, 250). In the systematic review, we also examined studies reporting on growth in length in infancy and subsequent PA. One study suggested that deviation in length conditioned on previous lengths at 3 months and 1 year were inversely associated with device-measured PA at age 13 years (250). Additional studies are needed to examine the association between early growth and PA and whether the association observed in our sample (**Paper II**) is clinically relevant.

Our results (**Paper II**) further suggest an interaction between birth weight at the higher end of the continuum and infant weight gain on the association with LTPA in boys. Figure 10 indicates small differences in the associations between birth weight z-score and LTPA across infant weight gain. It appears that boys within the normal birth weight range are hardly influenced by infant weight gain in regard to LTPA in childhood, and vice versa – boys with a normal weight gain in infancy is hardly influenced by a higher birth weight. Whereas the associations between birth weight and LTPA are in the opposite directions for boys with slow and rapid weight gain at the higher end of the birth weight continuum. However, these associations are weak and may not be clinically relevant.

We hypothesized that early life risk factors for obesity may influence PA via higher adiposity (**Paper II**). However, none of the associations were affected by BMI at age 3 years, possibly explained by the fact that a low maternal pre-pregnancy BMI and a low birth weight appears to be substantially more strongly associated with LTPA than a high maternal pre-pregnancy BMI and a high birth weight. Salonen et al. (247) observed that the positive association between birth weight and LTPA found in adults became non-significant after inclusion of adult lean body mass (247), indicating that muscle mass may be a possible mediator. Higher PA is associated with a higher lean body mass (209, 321), however, lean body mass may also enhance a higher PA level, as PA is likely more enjoyable with higher muscle strength. If a low maternal pre-pregnancy BMI and a low birth weight influence PA in boys via lower muscle mass, this may provide an

opportunity to target muscle strengthening activities in these predisposed groups as a possible intervention.

The large sample size in **Paper II** may have led to significant results with little clinical importance, and the effect estimates may at first sight appear small and clinically insignificant. For example, a one-unit higher maternal pre-pregnancy BMI at the lower end of the BMI scale was associated with 0.08 more frequent LTPA per week in the 7-year-old boys. This corresponds to nearly half an extra session of MVPA per week in boys whose mothers' pre-pregnancy BMI was 21 kg/m^2 compared to those whose mothers had a pre-pregnancy BMI of 15 kg/m^2. Depending on the length of the session, this may constitute some valuable minutes of MVPA per week. Nevertheless, we have not emphasized the effect estimates in the discussion of the results due to the parentally reported LTPA. As previously discussed, the sporadic nature of children's PA patterns makes precise measurements difficult, and although the validation study indicated that the PA questionnaire may be useful to rank children according to PA level, we do not know whether the questionnaire measures the actual frequency of PA per week. The observed associations should be replicated in future studies with more precise measurements of PA.

Both FGR (278, 279) and greater infant adiposity (280) have been linked to delayed motor development. Another possible, but rarely studied, mechanism of the association between pre- and postnatal factors and subsequent PA may thus be via delayed motor development and subsequent affected childhood motor skills and PA. Elhakeem et al. (245) observed that a low birth weight was associated with both a lower ability in school sports at age 13 and subsequent lower LTPA in adulthood. In the systematic review (**Paper I**), we identified three studies examining the association between motor development and later PA. One study, which may have been limited by a smaller sample size in addition to dichotomizing the exposure variable, did not observe any association (241). In contrast, two larger studies observed weak associations between a higher motor coordination score at 6 months (235) and earlier age at walking while supported (291) on later PA in adolescence. This has also been confirmed in studies published after the literature search in September 2014 (322-324). It has been discussed whether these fairly weak associations are clinically relevant (235). However, Aoyama et al. (322) suggested that for each month later age at onset of walking independently was associated with approximately five min less MVPA per day in childhood. Sanchez et al. (324) suggested a similar five min less MVPA per day in children who in infancy were categorized as having delayed gross motor development. Five min per day constitutes ~35 min of MVPA per week, which could be considered a substantial impact. It is likely that infants and children with earlier motor

development are more active because they find activities easier and more enjoyable. This can in turn facilitate the development of fundamental motor skills, which involve locomotor control (such as walking, running and jumping) and object control (such as overhand throwing, catching and kicking), and hence greater PA across childhood.

Does physical activity modify the associations between pre- and postnatal factors and cardiometabolic health and adiposity?

Our results indicate that some of the associations related to developmental overnutrition and greater adiposity may be attenuated by PA in childhood, whereas those related to developmental undernutrition and cardiometabolic health in childhood and adolescence are likely not. Furthermore, some of these associations might differ between boys and girls (**Paper III** and **Paper IV**).

Developmental overnutrition, childhood adiposity and effect modification by physical activity

A higher maternal pre-pregnancy BMI appears to be more strongly associated with BMI in 9- to 12-year-old boys than in girls (**Paper III**). Furthermore, the association was not modified by MVPA, nor by VPA, in girls. Conversely, in boys, the magnitude of the association appears to be contingent on VPA, suggesting that VPA may mitigate the association between maternal pre-pregnancy BMI and offspring BMI. Although the association between maternal pre-pregnancy BMI and childhood BMI was attenuated in those above the median in VPA, it was not fully eliminated. Therefore, a large amount of VPA seems necessary to mitigate the association. We did not observe an effect modification when fat mass and percent body fat were modeled as the outcomes, possibly explained by a lower sample and hence lower power in these analyses. To my knowledge, no other studies have examined the effect modification of PA on the association between maternal pre-pregnancy BMI and later adiposity in offspring. However, a recent study examined whether self-reported PA in childhood and adolescence modifies the association between intrauterine exposure to GDM and later adiposity (325). In boys and girls combined, the dichotomized PA variable (vigorous PA ≤/> 1 h/d) did not consistently interact with the associations using different measures of adiposity.

We did not observe any associations between birth weight for gestational age and body composition in childhood (**Paper III**). This is similar to the results from Chomtho et al. (326), but contrary to other studies (68, 116). Eriksson et al. (70) observed an association between birth weight and fat mass in boys, but not in girls. Moreover, none of the studies observed an

association between birth weight and measures of fat relative to fat-free or total body mass (68, 70, 116, 326), which is possibly explained by the association between birth weight and a larger size in general, rather than specifically an association with adiposity. We observed a stronger relationship between birth weight and BMI in girls than in boys, which is in agreement with a previous study that suggested a stronger association between birth weight and subsequent risk of obesity in girls than in boys (69). We further observed a positive association between birth weight and waist circumference in girls and boys combined (**Paper IV**). In addition, interaction analyses suggested no effect modification of either MVPA or VPA on the association between birth weight and body composition and BMI in either sex (**Paper III**). In contrast, our results further suggest that MVPA may attenuate the association between higher birth weight and abdominal adiposity in children, but not in adolescents (**Paper IV**). The discrepancy in the findings between **Paper III** and **Paper IV** may be due to different measures of adiposity, a substantially larger sample size and increased power in **Paper IV** or additional control of possible confounding factors in **Paper III** (gestational age, maternal pre-pregnancy BMI and a measure of parental education less prone to measurement error).

A 40-min difference in MVPA, moving from the 25th to the 75th percentile of MVPA in children, provided only a slight mitigation of the association between birth weight and waist circumference, that is the amount of MVPA needed to fully attenuate the association in children is likely substantial, if even possible (**Paper IV**). This result challenges previous observations in smaller and more homogeneous samples, in which no interaction was observed between birth weight and PA on the association with abdominal adiposity (268, 275). In contrast, Boone-Heinonen et al. (275) observed an effect modification of PA on the association between birth weight and subsequent BMI in girls.

We observed a significant interaction by sex, suggesting a stronger association between infant weight gain and subsequent adiposity in boys compared to girls (**Paper III**). Furthermore, there were significant interactions with both MVPA and VPA on the associations between infant weight gain with fat mass and percent body fat in boys. Boys with a rapid infant weight gain may thus be more vulnerable to an inactive lifestyle, and high intensity PA may mitigate the influence of rapid infant weight gain on adiposity measures. Our results revealed that boys who gained weight rapidly in infancy but were in the 75th percentile of VPA in childhood reduced their predicted fat mass by more than 1 kg compared to those with the same rapid infant weight gain but in the 25th percentile of VPA. For the boys below the median for MVPA, an increase in weight z-score of 0.67 is associated with a 1.55 kg higher fat mass ($B = 2.32 \times 0.67$) in childhood. Given the average fat mass in this sample of 10.0 kg (Table 7), an increase of this

magnitude is noteworthy. Neither MVPA nor VPA modified the association between infant weight gain and BMI, which may be explained by the inability of BMI to discriminate between fat mass and fat-free mass, where the latter represents the largest component. The observed effect modification in boys is contrary to the study by Kolle et al. (276) in which no effect modification of MVPA was observed on the association between infant conditional weight gain (0–2 years) and fat mass in 30-year-olds (both sexes combined). It is thus unclear whether the effect modification by MVPA and VPA observed in this study persists into adulthood.

Developmental undernutrition, cardiometabolic health and effect modification by physical activity

We observed that MVPA does not modify the association between a lower birth weight and an adverse cardiometabolic clustered risk score in children and adolescents, nor does it consistently modify the associations with single risk factors (**Paper IV**). In addition, the observed effect modification of MVPA or VPA on diastolic blood pressure, LDL cholesterol, HDL cholesterol and triglycerides may be clinically insignificant.

Our results are in agreement with others suggesting an inverse association between birth weight and both systolic- and diastolic blood pressure (57-59, 61-63), and a similar inverse association between MVPA and systolic- (adolescents only in our result) and diastolic blood pressure (168, 169) (**Paper IV**). None of the previous studies have examined whether MVPA modifies the associations between birth weight and both systolic- and diastolic blood pressure. Our sensitivity analysis suggests that VPA might modify the association between birth weight and diastolic blood pressure in children. Although diastolic blood pressure is consistently lower in the 75th percentile compared to the 25th percentile of VPA, the association between birth weight and diastolic blood pressure is minimally stronger in the most active. This may indicate different responses of VPA across different birth weights (i.e. children with a low birth weight may not respond to VPA to the same extent as children with higher birth weight). This interaction was not observed in adolescents, nor was it observed when systolic blood pressure was modeled the outcome.

Before taking into account an interaction with PA, our results are in agreement with most studies suggesting no association between birth weight and both HDL- and LDL cholesterol in children and adolescents (58, 59, 63, 65, 66) (**Paper IV**). However, MVPA and VPA may modify the association between birth weight and HDL- and LDL cholesterol in adolescents. It appears that a lower birth weight is associated with not only lower LDL cholesterol but also lower HDL cholesterol in the least active, whereas the association is in the opposite direction for more active

adolescents. We further observed an inverse association between birth weight and triglycerides that may be altered by VPA in adolescents; this inverse association is somewhat steeper at the 25th percentile than in the 75th percentile of VPA. Regardless, the predicted differences in LDL cholesterol, HDL cholesterol and triglycerides from a low to a high birth weight across the different levels of MVPA or VPA are small and likely not clinically meaningful. These interactions need to be confirmed in future research to investigate whether they are biased by confounding factors (e.g. pubertal status or nutrition), whether birth weight influences the response of PA on lipid levels in adolescents, and whether these interactions persist into adulthood and may become more clinically important in the development of cardiovascular diseases.

Similar to previous studies (57-59, 61-63), we observed that a lower birth weight is associated with insulin resistance in children, whereas in contrast to previous research (57-59) we did not observe any association between birth weight and insulin resistance in adolescents (**Paper IV**). A few previous studies have examined a possible effect modification of PA on the association between low birth weight and measures of insulin resistance with contradictory results. Findings by Ridgway et al. (268) corroborate ours, suggesting that device-measured PA appears not to modify the association between birth weight and HOMA-IR in children and adolescents. In contrast, Ortega et al. (269), observed a significant interaction between birth weight and device-measured PA for the association between birth weight and HOMA-IR, suggesting that the association was attenuated in the most active adolescents.

Furthermore, MVPA did not appear to modify the association between birth weight and clustered cardiometabolic risk score in the pooled sample in **Paper IV**. However, it is important to note that the clustered cardiometabolic risk score is consistently lower in the more active (75th percentile) compared with the less active (25th percentile) across the birth weight spectrum, and MVPA should thus be considered an important public health strategy in children and adolescents. By testing the statistical interaction between birth weight and MVPA on these associations, we also effectively examined whether MVPA is associated with cardiometabolic health across the birth weight spectrum. More specifically, a lack of observed interaction between birth weight and PA also indicates that children and adolescents born with a low or high birth weight respond to PA in a similar manner to those with a normal birth weight.

Many of the observed associations between birth weight and the included cardiometabolic risk factors emerged following adjustments for waist circumference (**Paper IV**). Therefore, similar to others (327), our results suggest that an inverse direct association exist between birth weight and

both HOMA-IR and triglycerides, and an inverse direct association exist between birth weight and clustered cardiometabolic risk score. Furthermore, the results indicate a positive indirect association of birth weight via higher waist circumference and the similar cardiometabolic risk factors. Further inverse associations were found between birth weight and both systolic- and diastolic blood pressure, in which became stronger in magnitude after adjustment of waist circumference. It is well established that the associations between birth weight and cardiometabolic risk factors in children and adolescents are influenced by adjustments for current body size (57, 61, 63, 327). One may argue that the associations between a low birth weight and cardiometabolic risk factors are outweighed by the positive relationship between birth weight and adiposity measures (61, 328). On the other hand, at any given level of waist circumference, a low birth weight is associated with an adverse cardiometabolic risk profile, which is apparent already in childhood, and increase the risk of cardiovascular diseases later in life (48, 54).

Differences between boys and girls

We observed that pre- and postnatal factors may influence later LTPA (**Paper II**) and measures of adiposity (**Paper III**) differently in boys and girls, where boys appear to be more vulnerable to a non-optimal pre- or postnatal environment. The observed sex differences may be explained by differences in early developmental responses in boys and girls (329). It has been suggested that boys are more vulnerable to adverse conditions in the prenatal environment because the male fetus exhibit faster growth rates compared to the female fetus (330-332). Furthermore, maternal pre-pregnancy obesity has been associated with sex-specific DNA methylation in offspring cord-blood (333).

Although some studies support a stronger association between pre- and postnatal factors and CRF (260), PA (232) and adiposity (117, 334) in boys compared to girls, this is not consistent in all studies. One study suggested a stronger association between birth weight and PA in girls (246), whereas others found no sex difference in CRF (261). Furthermore, Boone-Heinonen et al. (275) suggested an effect modification of PA on the association between birth weight and BMI in girls only. Our findings are also inconclusive; a formal test for interaction revealed no evidence of an interaction with sex on the associations between birth weight and cardiometabolic risk factors (**Paper IV**), and we observed a stronger association between birth weight and childhood BMI in girls compared to boys (**Paper III**).

Methodological considerations

Several methodological considerations are important to discuss in the interpretation of the results from the four included papers. In the following section, I discuss different sources of bias (internal validity), the generalizability of the results (external validity) and some additional considerations.

Internal validity

Different sources of bias (systematic error) may afflict the internal validity of epidemiological studies. Most of these can be classified into three general categories: selection bias, information bias and confounding (335).

Selection bias

In cohort studies (**Paper I–Paper IV**) and cross-sectional studies (**Paper I** and **Paper IV**) selection bias can manifest from procedures used to select the study sample (eligibility criteria) or from factors that influence study participation (self-selection). In cohort studies an additional factor can be differential loss to follow-up. Participation, or factors related to participation, can lead to selection bias if they are colliders on an open path between the exposure and outcome, that is, both the exposure and the outcome affect the selection either directly or via other factors (335, 336). Selection bias can lead to both an under- and overestimation of the effect (335). An evaluation of self-selection in the MoBa (**Paper II**) has previously been done by comparing MoBa participants to all women who gave birth in Norway during the inclusion period using information from the MBRN. The evaluation demonstrated that women in the youngest age group (<25 years), those living alone, mothers with more than two previous births, women with previous still births, maternal smokers, low birth weight (<2.5kg) and neonatal death were underrepresented in the MoBa, whereas multivitamin and folic acid supplement users were over-represented (337). Further differences exist in several variables between participants lost to follow-up and those included in the analyses (Appendix 5 – Table 1) (**Paper II**). In the sub-cohort (**Paper III** and **Paper IV**), the participation rate was low (Figure 4). Due to confidentiality of the study participants, we were only provided with summary statistics about those who participated and those who declined participation on selected variables using information from previously answered questionnaires and the MBRN. Table 2 in Appendix 5 suggests that there was little difference in these selected variables between those who accepted and those who declined participation in the sub-cohort of the MoBa. Information about differential loss to follow-up in the studies included in the systematic review (**Paper I**) and the

pooled analyses (**Paper IV**) are available elsewhere (233, 235, 236, 239-241, 244, 250, 291, 296-305, 316, 317). The important question is whether the differences lead to selection bias. In the previously mentioned evaluation of selection bias in the MoBa, the observed differences led to biased prevalence estimates but did not influence the estimates of a number of examined exposure-outcome associations (337). In contrast, another evaluation in the MoBa revealed that self-selection and loss to follow-up can cause biased exposure-outcome estimates when examining risk factors for ADHD (336). Nevertheless, selection bias is dependent on the specific exposure and outcome of interest and may not be transmissible to our results. We do not know of any factors that could lead to selection bias on the associations examined in **Paper I**–**Paper IV**. However, due to self-selection and differential loss to follow-up, we cannot completely exclude the possibility that our results are afflicted by selection bias.

Publication bias is a specific form of selection bias that is a major concern in systematic reviews and meta-analyses. Publication bias is the systematic failure to report or publish certain types of results – typically those that are non-significant or undesirable (335). We did not check for publication bias (e.g. via funnel plot) in the systematic review and meta-analysis (**Paper I**), but we generally identified few publications that make evaluation of publication bias difficult. However, it is unknown whether there are any unpublished results showing non-significant associations.

Information bias

Another possible source of bias in epidemiological studies can be caused by measurement error in the obtained information, often referred to as information bias (335). Measurement error can be classified as either a *differential measurement error* or a *nondifferential measurement error*. A differential measurement error occurs when the degree or direction of the measurement error is dependent on the values of the other variables in the analysis. The two key variables to consider in regard to information bias are the exposure variable for the outcome, and vice versa for the outcome variable (335). In cohort studies (**Paper I–Paper IV)**, where information is obtained prospectively at regular intervals, a possible measurement error is most likely to be nondifferential. That is, the measurement error of the exposure is unrelated to the values of the outcome, and vice versa for the outcome variable. Some exception exists, such as if the exposure leads to symptoms that increase the risk of the diagnosis of the outcome variable; however, this was not a concern in our analyses. Differential measurement errors produce biased estimates that could be either under- or overestimated, whereas nondifferential measurement errors can

produce biased estimates that are usually – especially with continuous variables – biased towards the null, that is, underestimating the association (335, 338).

In the systematic review (**Paper I**) and pooled analyses (**Paper IV),** some of the studies were cross-sectional studies with retrospective parental assessed birth weight (233, 244, 296-298, 301, 304, 305). This can potentially lead to differential measurement errors in exposure in the form of recall bias; for example, if a child demonstrates health constraints (e.g. a high blood pressure or insulin resistance) or a low PA level that is known to be related to a low birth weight, the parents are more likely to remember and recall the birth weight more accurately. However, few, if any, participants in these age groups would manifest visible signs of disease due to a low birth weight, and the impact of this potential information bias is probably not of great concern in our analyses (**Paper I** and **Paper IV**). On the other hand, retrospective assessed birth weight could more likely result in nondifferential measurement errors, although studies comparing retrospectively parentally reported birth weight with measured birth weight demonstrate high agreement (339), also across birth weight groups (340, 341). Nevertheless, birth weight is used as a proxy measure of fetal under- or overnutrition and, as previously discussed, may therefore produce nondifferential measurement errors even when accurately measured by, for instance, midwives (**Paper I–Paper IV**), especially when birth weight is not standardized by gestational age (**Paper IV**).

Furthermore, self-report is generally more prone to measurement errors than variables measured by trained personnel, as it may be affected either by the participant's ability to accurately recall the variable of interest or by his or her beliefs about the socially desirable answer. In addition to self-reported birth weight, we have several other self-reported exposures and/or outcomes in our analyses, including motor development (**Paper I**), child's weight and height (**Paper II** and **Paper III**), maternal pre-pregnancy weight and height (**Paper II** and **Paper III**) and LTPA (**Paper II**).

A study comparing self-reported BMI to measured BMI in the adult population suggests that self-reported BMI values tend to be overestimated at the low end of the BMI scale (<22 kg/m^2) and underestimated at the high end (>28 kg/m^2) (342) (**Paper II** and **Paper III**). The comparisons further indicate that more than 80% of the deviation between self-reported BMI and measured BMI does not exceed values within ±2 BMI units (342). The measurement error will thus be smaller when the self-reported BMI values are kept in their continuous form rather than categorized. The mothers in the MoBa were asked to report their children's weight and height using information from their children's health record cards, where weight and height have

been measured by nurses (**Paper II** and **Paper III**). However, we do not know whether the mothers have used this information when reporting the data via the questionnaire. In a validation study, the correlation between BMI at age 3 years obtained from the MoBa questionnaire and the BMI obtained from measurements was high (Pearson's r= 0.86, 95% CI = 0.81, 0.90) (343).

In addition to susceptibility to measurement error, the proxy reported PA questionnaire in **Paper II** is also limited by the assessment of only one domain of PA (namely, LTPA) and because it only captured frequency per week and not, for example, the duration of each session. Therefore, as previously discussed, we have not emphasized the effect estimates in the discussion of the results.

Although we considered device-measured PA, measured body composition via DXA and cardiometabolic risk factors and abdominal adiposity measured by trained personnel important strengths of **Paper III** and **Paper IV**, these methods are also prone to measurement error (198). Activity counts from Actigraph accelerometers (**Paper I–Paper IV**) have repeatedly been shown to significantly correlate with total PAEE derived from DLW in free-living children and adolescents (164), and the correlation is of moderate strength (165). Nevertheless, accelerometers underestimate activities with little vertical acceleration of the hip, such as bicycling and upper-body strength training, ambulatory activities carrying extra weight and water activities due to removal of the monitor (**Paper I**, **Paper III** and **Paper IV**). Furthermore, the use of a 60-sec epoch length may have led to underestimation of time spent in MVPA and VPA (**Paper I** and **Paper IV**) (344). Additional researcher-dependent choices may impact the PA level measured by accelerometers, including the choice of intensity cut-points, the valid day criterion (hours per day of measurement), the number of valid days required to reflect a participant's habitual PA level and the definition of non-wear time. In **Paper III**, we included all participants with at least one valid day of PA measurement. This one day may not be representative of the participant's usual PA level and may have led to increased measurement error, as the reliability increases with an increasing number of valid days and hours per day of measurements (345). However, in general, a strength of the accelerometer-assessed PA in our samples was the high compliance with wearing the monitor.

Confounding

Confounding is a central issue in epidemiological studies and is a factor that distorts the association between an exposure and an outcome. This implies that the effect of the exposure variable is biased due to a common cause of the exposure and the outcome. Confounding factors could produce biased estimates that could be either under- or overestimated (335).

We adjusted our analyses for factors that might have confounded the associations (**Papers II–Paper IV**). Due to the relatively small sample size, which limited our possibility to adjust for a wide range of possible confounding factors, we considered the results in **Paper III** to be explorative, aiming to suggest avenues for future research. Although we adjusted for the factors that we identified as being most important, the results may be biased by a lack of adjustments for additional maternal characteristics that possibly influence the pre- and postnatal factors (maternal pre-pregnancy BMI, birth weight and infant weight gain) and greater adiposity in the offspring. However, this is probably of greatest issue when maternal pre-pregnancy BMI is modeled as the exposure variable, as both birth weight and infant weight gain are adjusted for maternal pre-pregnancy BMI, which may serve as a surrogate confounder for many of the maternal characteristics associated with offspring adiposity. A strength of the analyses in **Paper II** is the large sample size, which allowed us to stratify the analyses by sex and adjust for several possible confounding factors, thereby increasing the internal validity of the results.

The observed associations may also be influenced by unmeasured confounding. In the ICAD project, few prenatal factors are available in the pooled dataset, which limited our ability to make additional adjustments (**Paper IV**). Genotype is another possible unmeasured confounding variable (**Paper I–Paper IV**). As previously discussed, the association between maternal pre-pregnancy BMI and offspring adiposity (**Paper III**) as well as possible offspring LTPA (**Paper II**) may be confounded by shared maternal-offspring genes and/or familiar lifestyle. Furthermore, some studies suggest that the association between birth weight and adult cardiometabolic disease is in part the result of shared genetic effects (89, 90) (**Paper IV**). The ability to control for confounding in the analyses could also be hampered even when the variable is adjusted for, for example due to measurement error in the confounding variable. This is known as residual confounding; that is, confounding left after control of the available confounder measurements (335). The harmonized variable parental education in **Paper IV**, may have produced residual confounding because the highest category (any post-compulsory education) combines persons with vastly different education levels (ranging from completion of high school to completion of college or university).

External validity

The previously discussed differences between the study population and the target population due to self-selection and loss to follow-up may not influence the internal validity; nevertheless, it may threaten the generalizability of the results to other groups. Therefore, generalization of the results to groups other than the group being studied (**Paper I–Paper IV**) should be done with

caution. The generalizability of the results is generally a question of whether any factors that distinguish the studied sample from another sample (to which we want to generalize the results) somehow modify the exposure–outcome association of interest (335). For example, if we had only studied boys in **Paper II** and **Paper III**, we could have wrongly generalized the results to girls.

When evaluating the generalizability of the results, an important factor is to consider whether any basic physiological differences exist between the studied group and an unstudied group that can potentially influence the association of interest (335). For example, there might be physiological differences between age-groups, and our result may not be correctly generalized to the adult population.

Other methodological considerations

Effect modification

The concept of interaction is based on the idea that the effect of one exposure on an outcome may depend on the presence of one or more other conditions (335). We evaluated interaction by testing the significance of product terms in the statistical model (**Paper II–Paper IV**) or by stratified analyses (**Paper IV** – children/adolescents). Statistical interaction can be examined both on an additive and a multiplicative scale. In our analyses, we examined interaction on the risk-difference scale (additive scale) by using linear regression models. More specifically, we examined whether the combined effect of two risk factors (pre- and postnatal factors and low PA) deviate from the effect of simply adding together the separate risks. This means that in the case of a significant interaction, the combined effect of two factors is more or less than the sum of their separate effects (273, 335).

By testing the statistical interaction between the pre- and postnatal factors and MVPA on cardiometabolic health and adiposity in children and adolescents, we also effectively examined whether MVPA/VPA is associated with cardiometabolic health/adiposity across the exposures (**Paper III** and **Paper IV**). We focused on whether PA modifies the associations between the pre- and postnatal factors on later cardiometabolic health and adiposity. However, the question of interest could also be turned around using the same statistical interaction, namely, whether the pre- and postnatal factors modify the association between PA and cardiometabolic risk factors/adiposity.

Covariates

A mediator is an intermediate on the pathway between the exposure and outcome (346). In **Paper II**, we hypothesized that the effect of maternal pre-pregnancy BMI, birth weight and infant weight gain on LTPA in children may be mediated by the child's BMI. We therefore examined the controlled direct effect by adjusting our analyses for child BMI at age 3 years.

Other possible mediators were included in the regression models because we wanted to examine the direct association, not the association mediated via the possible mediators (total association). The possible mediators that were controlled for include birth weight (**Paper II** and **Paper III**), infant weight gain (**Paper II** and **Paper III**) and waist circumference (**Paper IV**).

Other potentially non-confounding covariates were included in the model because they can explain some of the variability in the outcome variable. Including these variables in the model may therefore improve the precision of the estimates in linear regression models (346, 347). The included covariates were height (**Paper III**–**Paper IV**) and age (**Paper IV**).

Multiple imputation

Missing data are an unavoidable problem in epidemiological research (348, 349). This is especially relevant for regression analyses, as a small number of missing values in several variables can add up to a substantial proportion of missing participants in the finally adjusted regression model. An example of this is the high proportion of participants with missing data in **Paper II**. Although the number of missing in single variables was modest and ranged from 0–18% in the models without controlling for BMI at age 3 years (Appendix 1), the total proportion of participants with one or more of the included variables missing was 45%. Complete case analyses may therefore lead to substantial loss of power, less precise estimates or biased estimates, depending on the nature of the missing observations (348, 349). Among the participants included in our analyses (**Paper II–Paper IV**) we observed differences between those with missing values and those with complete data (Appendix 1–3). We therefore assumed that the data were missing at random (MAR), given the observed variables included in the imputation model. We used MI by chained equation which allowed us to generate imputations based on a set of imputation models – linear regression or predictive mean matching for continuous variables, ordered logistic regression for ordinal variables and logistic regression for binary variables. The results from the imputed dataset did not differ greatly from the complete case analyses (**Paper II–Paper IV**). However, the imputed datasets are only as good as our imputation model, and the MAR-assumption does not hold if a variable that influences missing

data is not included in the imputation model (348). Therefore, we cannot exclude the possibility that both the complete case analyses and the MI analyses might be biased by unmeasured factors.

In **Paper II** and **Paper III,** we imputed values on missing data in the exposure variables, whereas in **Paper IV**, we excluded all participants with missing data on birth weight prior to the analyses and MI. Missing data in the exposure do not cause bias in complete case analyses if the reasons for the missing data are unrelated to the outcome. However, exclusion of these participants may impact the precision and power (348). Ensuring more powerful analyses was particularly important in **Paper III**.

Quality assessment in systematic review and meta-analysis

Poor reporting of systematic reviews weakens their value, and adhering to the PRISMA Statement checklist is thus recommended when reporting a systematic review (350). A limitation of our systematic review and meta-analysis (**Paper I**) is that we did not specifically follow this checklist. The list comprises of 27 items, and although we adhered to most of them, we did not include any assessment of risk of bias in the retrieved publications (311, 350). The methodological quality of a systematic review is no better than the studies included in the review, and the performed QA did not properly evaluate the individual publication's susceptibility to risk of bias (selection bias, information bias and confounding) (311). Although many of the included studies were rated relatively high in quality, several of them had limitations that may have impacted the internal validity of the results, for example a lack of control of possible confounding factors (233, 316, 317) or assessment methods prone to measurement errors (240, 241, 244, 291). The standardized checklist included some evaluations of risk of bias (e.g. "controlled for confounding"). However, since each score was weighted equally in the summary score, more important items may have been underrated. A summary QA score may hence not reflect the most important considerations for the specific research question, and it is argued that a "one-size-fits-all" approach for assessing the methodological quality and risk of bias in systematic reviews is unlikely (311).

Conclusions

Based on the results of the four papers included in this doctoral thesis, the following conclusions can be drawn:

A linear association is unlikely to exist between birth weight and PA in children and adolescents. However, maternal pre-pregnancy BMI and birth weight may be non-linearly associated with PA in boys. Moreover, maternal pre-pregnancy BMI and birth weight are positively associated with LTPA at the lower ends of the pre-pregnancy BMI and birth weight continuums in boys, while the observed inverse associations at the higher ends of these continuums in boys may not be clinically important. In addition, infant weight gain may be weakly positively associated with PA in childhood. None of these associations appear to be mediated by childhood BMI. Furthermore, we observed no associations between maternal pre-pregnancy BMI, birth weight and infant weight gain on subsequent PA in girls. Moreover, earlier motor development may be associated with higher PA in children and adolescents.

The associations between maternal pre-pregnancy BMI and rapid infant weight gain with fat mass and BMI in childhood may be modified and attenuated by higher MVPA and VPA in boys, but not in girls. We observed no association between birth weight for gestational age and childhood body composition, nor were they modified by the level of MVPA or VPA. However, MVPA may, to some degree, attenuate the association between high birth weight and abdominal adiposity in children. Moreover, MVPA does not appear to modify the inverse association between birth weight and clustered cardiometabolic risk in children and adolescents, nor to consistently modify the associations between birth weight and the single cardiometabolic risk factors. It is however promising that higher levels of MVPA is consistently associated with a more favorable cardiometabolic risk profile across the birth weight spectrum.

More studies are warranted before firm conclusions can be drawn.

Implications and future perspectives

Pre- and postnatal factors may be associated with later PA in boys, but not in girls. The strongest influence appears to be at the lower end of the maternal pre-pregnancy BMI and birth weight continuums, indicating that fetal undernutrition may undesirably impact the PA level in boys. These results should be replicated in studies with a more precise measurement of PA. This more precise measurement is also important to evaluate the clinical importance of the findings. A subsequent step would be to examine whether PA, at least partly, mediates the association between pre- and postnatal factors and cardiometabolic health.

Due to the strong evidence of the beneficial health effects of PA, research is necessary to develop successful strategies to increase the PA level in boys who are possibly more prone to a lower PA level because of fetal undernutrition. This can be either through prenatal care to ensure optimal growth of the fetus or through PA interventions specifically aimed at targeting these groups of children and adolescents. Additional research on possible underlying mechanisms, for example whether the associations are mediated by muscle mass or muscle quality, may contribute important knowledge to the establishment of efficacious PA interventions. The observed sex differences should also be confirmed in future research before firm conclusions are drawn about different responses in boys and girls.

Infants with delayed motor development may be more prone to a lower PA level in childhood and adolescence. The clinical importance of delayed motor development should be further examined in studies with precise measurements of both the exposure and outcome variables. The extent to which motor development is substantially modifiable to have a meaningful impact on subsequent PA is uncertain, and an important question to explore in future research is whether children whose motor development was delayed in infancy could benefit from targeted motor skill training and hence a possible long-term effect on PA level.

From a public health perspective, it is promising that the greater adiposity accompanying a high maternal pre-pregnancy BMI and a rapid infant weight gain, and the greater abdominal adiposity accompanying a higher birth weight, appears to be slightly modifiable and attenuated by high-intensity PA, at least in boys. Future research should replicate the findings in large samples with additional control of possible confounding factors, examine whether the findings persist into adulthood and further examine the possible sex-dependent associations.

Higher levels of MVPA are associated with a more favorable cardiometabolic risk profile across the birth weight spectrum. Therefore, PA may be considered an important public health strategy

in all children and adolescents, but particularly those who are born with a low birth weight and who are hence prone to a clustering of cardiometabolic risk factors. Additional research should further explore some of the observed interactions (e.g. the interaction between birth weight and PA on lipids in adolescents) and further evaluate the clinical implications. Future research should also examine the impact of PA on the risk of cardiovascular diseases and mortality in adulthood across the birth weight continuum.

Finally, this thesis is limited to a few pre- and postnatal factors. Including additional factors in future studies would thus be beneficial.

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PAPER II

Pre- and postnatal factors and physical activity in childhood: The Norwegian Mother, Father and Child Cohort study

Guro Pauck Bernhardsen[1], Trine Stensrud[1], Wenche Nystad[2] and Ulf Ekelund[12]

[1]Norwegian School of Sports Sciences, Department of Sport Medicine, Oslo Norway; [2]Norwegian Institute of Public Health, Department of Non-communicable Diseases, Oslo, Norway.

Author information:

Author 1 (corresponding author):

Name: Guro Pauck Bernhardsen

Postal address:
Norwegian School of Sport Sciences, Guro Pauck Bernhardsen
P.O box 4014, Ullevål Stadion
0806 Oslo, Norway

Work phone: +47 23262293
e-mail: g.p.bernhardsen@nih.no

Abstract

Background: Few studies have examined the possibility that pre- and postnatal factors (maternal pre-pregnancy BMI, birth weight and infant weight gain) may be nonlinearly associated with later physical activity.

Methods: We used data from the Norwegian Mother, Father and Child Cohort study (MoBa) and the Medical Birth Registry of Norway (MBRN), including 48 672 children with available data on leisure time physical activity (LTPA) at child's age 7 years. We used restricted cubic- and linear splines or linear regression to examine the associations between maternal pre-pregnancy BMI, birth weight for gestational age and infant weight gain from birth to 1 year with LTPA (frequency/week) in 7-year-old children.

Results: We observed no associations between maternal pre-pregnancy BMI, birth weight and infant weight gain on subsequent LTPA in girls. Maternal pre-pregnancy BMI and birth weight may be non-linearly associated with LTPA in 7-year-old boys. The B (95%CI) for maternal pre-pregnancy BMI ≤ and > 21kg/m^2 were 0.08(0.04, -0.12) and -0.009 (-0.0017, -0.000), respectively for LTPA in boys. The B(95%CI) for birth weight (standardized for sex and gestational age) ≤ and > -1 z-score were 0.26(0.11,0.41) and -0.04(-0.07, -0.002), respectively for LTPA in boys. Infant weight gain (change in weight z-score from birth to 1year) may be weakly linearly associated with LTPA in boys, B(95%CI)=0.05(0.02, 0.08).

Conclusion: Pre- and postnatal factors may influence LTPA in childhood differently in boys and girls. Maternal pre-pregnancy BMI and birth weight are positively associated to LTPA at the lower ends of the pre-pregnancy BMI and birth weight continuums in boys. The negative associations at the higher ends of the continuums and the positive association between infant weight gain and LTPA in boys, may not be clinically important and needs further replication.

Keywords: Physical activity, determinants, DOHaD, birth weight, maternal pre-pregnancy BMI, infant weight gain, MoBa

Background

Environmental factors during fetal life, infancy and early childhood impact development of cardiovascular diseases and risk of obesity later in life (1-5). Early signs of disease are apparent already in childhood, in which a low- or high birth weight, high maternal pre-pregnancy body mass index (BMI) and a rapid infant weight gain are associated with obesity and cardiometabolic risk factors (6-12). Fewer studies have examined the possibility that pre- and postnatal factors may also influence subsequent health behaviors, e.g. participation in physical activity. The majority of previous studies have examined the association between birth weight and subsequent physical activity. Although two systematic reviews (13, 14) concluded that birth weight is unlikely to impact subsequent physical activity, most studies have examined only the linear association. However, it is likely that both a low- and high birth weight is associated with lower physical activity as both high- and low birth weight are linked to subsequent development of obesity and cardiovascular diseases (3, 4, 7). An inverse U-shaped relationship was suggested in a previous meta-analysis including 13 cohort-studies in adolescents and adults (15). Furthermore, it is inconclusive evidence whether maternal pre-pregnancy BMI and infant weight gain influence later participation in physical activity (16-23).

Early life risk factors for obesity may influence physical activity via adiposity, given the possibility of a bi-directional association between adiposity and physical activity (24-26). Specifically, it is likely that children prone to higher adiposity could refrain from engaging in physical activities with high intensities, and thereby entering a vicious circle with inactivity and excess adiposity. Indeed, it has been suggested that abdominal adiposity (waist circumference) mediated the association between birth weight and sedentary time (27).

Therefore, this study aimed to examine the associations between maternal pre-pregnancy BMI, birth weight and infant weight gain on leisure time physical activity (LTPA) in 7-year-old Norwegian

children, and to examine whether the possible associations are nonlinear. A secondary aim is to examine whether a possible association is mediated by child's BMI at age 3-years.

Methods

Study design and participants

We used data from The Norwegian Mother, Father and Child Cohort Study (MoBa). MoBa is a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health(28). All women attending a routine ultrasound examination at 17-20 weeks gestation at a Norwegian maternity unit (50 units out of 52 participated) between 1999 and 2008 were invited to participate. The women consented to participation in 41% of the pregnancies. The cohort now includes 114 500 children, 95 200 mothers and 75 200 fathers. The current study is based on version 10 of the quality-assured data files released for research in June 2017.

For the current study, we included children with available data on LTPA at child's age 7 years. Due to a different prenatal environment we excluded children from multiple births, and due to associated health implications, we excluded children born extremely or very preterm (<32 completed weeks of gestation). Mothers could participate with more than one child, and the total study sample comprised of 48 672 children from 37 261 mothers (Figure 1). The LTPA-questionnaire was included in the 2nd version of the 7-year questionnaire, and our analyses therefore includes children born in the period between 2002 and 2009. Information about participants lost to follow-up is provided in an additional file (Additional file 1).

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data protection agency and the approval from The Regional Committee for Medical Research Ethics. The Norwegian Health Registry Act currently regulates the MoBa-cohort. The Regional Committee for Medical and Health Research Ethics (South-East) has approved the current study.

Measurements

Children were followed up regularly with maternally reported questionnaires and linked to the Medical Birth registry of Norway (MBRN). MBRN is a national health registry containing information about all births in Norway.

Exposures

The mothers reported their height and pre-pregnancy weight in gestational week 18. We calculated maternal pre-pregnancy BMI by dividing weight by height squared (kg/m^2).

We obtained birth weight and gestational age (weeks) at birth from MBRN. Gestational age was estimated by ultrasound. In a few cases (<2%) gestational age from ultrasound was not available, and gestational age was based on the first day of the last menstrual period. We standardized birth weight by calculating sex- and gestational age-specific z-scores.

The mothers used information from their child's health record, where weight and length are measured by nurses, and reported their child's weight at 1-year via questionnaire. We calculated infant weight gain as change in sex-specific z-scores from birth to 1 year.

Outcome - Physical activity questionnaire and validation study

The mothers reported the number of times and how many hours per week their child participated in moderate to vigorous physical activity (MVPA) ("...the child becomes short of breath or sweaty") outside of school-hours. Hours per week were categorized in the questionnaire into “1-2 hours per week", "3-4 hours per week", "5-7 hours per week", "8-10 hours per week" and "11 hours or more per week" during both summer and winter. We recoded these categories to 1.5, 3.5, 6, 9 and 11 hours per week, respectively, and calculated the average for summer and winter combined.

We compared the LTPA-questionnaire with accelerometer assessed physical activity, in an independent convenient sample of 82 mother- and child pairs. The children wore an Actigraph accelerometer (Actigraph GT3X+; LLC, Pensacola, Florida, USA) around the waist for seven

consecutive days, removing it only when sleeping or during water-based activities. We used ActiLife (version 6.13.3) to process the data and used an epoch length of 10 seconds. We excluded overnight activity (00:00-05:59) from our analyses and defined non-wear time as 20 minutes or more of consecutive zero counts. We considered a day valid if the participant wore the monitor for at least 480 minutes, and participants with at least three valid days of measurement were included in the analysis. We defined MVPA as minutes spent in counts per minute (cpm) ≥2296, in accordance with cut-points developed by Evenson et al. (29, 30). The mothers received and answered the LTPA-questionnaire twice by e-mail, first time approximately one week after the children finished using the accelerometer and the second time 14 days after they return the first questionnaire. We removed MVPA recorded by the accelerometer during school hours (08:00-13:00) before comparison with the questionnaire data. Of the 82 subjects included, 77 (53% girls) completed three or more days of activity monitoring and answered the questionnaire. The mothers' and children's mean age (sd) were 40.4 (4.3) years and 7.9 (0.7) years, respectively. Mean (SD) BMI in the children were 16.3 (1.5) m/kg^2. The mothers reported on average (SD) children's participation in LTPA 4.5 (1.8) and 6.0 (2.4) times and hours per week, respectively. On average (SD) the mothers answered the first questionnaire 14.4 (6.5) days after their child finished wearing the accelerometer, and the second questionnaire 19.5 (7.0) days after the first questionnaire. The partial Pearson correlation coefficients, adjusting for child's sex and BMI (kg/m^2), between accelerometer assessed LTPA and the questionnaire were r=0.32 (p=0.0056) and r=0.09 (p=0.46) for frequency and hours per week, respectively. The partial Pearson correlation coefficients, using the same adjustments, between the first and second questionnaire were r=0.69 (p=0.000) and r=0.69 (p=0.000) for frequency and hours per week, respectively. The absolute agreement between the first and second questionnaire were ICC (intraclass correlation coefficient)=0.71 (p=0.000) and ICC=0.69 (p=0.000) for frequency and hours per week, respectively.

The results of this validation study suggested that the question about frequency of LTPA participation per week can be used for ranking children according to level of LTPA.

Mediator

A secondary aim of this study was to examine whether the possible associations between the exposures and LTPA were mediated by BMI at age 3 years. Weight and height at age 3 years were maternally reported using information from the child's health record, via questionnaire. We calculated BMI by dividing weight by height squared (kg/m^2) and included BMI at age 3 years in the model as a possible mediator.

Confounders

Potential confounders include factors that might influence the exposure (maternal pre-pregnancy BMI, birth weight or infant weight gain) and LTPA in childhood and are included in the statistical models depending on the exposure. We obtained child's sex (boy/girl), maternal age at the time of delivery (years), maternal parity at the time of delivery (0/1/2/3/≥4), and maternal smoking during pregnancy (yes/no) from the MBRN. We obtained information about completed and ongoing maternal and paternal education via questionnaire in gestational week 17-20 (<high school/high school/ college or university 1-4 years/>4 years of college or university). If the mother reported ongoing education on herself or the father, this education level was used instead of completed (7.6% and 5.6 % of the mothers and father reported ongoing education, respectively). We obtained breastfeeding from birth to 4 months (exclusive/partial/none) via the maternally reported questionnaire at child's age 6 months.

Statistical analyses

Descriptive statistics of participants are presented as mean and standard deviation (SD), median and 25^{th} and 75^{th} percentile or number of participants and proportions, depending on the data. We tested for differences between boys and girls using independent samples t-tests, Mann-Whitney two-sample test and chi squared statistics

A formal interaction test showed that some of the associations may differ between boys and girls, and we have therefore stratified all analyses by sex.

We visually assessed the dose-response relationships between the exposures and LTPA in the adjusted models (without possible mediators) using fractional polynomials and estimated the approximate number and placement of knots with restricted cubic- and linear splines. We tested multiple placements of knots and compared the fits by Akaike information criterions (AICs). In cases were the best fit were non-linear, we tested deviation from the linear model by likelihood-ratio test. The models with the best fit included linear splines (maternal pre-pregnancy BMI and birth weight (boys)) and linear (birth weight (girls) and infant weight gain) models. The placements of the knots are graphically illustrated in Figure 2-4. We used mixed linear regression with or without linear splines, including the mother as the random factor to take into account the dependencies between siblings. All models were adjusted for maternal age, maternal parity, maternal education, paternal education and maternal smoking during pregnancy and child's age at completement of the physical activity-questionnaire. When birth weight was modelled the outcome, we further adjusted for maternal pre-pregnancy BMI (linear splines) and when infant weight gain was modelled the outcome, we included maternal pre-pregnancy BMI (linear splines), birth weight (linear splines or linear depending on sex), and breastfeeding as possible confounders.

Maternal pre-pregnancy BMI, birth weight and infant weight gain are affected by each other (6, 31). We therefore tested for interactions between the exposures (maternal pre-pregnancy BMI*birth weight and birth weight*infant weight gain) by including interaction terms in the model. If no interaction, we further examined whether birth weight and infant weight gain were mediators on an association between maternal pre-pregnancy BMI and LTPA, and whether infant weight gain was a mediator on the association between birth weight and LTPA, by evaluating the controlled direct effect (32, 33). We further included child's BMI in the model to assess the controlled direct effect in a similar manner. Child's BMI was included in the model with all the other possible mediators due to the strong confounding assumptions necessary in mediation analyses (32, 33). There was no interaction between any of the exposures and child's BMI ($p>0.05$). We did not test for mediation if no exposure-outcome association was observed.

We graphically illustrated predicted LTPA with 95%CI across the exposures.

Number of participants with missing on one or more of the exposures and included covariates was 45%, for both boys and girls, in which increased to 60% when BMI was included as a possible mediator. We replaced missing values using fully conditional specifications (FCS) multiple imputation (predictive mean matching, logistic regression and ordered logistic regression). We imputed a total of 20 datasets separately for boys and girls, based on all variables in the models in addition to auxiliary variables. More information about the imputation method, imputation model, number of missing values for each variable, and complete case analyses are provided in Additional Information (Additional file 2).

We used Stata/SE version 16.0 for the statistical analyses. The statistical significance level was 5% for all analyses.

Results

Table 1 shows the descriptive characteristics of study participants. Boys had on average higher weight at birth and 1 year and were more physically active by the age of 7 years compared to girls. The mothers were highly educated, in which 74% reported education from college or university, the majority were normal weight at onset of pregnancy and primiparous.

Table 1: Descriptive characteristics of study participants stratified by sex, shown as mean (sd) for continuous variables and frequency (%) for categorical variables unless otherwise stated.

Variable	Boys n=24 823	Girls n=23 849
Maternal characteristics		
Maternal pre-pregnancy BMI (kg/m^2)	23.9 (4.1)	23.9 (4.1)
Maternal pre-pregnancy weight status (cat)		
Underweight, n(%)	702 (2.9 %)	635 (2.7 %)
Normal weight, n(%)	16 108 (67.1 %)	15 549 (67.4 %)
Overweight, n(%)	5 164 (21.5 %)	4 937 (21.4 %)
Obese, n(%)	2 024 (8.4 %)	1 951 (8.5 %)
Maternal age[a] (years)	30.6 (4.4)	30.6 (4.4)
Maternal parity[a] (cat)		
Primiparous, n(%)	11 335 (45.7 %)	10 815 (45.3 %)
1, n(%)	8 792 (35.4 %)	8 558 (35.9 %)
2, n(%)	3 700 (14.9 %)	3 534 (14.8 %)
≥3, n(%)	996 (4.0 %)	942 (3.9 %)
Maternal education[b] (cat)		
< High school, n(%)	1 076 (4.5 %)	1 033 (4.4 %)
High school, n(%)	5 156 (21.4 %)	5 014 (21.6 %)
College/university 1-4 years, n(%)	10 983 (45.6 %)	10 354 (44.6 %)
College/university >4 years, n(%)	6 879 (28.5 %)	6 796 (29.3 %)
Paternal education[b] (cat)		
< High school, n(%)	1 887 (8.1 %)	1 866 (8.4 %)
High school, n(%)	7 943 (34.2 %)	7 482 (33.6 %)
College/university 1-4 years, n(%)	7 011 (30.2 %)	6 783 (30.4 %)
College/university >4 years, n(%)	6 361 (27.4 %)	6 162 (27.6 %)
Maternal smoking in pregnancy (cat)		
No, n(%)	18 902 (91.1 %)	18 089 (91.2 %)
Yes, n(%)	1 849 (8.9 %)	1 748 (8.8 %)
Child 0-3 years old characteristics		
Child birth weight (g)	3 672 (532)	3 551 (509)*
Child gestational age at birth (weeks)[c]	40 (39-41)	40 (39-41)*
Breastfeeding 0-4 months (cat)		*
Exclusive, n(%)	12 798 (59.4%)	13 050 (63.0%)
Partial, n(%)	8 488 (39.4%)	7 435 (35.9%)
None, n(%)	275 (1.3%)	240 (1.2%)
Child weight 1 year (kg)	10.3 (1.1)	9.6 (1.0)*
Child BMI 3 years (kg/m^2)	16.2 (1.5)	16.0 (1.5)*
Child 7 years old characteristics		
Child age follow-up	7.1(0.16)	7.1(0.16)
Child LTPA (frequency/week)	4.3 (2.3)	3.7 (2.1)*
Child BMI 7 years (kg/m^2)	15.8 (1.8)	15.8 (2.0)

*p<0.05 for difference between boys and girls

[a] At time of delivery

[b] Highest completed or ongoing education in pregnancy week 17-20

[c] median (25th-75th percentile)

Figure 2 shows the adjusted associations between maternal pre-pregnancy BMI and LTPA separately for boys and girls, and the unstandardized regression coefficients with 95%CI for the linear splines below or above maternal pre-pregnancy BMI at 21 kg/m^2 and 20 kg/m^2, for boys and girls respectively. For boys, the association was positive below the maternal pre-pregnancy BMI of 21kg/m^2, i.e. a lower maternal pre-pregnancy BMI is associated with lower participation in LTPA in childhood. For maternal pre-pregnancy BMI above 21 kg/m^2, there was a negative association. The magnitude of the association was stronger in boys whose mothers had a lower pre-pregnancy BMI compared with boys whose mothers had higher pre-pregnancy BMI. There was no association between maternal pre-pregnancy BMI and childhood LTPA in girls. The unadjusted estimates for LTPA in boys were B(95%CI) = 0.08 (0.04,0.12) and -0.02(-0.03, -0.01) for maternal pre-pregnancy BMI ≤ and >21kg/m^2, respectively. The unadjusted estimates for LTPA in girls were B(95%CI) = 0.04(-0.02, 0.10) and -0.001 (-0.008, 0.006) for maternal pre-pregnancy BMI ≤ and >20kg/m^2, respectively.

Birth weight z-scores, standardized for gestational age and sex, showed a positive association with LTPA in boys with birth weight z-score below or equal to -1, whereas the association was negative for boys with birth weight z-score above -1 in the adjusted analyses (Figure 3). The positive association at the lowest end of the birth weight continuum was stronger than the negative association with higher birth weight. We observed no association between birth weight z-scores and LTPA in girls (Figure 3). The unadjusted estimates (B(95%CI)) for LTPA in boys were 0.29(0.13,0.44) and -0.05 (-0.09, -0.02) for birth weight ≤ and >-1 z-scores, respectively. The unadjusted estimate (B(95%CI)) for the association between birth weight and LTPA in girls was B(95%CI) = -0.02 (-0.05, 0.00).

A positive association between infant weight gain and subsequent LTPA was observed in the adjusted model in boys, but not in girls (Figure 4). The unadjusted estimates were B(95%CI) = 0.04(0.01, 0.07) and 0.0003 (-0.023, 0.028) for boys and girls, respectively.

No interaction was observed between maternal pre-pregnancy BMI and birth weight on the association with LTPA in childhood (p=0.349-0.659 and p=0.074-0.270, for boys and girls

respectively). We observed a significant interaction between birth weight and infant weight gain on the association with LTPA above birth weight z-score -1 (p=0.033), but not below birth weight z-score -1 (p=0.113), in boys. No interaction was observed in girls (p=0.279). We graphically illustrated the interaction in boys (Figure 5) by showing the predicted LTPA across birth weight z-scores and a slow (z-score=-0.67), normal (z-score=0) and rapid (z-score=0.67) infant weight gain, from the regression model including the interaction term birth weight(splines)*infant weight gain. The association was slightly positive in those with a rapid infant weight gain and slightly negative in those with a slow infant weight gain above birth weight z-score -1.

The association between maternal pre-pregnancy BMI and LTPA in boys was not mediated by birth weight (splines) or infant weight gain (≤21 kg/m^2: B(95%CI) =0.08(0.03, 0.12)); >21 kg/m^2: B(95%CI) =(-0.008(-0.017, 0.000)), nor child's BMI at 3 years (≤21 kg/m^2: B(95%CI) =0.08 (0.03, 0.12)); >21 kg/m^2: B(95%CI) =-0.008(-0.017, 0.000). Additional Information (Additional File 3) illustrates that the interaction between birth weight and infant weight gain on LTPA in boys, were not mediated by BMI at age 3 years.

The results with multiple imputation did not differ substantially from complete case analyses (Additional File 2).

Discussion:

Maternal pre-pregnancy BMI, birth weight and infant weight gain may influence later LTPA in childhood differently in boys and girls. Maternal pre-pregnancy BMI, birth weight and infant weight gain were not associated with LTPA in 7-year-old girls. In opposite, a non-linear association was observed between maternal-pre pregnancy BMI and birth weight with LTPA in boys, and a weak linear association was observed between infant weight gain and LTPA. A lower maternal pre-pregnancy BMI and a lower birth weight may have a larger impact on boys' LTPA, compared to a high maternal pre-pregnancy BMI and high birth weight, respectively. The observed positive association between infant weight gain and LTPA in boys is likely clinically insignificant, however, the effect

estimates should be evaluated in studies with more precise PA-assessment. None of these associations appears to be mediated by child's BMI at age 3 years.

Few comparable studies have examined the association between maternal pre-pregnancy BMI and subsequent physical activity in the offspring. Previous research, combining males and females, show no linear association between maternal pre-pregnancy BMI in children and adolescents (22), nor in adults (20). Data from Mintjens et al. (19) suggested no association between maternal pre-pregnancy overweight (>25 kg/m^2) or normal weight (<25 kg/m^2) and physical activity-levels in offspring. However, by dichotomizing maternal BMI, a possible non-linear association is masked as children whose mothers are underweight are categorized similar to those whose mothers were normal weight. In a secondary analysis from that study, maternal pre-pregnancy BMI modelled as a continuous variable was negatively associated with MVPA (19). Furthermore, no association was observed between categories of maternal pre-pregnancy BMI and a subsequent inactive lifestyle in Brazilian adolescents (16). Tikanmaki et al. (23) observed a quadratic association between maternal pre-pregnancy BMI and self-reported physical activity in adolescents. However, when maternal pre-pregnancy BMI was categorized into underweight, normal weight, overweight and obese, only adolescents whose mothers were obese before pregnancy were less physically active than adolescents whose mothers were normal weight. This is probably explained by loss of information and power when categorizing a continuous variable (34, 35). Contrary to our results, the association was observed in both girls and boys, although stronger in boys (23). Traditionally the focus have been on the linear association and the detrimental effect of mothers being overweight or obese on both physical activity (19, 20, 22) and health outcomes (1, 5, 12, 36) in the offspring. Our results show that maternal pre-pregnancy underweight may have a stronger impact on subsequent LTPA, at least in boys.

We observed that both a low- and high birth weight may lead to reduced LTPA in childhood, although only in boys. An inverse U-shaped association was previously demonstrated using categories of birth

weight in one large meta-analysis including more than 40 000 adolescents and adults from 13 Nordic cohort studies, in sex combined analyses (15). In contrast, the study by Tikanmaki et al.(23), suggested no quadratic, nor linear, association between birth weight z-scores and physical activity in 16-year-olds, in similar sex combined analyses. Previous studies have either observed no linear relationship (13, 18, 22, 37-40) or no association between categories of birth weight and physical activity in children and/or adolescents (16, 41) or adults (20). Some of these studies have used only two categories of birth weight (20, 41), which precludes detection of any non-linear relationship. Gopinath et al. (42) observed that adolescents in the highest compared to the lowest birth weight quartile, for boys and girls combined, spent more time in self-reported physical activity. Similarly, two studies reported that low birth weight was associated with lower odds of participating in self-reported LTPA in adults (43) and children (44), compared to higher categories of birth weight. Contrary to our results, this was only observed in girls in one of the studies (44). A linear positive association was also demonstrated between birth weight and self-reported LTPA in 57-70-years-old men and women (21). The inconsistent results across studies may be due to large differences in analyses used. Categorization of continuously distributed exposures is highly dependent on choice of cut-points, in addition to the assumed homogeneity of association within groups leading to inaccurate estimations and substantially loss of power (34, 35).

Moreover, few studies have examined whether infant weight gain influence subsequent physical activity, and analyzed boys and girls combined. No association was observed between quartiles of weight gain from 0-1 year and self-reported physical activity in 10-12-year-olds (16), nor a linear association between infant weight gain and device-measured physical activity in children (18) and adolescents (17). Smaller sample sizes may explain the discrepancy with our findings, albeit the two latter studies included more precise assessments of physical activity.

Our results further suggested an interaction between birth weight at the higher end of the continuum and infant weight gain on the association with LTPA in boys. An increase in z-score equal

to or larger than 0.67 is commonly referred as rapid infant weight gain, as 0.67 represents the difference between each displayed percentile line on standard infant growth charts (10, 45). Similarly, a decline in z-score equal to or larger than 0.67 is considered a slow infant weight gain. Our data (Figure 5) indicates small differences in the associations between birth weight z-score and LTPA across infant weight gain. It appears that boys with a normal birth weight are unaffected by infant weight gain in relation to LTPA in childhood, whereas the associations are in opposite directions for boys with a slow and rapid weight gain at the higher end of the birth weight continuum. The associations are albeit weak and may not be clinically relevant.

We hypothesized that early life risk factors for obesity may influence physical activity via higher adiposity. However, none of the associations were affected by BMI at 3 years, possibly explained by the fact that a low maternal pre-pregnancy BMI and low birth weight appears to be substantially stronger associated with LTPA than a high maternal pre-pregnancy BMI and a high birth weight. Salonen et al. (21), observed that the positive association between birth weight and LTPA observed in adults became non-significant after inclusion of adult fat free mass (21), indicating that muscle mass may be a possible mediator. Thus, a low maternal pre-pregnancy BMI and a low birth weight may lead to lower physical activity due to lower muscle mass (36, 46, 47), muscle strength (48-50), muscle quality (51) or cardiorespiratory fitness (46, 52, 53). Skeletal muscle mass, BMI, physical fitness and physical activity may mutually affect each other. If a low maternal pre-pregnancy BMI and a low birth weight influence physical activity in boys via lower muscle mass, this may provide an opportunity to target muscle strengthening activities in these predisposed groups as a possible intervention.

Observed sex-dependent influences of prenatal and postnatal factors are also observed in a sub-sample of the present cohort (54), and some have observed weaker associations in girls compared to boys on aerobic fitness (52) and physical activity (23). It has been suggested that boys are more vulnerable to adverse conditions in the prenatal environment, due to the male fetus exhibiting faster

growth rates compared to the female fetus (55-57). Boys are also more likely to put on weight more rapidly in infancy (31).

Strengths of this study are the large population-based pregnancy cohort with frequently follow-ups during pregnancy and in childhood, and linkage to the MBRN. We have examined the associations using splines, in which acknowledge the continuous nature of the expoasures and make full use of the information available and is thus the preferred method to examine non-linear relationships (34, 35). However, these results should be interpreted keeping some important considerations in mind. Some of the variables are based on self-reports, which may be prone to measurement error. Maternal pre-pregnancy BMI might be overestimated at the lower end and underestimated at the higher end of the BMI-scale (58). Furthermore, the sporadic nature of children's physical activity pattern makes precise measurements difficult. The validation study showed that the questionnaire may be useful to rank children according to physical activity-level. However, we do not know whether the questionnaire measure the actual frequency of physical activity per week. Non-differential measurement error of LTPA across values of the exposure-variables may lead to underestimated effect sizes. Thus, the effect estimates should be interpreted with care and are not emphasized in our discussion of the results. Simultaneously, the large sample size may have led to significant results with little clinical importance. Thus, as previously discussed, some of the associations in boys may not be clinically relevant. However, the observed associations should be replicated in future studies with more precise measurements of physical activity. Differential loss to follow-up may threaten the generalizability of the results to groups other than the group being studied (Additional file 1).

Conclusion

We observed no associations between maternal pre-pregnancy BMI, birth weight and infant weight gain on subsequent LTPA in girls. Maternal pre-pregnancy BMI and birth weight may be non-linearly associated, whereas infant weight gain may be weakly linearly associated, with LTPA in 7-year-old

boys. Maternal pre-pregnancy BMI and birth weight are positively associated with LTPA at the lower ends of the pre-pregnancy BMI and birth weight continuums. The negative associations at the higher ends of the continuums and the positive association between infant weight gain and LTPA, may not be clinically relevant and needs further replication. None of these associations appears to be mediated by BMI in childhood.

List of abbreviations:

BMI- Body mass index

cpm- counts per minute

LTPA- Leisure time physical activity

MBRN- The Medical Birth Registry of Norway

MoBa- The Norwegian Mother, Father and Child Cohort Study

MVPA- Moderate to vigorous physical activity

Declarations

Ethics approval and consent to participate

The Regional Committee for Medical and Health Research Ethics (South-East) has approved the current study.

Consent for publication

Not applicable

Availability of data and materials

The consent given by the participants does not open for storage of data on an individual level in repositories or journals. Researchers who want access to data sets for replication should submit an application to datatilgang@fhi.no. Access to data sets requires approval from the Regional committees for medical and health research ethics in Norway and a formal contract with MoBa.

Competing interest

The authors declare that they have no competing interests.

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Authors' contributions

All authors conceptualized the specific research question and planned the analyses. GPB analyzed the data and drafted all versions of the manuscript. UE contributed with drafting the manuscript. WN, TS and UE critically reviewed all versions of the manuscript and approved the final version.

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Additional Files

Additional information- File 1: Descriptive characteristics of participants stratified by loss to follow up and participants included in the analyses (pdf)

Additional Information – File 2: Information on imputation method, number of missing values, participants with complete and incomplete data and complete case analyses (pdf)

Additional information – File 3: Predicted LTPA with 95%CI in childhood across birth weight and change in infant weight gain (0-1y) z-score from 0-1 year at -0.67, 0 and 0.67 (pdf)

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Figures:

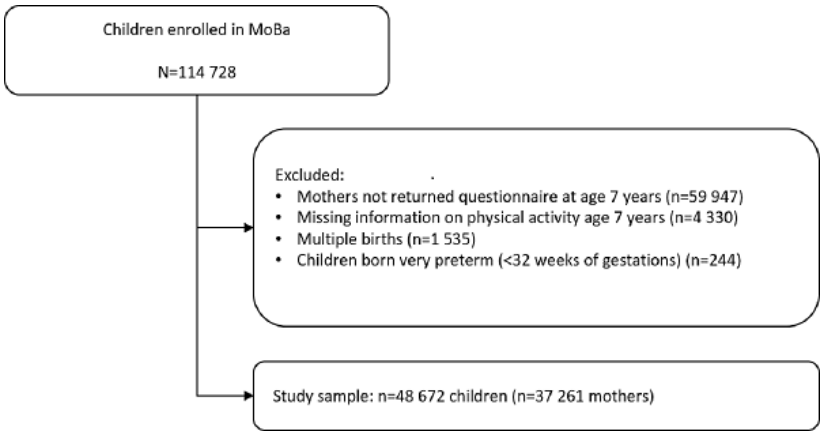

Figure 1: Study population flow chart

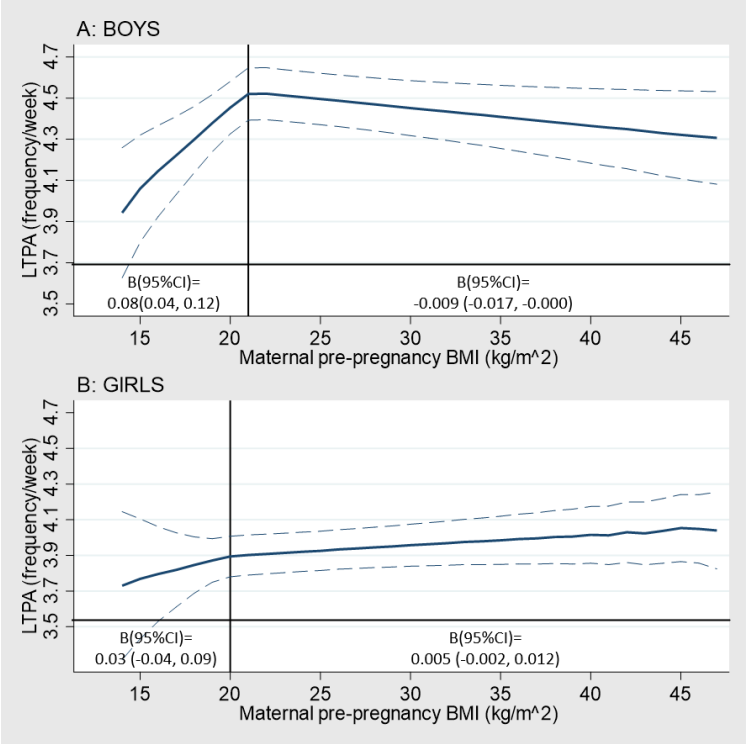

Figure 2: Predicted LTPA with 95% CI in childhood across maternal pre-pregnancy BMI, and unstandardized regression coefficients (95%CI), from linear mixed model including linear splines, in boys (A) and girls (B).

Deviation from linearity (likelihood-ratio test); boys p>0.001, girls p=0.135.
Analyses adjusted for maternal age, parity, maternal education, paternasl education, maternal smoking during pregnancy, and child's age at follow-up.
BMI- Body mass index; LTPA- Leisure time physical activity (frequency/week)

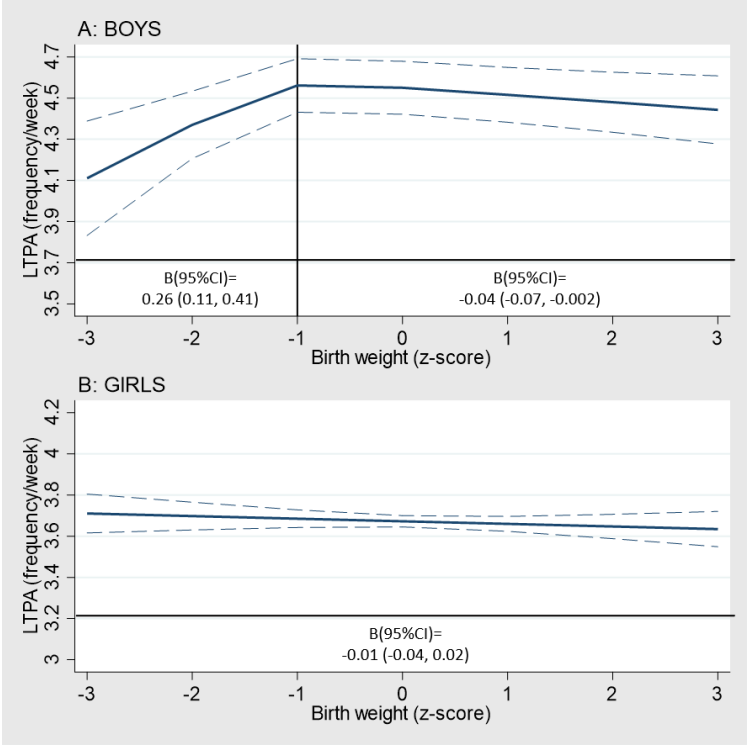

Figure 3: Predicted LTPA with 95%CI in childhood across birth weight for gestational age z-scores, and unstandardized regression coefficients (95%CI), from linear mixed model including linear splines (A) or linear model (B), for boys (A) and girls (B).

Deviation from linearity (likelihood-ratio test); boys p<0.001.

Analyses adjusted for maternal pre-pregnancy BMI, maternal age, parity, maternal education, paternal education, maternal smoking during pregnancy, and child's age at follow-up.

BMI- Body mass index; LTPA- Leisure time physical activity (frequency/week)

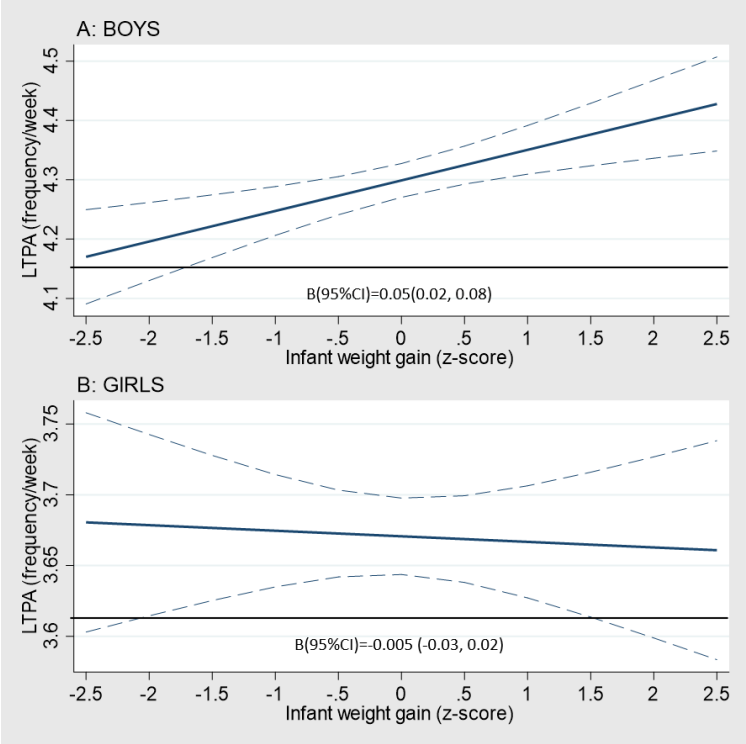

Figure 4: Predicted LTPA with 95%CI in childhood across infant weight gain (change in z-scores from birth to 1 year), and unstandardized regression coefficients (95%CI), from linear mixed model, for boys (A) and girls (B).

Analyses adjusted for birth weight z-score, maternal pre-pregnancy BMI, maternal age, parity, maternal education, paternal education, maternal smoking during pregnancy, breastfeeding from 0-4 months and child's age at follow-up.

BMI- Body mass index; LTPA- Leisure time physical activity (frequency/week)

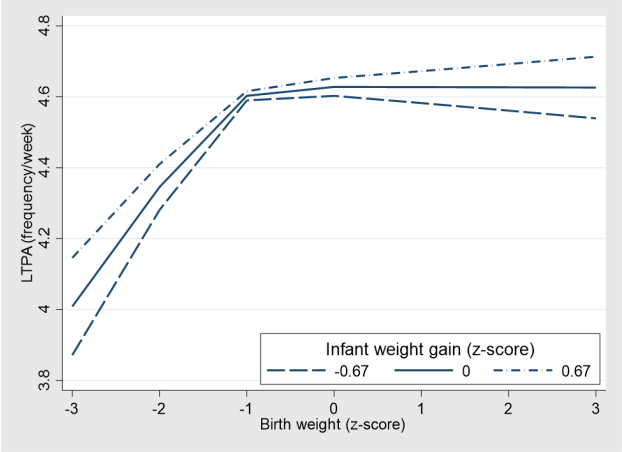

Figure 5: Predicted LTPA with 95%CI in childhood across birth weight and infant weight gain at change in z-score from 0-1 year at -0.67, 0 and 0.67. Predicted values from linear mixed model including interaction term (birth weight*infant weight gain).

Analyses adjusted for maternal pre-pregnancy BMI, maternal age, parity, maternal education, paternal education, maternal smoking during pregnancy, breastfeeding from 0-4 months and child's age at follow-up.

BMI- Body mass index; LTPA- Leisure time physical activity (frequency/week)

PAPER III

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ORIGINAL ARTICLE

WILEY

Early life risk factors for childhood obesity—Does physical activity modify the associations? The MoBa cohort study

Guro Pauck Bernhardsen[1] | **Trine Stensrud**[1] | **Wenche Nystad**[2] | **Knut Eirik Dalene**[1] | **Elin Kolle**[1] | **Ulf Ekelund**[1,2]

[1]Department of Sport Medicine, Norwegian School of Sports Sciences, Oslo, Norway

[2]Department of Non-communicable Diseases, Norwegian Institute of Public Health, Oslo, Norway

Correspondence
Guro Pauck Bernhardsen, Department of Sport Medicine, Norwegian School of Sports Sciences, P.O box 4014, Ullevål Stadion, Oslo 0806, Norway.
Email: g.p.bernhardsen@nih.no

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Objectives: High maternal pre-pregnancy body mass index (BMI), high birth weight, and rapid infant weight gain are associated with increased risk of childhood obesity. We examined whether moderate-to-vigorous physical activity (MVPA) or vigorous physical activity (VPA) in 9- to 12-year-olds modified the associations between these early life risk factors and subsequent body composition and BMI.

Methods: We used data from a sub-cohort of the Norwegian Mother and Child Cohort Study (MoBa), including 445 children with available data on accelerometer assessed physical activity (PA). All participants had data on BMI, 186 of them provided data on body composition (dual energy X-ray absorptiometry (DXA)). We used multiple regression analyses to examine the modifying effect of PA by including interaction terms.

Results: Maternal pre-pregnancy BMI and infant weight gain were more strongly related to childhood body composition in boys than in girls. Higher VPA attenuated the association between maternal pre-pregnancy BMI and BMI in boys (low VPA: $B = 0.32$, 95% CI = 0.22, 0.41; high VPA $B = 0.22$, 95% CI = 0.12, 0.31). Birth weight was unrelated to childhood body composition, and there was no effect modification by PA. PA attenuated the associations between infant weight gain and childhood fat mass (low MVPA: $B = 2.32$, 95% CI = 0.48, 4.17; high MVPA: $B = 1.00$, 95% CI = 0.10, 1.90) and percent fat (low MVPA: $B = 3.35$, 95% CI = 0.56, 6.14; high MVPA: $B = 1.41$, 95% CI = −0.06, 2.87) in boys, but not girls.

Conclusion: Findings from this study suggest that MVPA and VPA may attenuate the increased risk of an unfavorable body composition and BMI due to high maternal pre-pregnancy BMI and rapid infant weight gain in boys, but not in girls.

KEYWORDS
birth weight, childhood BMI, childhood body composition, infant weight gain, maternal pre-pregnancy BMI, physical activity

1 | INTRODUCTION

Childhood obesity is related to several short-term health consequences[1] and is a strong predictor of adult obesity with the accompanying risks of cardiovascular diseases and mortality.[2,3] The development of obesity may start before birth, with intrauterine and early life exposures having long-term effects on biology, leading to an increased fat mass and risk of obesity later in life.[4,5] Previous research has established high maternal pre-pregnancy body mass index (BMI), high birth weight, and rapid infant weight gain as risk factors for childhood obesity.[1,6-8] Maternal pre-pregnancy obesity is associated with three times increased odds for childhood overweight or obesity.[9] Similarly, high birth weight (>4.0 kg) is associated with a twofold increased odds of obesity compared to normal birth weight (2.5-4.0 kg).[10] Both high and low birth weight have been linked to subsequent development of obesity and noncommunicable diseases.[11] Furthermore, low birth weight, reflecting under-nourishment and fetal growth restriction, is often accompanied by rapid postnatal weight gain, which is an independent additional risk factor for later obesity,[6] with a nearly twofold increase in the odds of childhood obesity in those children increasing their weight by at least one standard deviation (*z*-score) between birth and 1 year.[6]

Body mass index is frequently used to define overweight and obesity. However, using BMI as a proxy for adiposity has obvious limitations due to its inability to differentiate between fat mass and fat-free mass. In studies where detailed measurements of body composition are available, higher maternal pre-pregnancy BMI, higher birth weight, and rapid infant weight gain are associated with subsequent higher fat mass in childhood.[12-15]

Furthermore, previous studies suggest that physical activity (PA), especially high intensity PA, is associated with lower fat mass in children.[16,17] Hence, PA may be an important strategy to prevent an unfavorable body composition, particularly in those children prone to higher adiposity as a result of high maternal pre-pregnancy BMI, high birth weight, or rapid infant weight gain. Moreover, it could be hypothesized that higher PA may attenuate the positive associations between maternal pre-pregnancy BMI, birth weight and infant weight gain, and subsequent adiposity.

Currently, the evidence is inconclusive. One study suggested that PA does not modify the associations between birth weight, fat mass index (fat mass/m^2), and waist circumference in 9- and 15-year-olds.[18] In contrast, others have suggested an effect modification on the association between birth weight and higher risk of obesity by self-reported moderate-to-vigorous physical activity (MVPA) in girls, but not boys.[19] Kolle et al[20] examined the associations between weight gain in infancy (0-2 years) and childhood (2-4 years) with subsequent fat mass in 30-year-olds and observed that the association between weight gain in childhood and fat mass index in adulthood was attenuated by objectively measured MVPA. No effect modification of MVPA was observed on the association between infant weight gain and subsequent fat mass index. Thus, additional research is needed to examine whether PA mitigates the associations between early life exposures and long-term risk of obesity.

Examining the modifying effect of PA on early life obesity risk factors is important to obtain a more comprehensive understanding of the underlying biological processes for obesity development and for potentially efficacious prevention strategies. The aim of this study was to examine if MVPA or vigorous PA (VPA) in childhood modifies the associations between maternal pre-pregnancy BMI, birth weight, and infant weight gain with precisely measured body composition and BMI in 9- to 12-year-old Norwegian boys and girls.

2 | METHODS

2.1 | Study design and participants

We used data from a sub-cohort of the Norwegian Mother and Child Cohort Study (MoBa). MoBa is an ongoing prospective population-based cohort study managed by the Norwegian Institute of Public Health (NIPH).[21] All women attending a routine ultrasound examination at 17-20 weeks gestation at Norwegian maternity units that deliver more than 100 births annually (50 units out of 52 participated between 1999 and 2008) were invited to participate. More than 100 000 children have been followed-up from birth. In this study, we used data from a sub-cohort of 1603 participants born between 2002 and 2004, living within a 1-hour radius from one of four test centers. These participants were invited to undergo additional testing, including anthropometric, body composition, and PA measurements. The tests were conducted between 2013 and 2015, in Oslo, Bergen, Stavanger and Fredrikstad. A total of 470 children agreed to participate (participation rate 29.3%), of which 445 participants provided complete PA data (flowchart of participants in Figure S1). A dual X-ray absorptiometry (DXA) scan was only available at the test center located in Oslo; thus, body composition measurements were only performed in 186 participants. Therefore, the number of participants included in different analyses differs depending on the outcome measure.

The establishment of MoBa and initial data collection was based on a license from the Norwegian Data protection agency and the approval from The Regional Committee for Medical Research Ethics. The MoBa cohort is currently regulated by the Norwegian Health Registry Act. The present substudy was additionally approved by The Regional Committee for Medical Research Ethics (REC South East). A written informed consent was obtained from the children's parents prior to all measurements.

2.2 | Measurements

2.2.1 | Exposures

The mothers reported their pre-pregnancy weight and height in gestational week 18. We obtained birth weight and gestational age at birth which was estimated using ultrasound, from the Medical Birth Registry of Norway (MBRN). MBRN is a national health registry containing information about all births in Norway. We standardized birth weight as sex- and gestational age-specific *z*-scores using information from more than 100 000 births in the MoBa cohort. The mothers reported their children's weight at 1-year via questionnaire. We advised the mothers to use the measured weight recorded on their child's health record. We calculated infant weight gain as change in sex-specific *z*-scores from birth to 1 year, using the mean and standard deviation (SD) from the entire MoBa cohort.

2.2.2 | Outcomes

The participants and their parents were asked to attend their nearest test center where trained personnel performed body composition and anthropometric measurements. The participants wore light clothing during body weight and height measurements, which were performed using a mechanical scale and a stadiometer, respectively. We calculated BMI by dividing weight by height squared (kg/m^2).

Trained personnel performed the DXA-measurements using a Lunar iDXA (GE Healthcare Lunar) (enCORE Pediatric whole-body analysis Software Version 14.10.022). The participants underwent a whole-body scan, wore light clothes, and removed all loose metal items prior to scanning. The test personnel calibrated the scanner daily according to the Lunar iDXA enCORE manual.

2.2.3 | Covariates

Parental education was self-reported via questionnaire at gestational week 18. We estimated parental education as the highest completed or ongoing education by either the mother or the father.

We also modeled measured birth weight and self-reported maternal pre-pregnancy BMI as covariates when not modeled as the exposure of interest.

For descriptive statistics, we defined childhood underweight, overweight, and obesity using the International Obesity Task Force (IOTF) criteria, whereby "underweight" corresponds to an adult BMI value of ≤18.5 kg/m^2, "overweight" corresponds to an adult BMI value of ≥25kg/m^2, and "obesity" corresponds to an adult BMI value of ≥30 kg/m^2.[22,23]

2.2.4 | Effect modifier—physical activity

We measured PA using Actigraph accelerometers (Actigraph GT3X+; LLC), previously validated in free living conditions among children.[24] The participants wore the monitor on their right hip and were instructed to wear the accelerometer during all waking hours for seven consecutive days (in addition to the day the monitor was attached), except while bathing or doing other water-based activities. To eliminate reactivity bias, we set the monitors to start recording at 06:00 the day after the participants received the monitors.[25] We used ActiLife (version 6.13.3) to process the data and used an epoch length of 10 seconds. We excluded overnight activity (00:00-05:59) from our analyses and defined non-wear time as 20 minutes or more of consecutive zero counts. A day was considered valid if the participant wore the monitor for at least 480 minutes. Ninety-eight percent of the participants provided three or more valid days of activity recordings, and there was no difference in MVPA and VPA between these children and those who provided less than three valid day. Ninety-four percent of the participants provided at least one valid weekday and one weekend, with no difference in MVPA and VPA compared to those children that did not. Hence, all participants providing at least one valid day were included in the analyses. MVPA (min/d) was defined as ≥2296 counts per minute (cpm), whereas VPA (min/d) was defined as ≥4012 cpm,[26] as recommended to estimate PA intensities in children.[27]

2.3 | Statistical analyses

Descriptive statistics of participants are presented as mean and SD for continuous variables and number of participants and proportions (%) for categorical variables (parental education and BMI classification). We tested for differences between boys and girls using independent samples *t* tests for continuous variables, Mann-Whitney two-sample tests for parental education and chi-squared tests for categorical data (underweight, normal weight, overweight, and obese). We used multiple regression to examine the associations between early life measurements (maternal pre-pregnancy BMI, birth weight *z*-score, and infant weight gain), childhood body composition, and BMI. We examined for linearity between independent and dependent variables and each model for normal distribution of residuals and homoscedasticity. We included a sex interaction term as previous studies have observed sex-dependent associations.[19,28] The formal interaction tests showed that certain associations may differ between boys and girls ($P < 0.05$), thus we stratified all analyses by sex. We adjusted each model for parental education. When PA and BMI were modeled as the outcome we additionally adjusted for current age, whereas models

including body composition (ie fat mass, percent fat, and fat-free mass) as the outcome measure were additionally adjusted for current height. Furthermore, other possible covariates were included depending on the exposure. For example, when maternal pre-pregnancy BMI and infant weight gain were modeled as the exposures, we additionally adjusted the analyses for birth weight. Similarly, the models including birth weight as the main exposure were adjusted for maternal pre-pregnancy BMI. To test if MVPA or VPA modified the associations, we included the interaction terms; early life risk factor × MVPA or early life risk factor × VPA into separate models. In the case of a significant interaction, we graphically displayed the predicted values of the outcome variable (calculated from the adjusted regression models with the interaction terms), at given values of the exposure of interest and the 25th, 50th, and 75th percentile of MVPA and VPA. In addition, we stratified the participants using a median split in MVPA and VPA and examined the magnitude of the associations in the models without the interaction term.

The number of participants with missing values for one or more variables was 50 (20.7%) and 37 (18.2%) for boys and girls, respectively. We replaced missing values on exposures and covariates using fully conditional specification (FCS) multiple imputation (predictive mean matching and ordered logistic regression). We imputed a total of 20 datasets separately for boys and girls, based on all variables in the full models in addition to auxiliary variables. More information about the imputation method, imputation model, number of missing values for each variable, and complete case analyses are provided in File S1.

The statistical significance level was 5% for all analyses. We used Stata/SE version 14.2 to conduct the analyses.

3 | RESULTS

Table 1 summarizes the characteristics of the total study sample and our sub-group with available DXA measurements. Overall, boys had a significantly higher birth weight and weight at 1 year than girls, whereas girls had higher fat mass and percent fat mass in childhood. On average, participants wore the accelerometer for 6.5 (SD 1.34) days, and for 786 (SD 55) min/d. Boys spent significantly more time in MVPA and VPA than the girls.

Tables 2 and 3 show the results from the multiple regression analyses examining the associations between exposures and outcomes and the effect modification by physical activity for boys and girls, respectively.

The results from the complete case analyses are provided in File S1, Table S3. The effect estimates are similar, but some confidence intervals are wider, in the complete case analyses.

3.1 | Maternal pre-pregnancy BMI

A higher maternal pre-pregnancy BMI was associated with higher fat mass, fat-free mass, percent fat, and BMI in boys. For example, a 1-unit increase in maternal BMI was associated with a 0.45 kg (95% CI = 0.28, 0.63) higher childhood fat mass and a 0.64% (95% CI = 0.36, 0.93) higher percent fat (Table 2). There were no significant associations between maternal pre-pregnancy BMI and the body composition measures in girls (Table 3). The association with BMI was weaker in girls than in boys. There was no evidence that these associations differed according to time spent in MVPA or VPA in girls. However, the test for interaction showed that the association between maternal pre-pregnancy BMI and childhood BMI was modified by time spent in VPA in boys, indicating that higher levels of VPA attenuated the association.

Figure 1 shows the predicted values of the children's BMI at given values of maternal pre-pregnancy BMI and the 25th, 50th, and 75th percentile of VPA. For example, a maternal pre-pregnancy BMI of 30 kg/m^2 (corresponding to mother being obese) gives predicted values of 20.0, 19.5, and 19.0 kg/m^2 at the 25th, 50th, and 75th percentile of VPA, respectively.

The association between maternal pre-pregnancy BMI and childhood BMI was stronger (B = 0.32, 95% CI = 0.22, 0.41) in the participants below the median VPA (<28 minutes per day), compared with those above (B = 0.22, 95% CI = 0.12, 0.31).

3.2 | Birth weight *z*-score

The gestational age- and sex-specific birth weight z-scores were not associated with fat mass, fat-free mass, or percent fat mass in boys or girls (Tables 2 and 3). We observed a positive association between birth weight and BMI in childhood in girls, whereby 1 z-score higher birth weight was associated with 0.34 (95% CI = 0.05, 0.64) higher BMI (Table 3). Including the interaction terms birth weight × MVPA and birth weight × VPA into the models showed no evidence of effect modification by PA (Tables 2 and 3).

3.3 | Infant weight gain

Change in weight z-scores from birth to 1 year was positively associated with the different components of body composition and BMI in boys (Table 2). For example, a 1-unit increase in z-score from birth to 1-year was associated with 1.45 kg (95% CI = 0.59, 2.31) higher childhood fat mass in boys. We did not observe any associations between infant weight gain and adiposity measures in girls (Table 3). MVPA

TABLE 1 Characteristics of the study participants at birth and follow-up (9 to 12 y old). All values are mean (SD) unless otherwise specified

	All participants		Participants with DXA	
	Boys (n = 242)	Girls (n = 203)	Boys (n = 98)	Girls (n = 88)
Age (y)	10.9 (0.66)	10.9 (0.66)	10.9 (0.63)	11.0 (0.63)
Birth weight (kg)	3.70 (0.62)*	3.58 (0.54)*	3.76 (0.62)*	3.54 (0.58)*
Gestational age (wk)	39.5 (1.96)	39.5 (1.52)	39.8 (1.84)	39.5 (1.84)
Weight 1 y (kg)	10.30 (1.01)*	9.59 (0.99)*	10.43 (1.07)*	9.56 (1.04)*
Maternal pre-pregnancy BMI (kg/m^2)	23.9 (4.3)	23.8 (4.1)	23.7 (4.1)	24.0 (3.9)
Parental education[a], n (%)				
<High school	6 (2.5%)	4 (2.0%)	2 (2.1%)	3 (3.5%)
High school	50 (20.9%)	48 (24.0%)	18 (18.7%)	13 (15.1%)
College/university 1-4 y	95 (39.7%)	80 (40.0%)	40 (41.7%)	36 (41.9%)
College/university > 4 y	88 (36.8%)	68 (34.0%)	36 (37.5%)	34 (39.5%)
Weight (kg)	39.2 (7.3)	39.1 (7.7)	39.2 (6.9)	40.0 (8.4)
Height (m)	1.47 (0.07)	1.48 (0.08)	1.48 (0.06)	1.49 (0.08)
Fat mass (kg)	NA	NA	10.0 (4.19)*	11.5 (4.6)*
Fat-free mass (kg)	NA	NA	29.4 (3.56)	28.6 (4.84)
Percent fat mass (%)	NA	NA	24.7 (6.15)*	28.1 (5.76)*
BMI (kg/m^2)	17.9 (2.47)	17.7 (2.30)	17.8 (2.46)	17.9 (2.33)
Underweight (yes), n (%)	18 (7.4%)	18 (8.9%)	9 (9.2%)	4 (4.5%)
Normal weight (yes), n (%)	189 (78.1%)	161 (79.3%)	76 (77.5%)	72 (81.8%)
Overweight/obesity (yes), n (%)	35 (14.5%)	24 (11.8%)	13 (13.3%)	12 (13.6%)
Obesity (yes), n (%)	5 (2.1%)	1 (0.5%)	3 (3.1%)	1 (1.14%)
SED (min/d)	496 (59.0)	506 (57.3)	501 (61.6)	508 (55.6)
MVPA (min/d)	74 (26.5)*	58 (19.0)*	75 (26.9)*	59 (17.4)*
VPA (min/d)	29 (14.6)*	21 (10.3)*	30 (15.7)*	21 (8.7)*

Abbreviations: BMI, Body mass index (weight/height^2); MVPA, Moderate-to-vigorous physical activity; NA, Not available; SED, Sedentary time; VPA, Vigorous physical activity.

[a]The education level of the parent with the highest completed or ongoing education (mother or father).

*$P < 0.05$ for difference between boys and girls.

and VPA attenuated the associations between infant weight gain, fat mass, and percent fat in boys.

Figure 2 shows the predicted values of fat mass and percent fat across infant weight gain *z*-scores and the 25th, 50th, and 75th percentile of MVPA and VPA in boys. The predicted fat mass in boys given a 0.67 increase in weight *z*-score from birth to 1-year (corresponding to upward centile crossing on standard infant growth charts) were 11.9 kg, 11.3 kg, and 10.7 kg in the 25th, 50th, and 75th percentile of VPA, respectively. Similarly, the predicted percentage body fat for a 0.67 increase in weight *z*-score was 27.5%, 26.6%, and 25.6%, for the 25th, 50th, and 75th percentile of VPA, respectively.

In median split analyses, the association between infant weight gain and fat mass was stronger in the low MVPA group ($B = 2.32$, 95% CI = 0.50, 4.17) compared with the high ($B = 1.00$, 95% CI = 0.10, 1.91) MVPA group (high MVPA > 73.6 min/d). The association with percent fat mass in those below the median for MVPA was $B = 3.35$(95% CI = 0.55, 6.14) compared with those above the median $B = 1.41$(95% CI = −0.06, 2.87).

4 | DISCUSSION

Our results indicate that high maternal pre-pregnancy BMI and rapid infant weight gain are stronger predictors for childhood fat mass and BMI in boys than in girls. Furthermore, it appears that some of these associations are attenuated by PA in boys. The results also indicate that birth weight is not associated with body composition in either sexes, nor modified by MVPA or VPA.

A 1-unit higher maternal pre-pregnancy BMI was associated with 0.28 (95% CI = 0.22, 0.35) higher BMI in 9- to 12-year-old boys and 0.10 (95% CI = 0.02, 0.18) higher BMI in girls. MVPA and VPA did not modify this association in girls. Conversely, in boys the magnitude of the association appears

TABLE 2 Unstandardized regression coefficients, with 95% CI, for the associations between MVPA, VPA and early life exposures with body composition measures and BMI in 9 to 12-year-old boys, and interaction between early life exposures and MVPA/VPA (in separate models)

	Fat mass (kg)	Fat-free mass (kg)	Percent fat (%)	BMI (kg/m^2)
	n = 98	n = 98	n = 98	n = 242
MVPA (min/d)[a]	**−0.03 (−0.06, −0.00)**	−0.01 (−0.03, 0.02)	−0.05 (−0.09, 0.00)	**−0.01 (−0.03, −0.00)**
VPA (min/d)[a]	**−0.05 (−0.11, −0.00)**	−0.01 (−0.05, 0.03)	**−0.09 (−0.16, −0.01)**	**−0.03 (−0.06, −0.01)**
Maternal pre-pregnancy BMI (kg/m^2)[b]	**0.45 (0.28, 0.63)**	**0.14 (0.02, 0.25)**	**0.64 (0.36, 0.93)**	**0.28 (0.22, 0.35)**
× MVPA (interaction term)	−0.007 (−0.02, 0.00)	−0.005 (−0.01, 0.00)	−0.008 (−0.02, 0.01)	−0.001 (−0.00, 0.00)
× VPA (interaction term)	−0.010 (−0.02, 0.00)	−0.006 (−0.02, 0.00)	−0.014 (−0.04, 0.01)	**−0.005 (−0.01, −0.00)**
Birth weight (*z*-score)[c,d]	0.24 (−0.45, 0.93)	0.07 (−0.37, 0.51)	0.34 (−0.76, 1.44)	0.13 (−0.14, 0.40)
× MVPA (interaction term)	0.010 (−0.01, 0.03)	0.000 (−0.01, 0.01)	0.031 (−0.00, 0.06)	0.000 (−0.01, 0.01)
× VPA (interaction term)	0.012 (−0.02, 0.05)	0.004 (−0.02, 0.03)	0.039 (−0.01, 0.09)	0.001 (−0.01, 0.01)
Infant weight gain (*z*-score)[b,e]	**1.45 (0.59, 2.31)**	**0.77 (0.26, 1.28)**	**2.09 (0.74, 3.43)**	**0.75 (0.38, 1.11)**
× MVPA (interaction term)	**−0.026 (−0.05, −0.01)**	−0.003 (−0.01, 0.01)	**−0.035 (−0.06, −0.00)**	0.000 (−0.01, 0.01)
× VPA (interaction term)	**−0.068 (−0.10, −0.02)**	−0.005 (−0.03, 0.02)	**−0.085 (−0.14, −0.03)**	−0.002 (−0.02, 0.02)

Note: Significant results are highlighted in bold letters.

Abbreviations: BMI, Body mass index; MVPA: Moderate-to-vigorous physical activity; VPA, Vigorous physical activity.

[a]Adjusted for highest parental education and current age.

[b]Adjusted for highest parental education, birth weight and current height (for body composition outcomes only) and current age (for BMI outcome only).

[c]Adjusted for highest parental education, maternal pre-pregnancy BMI and current height (for body composition outcomes only) and current age (for BMI outcome only).

[d]Sex and gestational age-specific *z*-scores.

[e]Change in sex-specific *z*-scores from birth to 1 y.

to be contingent on VPA, suggesting that VPA might mitigate the increased risk of high childhood BMI that accompanies a higher maternal pre-pregnancy BMI. The predicted BMI in childhood given a maternal pre-pregnancy BMI of 30kg/m^2 was 0.9 higher in the 25th compared to 75th percentile of VPA. This difference is equivalent to a difference of about 17 minutes of VPA between the 25th and the 75th quartile. The association between maternal pre-pregnancy BMI and childhood BMI is attenuated in those above the median in VPA, although not fully eliminated. These results suggest that a large amount of VPA is necessary to mitigate the increased risk of higher childhood BMI associated with high maternal pre-pregnancy BMI. We did not observe an effect modification when fat mass and percent fat were modeled as the outcomes, and this should be further examined in larger studies. From a public health perspective, it is promising that higher childhood BMI accompanying a high maternal pre-pregnancy BMI appears modifiable by PA, at least in boys.

Some previous studies have observed a positive association between birth weight and subsequent risk of obesity,[10] whereas others have suggested a possible U-shaped relationship.[29] We did not observe any associations between birth weight for gestational age and body composition in childhood. This is similar to the results from Chomtho et al,[30] but contrary to other studies.[14,31] Eriksson et al[12] observed an association between birth weight and fat mass in boys, but not in girls. Neither of the studies observed an association between birth weight and measures of fat relative to fat-free or total body mass,[12,14,30,31] which is possibly explained by the association between birth weight and larger size in general, rather than specifically an association with adiposity.

However, we observed a stronger relationship between birth weight and BMI in girls than in boys, which is in agreement with a previous study that showed a stronger association between birth weight and subsequent risk of obesity in girls than in boys.[29] The lack of effect modification by PA on the association between birth weight and childhood adiposity is consistent with the results from Ridgway et al,[18] but in contrast to Boone-Heinonen et al [19] who observed an effect modification in girls. However, none of these studies adjusted their analyses for gestational age. Thus, these results may therefore be confounded by natural high and low birth weight from being born before or after term. However, we cannot exclude a genetic contribution to low or high birth weight, that is, birth weight for gestational age may not be an adequate measure of intrauterine growth.[32]

Infants who have experienced growth restraint in utero, often measured by a low birth weight, tend to gain weight rapidly—a so-called catch up growth.[33] Rapid infant weight gain is consistently associated with higher fat mass [34] and has been considered one of the most important early life risk factors for obesity.[35] We observed a significant interaction

TABLE 3 Unstandardized regression coefficients, with 95% CI, for the associations between MVPA, VPA and early life exposures with body composition measures and BMI in 9 to 12-year-old girls, and interaction between early life exposures and MVPA/VPA (in separate models)

	Fat mass (kg)	Fat-free mass(kg)	Percent fat (%)	BMI (kg/m^2)
	n = 88	**n = 88**	**n = 88**	**n = 203**
MVPA (min/d)[a]	−0.03 (−0.08, 0.03)	−0.01 (−0.06, 0.05)	−0.02 (−0.09, 0.05)	−0.00 (−0.02, 0.01)
VPA (min/d) [a]	−0.04 (−0.15, 0.07)	−0.00 (−0.11, 0.11)	−0.04 (−0.18, 0.10)	−0.01 (−0.04, 0.02)
Maternal pre-pregnancy BMI (kg/m^2)[b]	0.20 (−0.04, 0.45)	0.07 (−0.05, 0.20)	0.25 (−0.10, 0.61)	**0.10 (0.02, 0.18)**
× MVPA (interaction term)	−0.003 (−0.02, 0.01)	−0.003 (−0.01, 0.01)	0.001 (−0.02, 0.02)	−0.000 (−0.00, 0.00)
× VPA (interaction term)	−0.006 (−0.03, 0.02)	−0.003 (−0.02, 0.01)	−0.000 (−0.04, 0.04)	−0.003 (−0.01, 0.00)
Birth weight (*z*-score)[c,d]	0.25 (−0.58, 1.09)	0.39 (−0.05, 0.84)	0.21 (−1.00, 1.41)	**0.34 (0.05, 0.64)**
× MVPA (interaction term)	0.017 (−0.04, 0.07)	0.015 (−0.01, 0.04)	0.036 (−0.04, 0.11)	0.000 (−0.01, 0.02)
× VPA (interaction term)	−0.001 (−0.11, 0.11)	0.033 (−0.03, 0.09)	0.024 (−0.14, 0.19)	−0.005 (−0.04, 0.03)
Infant weight gain (*z*-score)[b,e]	0.04 (−1.24, 1.33)	−0.16 (−0.75, 0.44)	0.28 (−1.38, 1.94)	0.37 (−0.06, 0.81)
× MVPA (interaction term)	−0.021 (−0.08, 0.04)	0.002 (−0.02, 0.03)	−0.041 (−0.12, 0.03)	0.003 (−0.02, 0.02)
× VPA (interaction term)	−0.025 (−0.17, 0.12)	0.005 (−0.06, 0.07)	−0.072 (−0.25, 0.10)	0.013 (−0.03, 0.05)

Note: Significant results are highlighted in bold letters.

Abbreviations: BMI, Body mass index; MVPA: Moderate-to-vigorous physical activity; VPA, Vigorous physical activity.

[a]Adjusted for highest parental education and current age.

[b]Adjusted for highest parental education, birth weight and current height (for body composition outcomes only) and current age (for BMI outcome only).

[c]Adjusted for highest parental education, maternal pre-pregnancy BMI and current height (for body composition outcomes only) and current age (for BMI outcome only).

[d]Sex and gestational age-specific *z*-scores.

[e]Change in sex-specific *z*-scores from birth to 1 y.

by sex suggesting a stronger association in boys compared to girls. Furthermore, there were significant interactions with both MVPA and VPA on the associations between infant weight gain with fat mass and percentage body fat in boys (Table 2).

Figure 2 indicates that boys with a rapid infant weight gain may be more vulnerable to an inactive lifestyle, and that high-intensity PA may mitigate, although not eliminate, the influence of rapid infant weight gain on adiposity. An increase in *z*-score equal to or larger than 0.67 is commonly referred to as upward centile crossing and defined as rapid infant weight gain, as 0.67 represents the difference between each displayed percentile line on standard infant growth charts (ie, 2nd, 10th, 25th, 50th, 75th, 90th, and 98th percentile lines).[36,37] According to these definition criteria, 18.7% of the girls and 22.5% of the boys in the present study have had a rapid infant weight gain. Our results indicate that boys who gained weight rapidly in infancy but being in the 75th percentile of VPA in childhood reduce the predicted fat mass by more than 1 kg compared to those being in the 25th percentile of VPA. For the low active boys below the median for MVPA, an increase in weight *z*-score of 0.67 is associated with 1.55 kg higher fat mass ($B = 2.32 \times 0.67$) in childhood. Given the average fat mass in this sample of 10.0 kg, an increase in this magnitude is noteworthy. Neither MVPA nor VPA modified the association between rapid infant weight gain and BMI, which may be explained by the inability of BMI to discriminate between

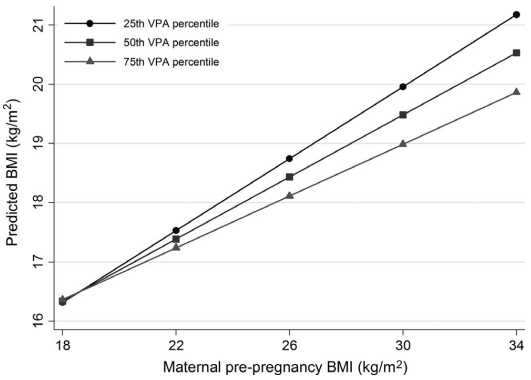

FIGURE 1 Predicted childhood BMI across values of maternal pre-pregnancy BMI and the 25th, 50th, and 75th percentile of VPA, in 9- to 12-year-old boys. Predicted values calculated from multiple regression model with interaction term (maternal pre-pregnancy BMI × VPA). 25th VPA percentile = 19.7 min/d, 50th VPA percentile = 28.3 min/d, 75th VPA percentile = 37.2 min/d. Adjusted for birth weight, parental education and age. BMI, Body mass index; VPA, Vigorous physical activity

fat mass and fat-free mass, where fat-free mass represents the largest component (in average 29.5 kg compared with 10.0 kg fat mass, Table 1). This underscores the importance of including valid measures of body composition when examining determinants of childhood obesity. The results in the present

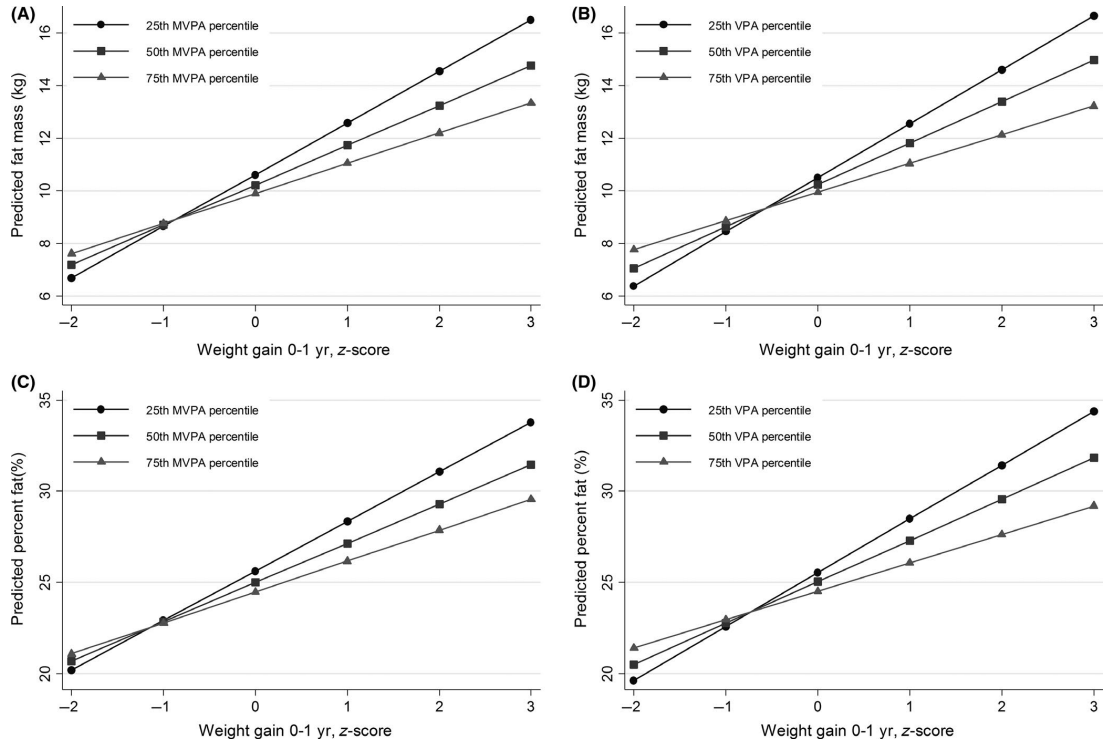

FIGURE 2 Predicted childhood fat mass (A and B) and percent fat (C and D) across values of infant weight gain and the 25th, 50th, and 75th percentile of MVPA (A and C) and VPA (B and D), in 9- to 12-year-old boys. Predicted values calculated from multiple regression models with interaction terms (infant weight gain × MVPA/VPA). 25th MVPA percentile = 55.3 min/d, 50th MVPA percentile = 73.8 min/d, 75th MVPA percentile = 88.8 min/d. 25th VPA percentile = 19.7 min/d, 50th VPA percentile = 28.3 min/d, 75th VPA percentile = 37.2 min/d. Adjusted for birth weight, height, and parental education. MVPA, Moderate-to-vigorous physical activity; VPA, Vigorous physical activity

study are contrary to the study by Kolle et al,[20] in which no effect modification of MVPA was observed on the association between infant conditional weight gain (0-2 years) and fat mass in 30-year-olds (both sexes combined). Thus, it is unclear whether the effect modification by MVPA and VPA observed in this study persists into adulthood.

The underlying mechanism for the association between rapid infant weight gain and subsequent development of obesity is not clear, and some have suggested that it may be that increased growth simply results in larger size.[1] Another proposed theory is that an undernourished prenatal environment leads to developmental responses to which the fetus anticipates it may be exposed to after birth, possibly resulting in a mismatch between the prenatally undernourished and postnatally nourished environments, thus leading to a rapid infant weight gain and increased risk of adult disease and obesity.[4,38] We adjusted our analyses for birth weight. In combination with previous findings suggesting that birth weight does not modify the association between infant weight gain and childhood BMI,[6] it appears that rapid infant weight gain, at least in boys, is associated with increased risk of an unfavorable body composition regardless of birth weight. The question arises whether the underlying mechanism for development of later adiposity is the same for those who were growth restricted in utero and thereafter rapidly gained weight during infancy, compared to those who experienced a rapid infant weight gain without previous in utero growth restriction? Thus, it would be interesting to examine if PA modifies the association between rapid infant weight gain and later adiposity similarly in these two groups.

The observed sex differences may be explained by differences in early developmental responses in boys and girls.[39,40] Our results suggest that boys may be more vulnerable to high maternal BMI and rapid weight gain than girls, and that elevated fat mass and BMI due to early life risk factors can be more easily reduced by MVPA and/or VPA in boys. Other possible explanations are differences in pubertal status between boys and girls and differences in PA levels. A high amount of PA appears necessary to attenuate the increased risk related to a high maternal pre-pregnancy BMI and rapid

infant weight gain, and on average, boys are more likely to accumulate high amounts of MVPA and VPA. Lastly, due to the small sample size, we cannot exclude possible significant associations and an effect modification by PA in girls.

4.1 | Strengths and limitations

This study should be interpreted keeping some strengths and limitations in mind. Although we consider it a strength that we examined associations between several early life risk factors on both body composition and BMI, the number of statistical tests increases the risk of a chance findings. Therefore, we consider our study explorative in nature aiming to suggest avenues for future research. The small sample size limited the possibility for a more refined stratification into tertiles or quartiles of PA when significant interactions between the main exposure and PA were observed. Sample size also limited the possibility to include additional covariates in our models, for example diet. It is likely that highly active children may also eat more healthily. Low statistical power can lead to type II errors, and we therefore examined associations using BMI as the outcome variable with a larger sample size. To compensate for the low number of participants in some of our analyses, we conducted multiple imputations. However, this does not fully address the issue of low sample size. Another important limitation is that body composition and BMI were measured at the same time point as PA. Ideally, multiple measures of PA conducted during childhood may increase the possibility to infer causality. The study sample is active and healthy, that is, only 1.3% of the children were classified as obese and the majority satisfied the recommended PA level of ≥60 min/d of MVPA. However, activity levels are similar to that observed in representative samples of Norwegian 9- to 15-year-olds.[41] Furthermore, although the vast majority of the participants have highly educated parents, there were no differences between participants and nonresponders concerning parental education, birth weight, maternal pre-pregnancy BMI, maternally reported PA at age 7 and children's BMI at age 7 (data not shown). Nevertheless, we cannot exclude the possibility of selection bias, which is not unfamiliar in epidemiological studies [42] and may influence the generalizability of the results.

Our objective measures of body composition by DXA and PA by accelerometry are strengths of this study, providing an opportunity to examine the modifying effect of both moderate and vigorous intensity PA on early life and childhood obesity associations.

4.2 | Perspective

Prevention of obesity is an important public health goal, and although high intensity PA is associated with lower adiposity in young children,[16] it is unclear whether PA attenuates the increased risk of childhood obesity accompanying high maternal pre-pregnancy BMI, high birth weight and rapid infant weight gain.[18-20] The results from this study in Norwegian children suggest that the associations between maternal pre-pregnancy BMI and rapid infant weight gain with fat mass and BMI in 9- to 12-year-olds are attenuated by higher MVPA and VPA in boys, but not in girls. We observed no association between birth weight for gestational age and childhood body composition, nor modified by level of MVPA or VPA.

High-intensity PA may be considered as one of many public health strategies to curb childhood obesity, especially in boys who are prone to obesity due to high maternal pre-pregnancy BMI and rapid infant weight gain. These results should be confirmed in larger studies.

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ORCID

Guro Pauck Bernhardsen https://orcid.org/0000-0003-1622-2911

Knut Eirik Dalene https://orcid.org/0000-0002-4401-301X

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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PAPER IV

Birth weight, cardiometabolic risk factors and effect modification of physical activity in children and adolescents: Pooled data from 12 international studies

Guro Pauck Bernhardsen, MSc[1]; Trine Stensrud, PhD[1]; Bjørge Herman Hansen, PhD[12]; Jostein Steene-Johannesen, PhD[1]; Elin Kolle, PhD[1]; Wenche Nystad, Prof[3]; Sigmund Alfred Anderssen, Prof.[1]; Pedro C Hallal, PhD[4]; Kathleen F Janz[5], Prof.; Susi Kriemler, PhD[6]; Lars Bo Andersen, Prof[17]; Kate Northstone[8], PhD; Geir Kåre Resaland, Prof.[9]; Luis Sardinha, Prof.[10]; Esther MF van Sluijs, PhD[11]; Mathias Ried-Larsen, PhD[12]; Ulf Ekelund, Prof[1] ; On behalf of the International Children's Accelerometry Database (ICAD) Collaborators

[1]Department of Sports Medicine, Norwegian School of Sport Sciences, Oslo, Norway

[2] University of Agder, Kristiansand, Norway

[3] Chronic Diseases and Aging, Norwegian Institute of Public Health, Oslo, Norway

[4] Federal University of Pelotas, Pelotas, Brazil

[5] Department of Health and Human Physiology, University of Iowa, Iowa City, US

[6] Epidemiology, Biostatistics and Public Health Institute, University of Zürich, Switzerland

[7] Department of Sport, Food and Natural Sciences, Campus Sogndal, Western Norway University of Applied Sciences, Sogndal, Norway

[8] Population Health Sciences, Bristol Medical School, University of Bristol, UK

[9] Center for Physically Active Learning, Faculty of Education, Arts and Sports, Campus Sogndal, Western Norway University of Applied Sciences, Sogndal, Norway

[10] Exercise and Health Laboratory, Faculty of Human Faculty of Human Kinetics, Universidade de Lisboa, Lisbon, Portugal

[11]Centre for Diet and Activity Research (CEDAR) & MRC Epidemiology Unit, University of Cambridge, Cambridge, UK

[12] Centre for Physical Activity Research, Rigshospitalet Copenhagen, Capital Region of Denmark, Denmark

Running title: Birth weight, cardiometabolic risk and physical activity

Corresponding author:

Guro Pauck Bernhardsen

Department of Sports Medicine, Norwegian School of Sport Sciences, Oslo, Norway

e-mail: g.p.bernhardsen@nih.no

(+47)23262293/(+47)90972519

The authors declare no conflict of interest.

Abstract

Objectives: Low and high birth weight is associated with higher levels of cardiometabolic risk factors and adiposity in children and adolescents, and increases the risk of cardiovascular diseases, obesity and early mortality later in life. Moderate-to-vigorous physical activity (MVPA) is associated with lower cardiometabolic risk factors and may mitigate the detrimental consequences of high or low birth weight**.** Thus, we examined whether MVPA modified the associations between birth weight and cardiometabolic risk factors in children and adolescents.

Methods: We used pooled individual data from 12 cohort- or cross-sectional studies including 9 100 children and adolescents. Birth weight was measured at birth or maternally reported retrospectively. Device-measured PA data were collected between 1997 and 2015. We tested for associations between birth weight, MVPA and cardiometabolic risk factors using multilevel linear regression, including study as a random factor. We tested for interaction between birth weight and MVPA by introducing the interaction term in the models (birth weight x MVPA).

Results: Most of the associations between birth weight (kg) and cardiometabolic risk factors were not modified by MVPA (min/day), except between birth weight and waist circumference (cm) in children (p=0.005) and HDL-cholesterol (mmol/l) in adolescents (p=0.040). Sensitivity analyses suggested that some of the associations were modified by VPA, i.e. the associations between birth weight and diastolic blood pressure (mmHg) in children (p=0.009) and LDL- cholesterol (mmol/l) (p=0.009) and triglycerides (mmol/l) in adolescents (p=0.028).

Conclusion: MVPA appears not to consistently modify the associations between low birth weight and cardiometabolic risk. In contrast, MVPA may mitigate the association between higher birth weight and higher waist circumference in children. MVPA is consistently associated with a lower cardiometabolic risk

across the birth weight spectrum. Optimal prenatal growth and subsequent PA are both important in relation to cardiometabolic health in children and adolescents.

Introduction

The developmental origin of health and disease concept (DOHaD) suggests that fetal and infant life could be critical periods for development of cardiovascular diseases (1). Birth weight, used as a proxy measure for fetal growth, is related to later risk of cardiovascular diseases, obesity and mortality (2-4). Early signs of disease is apparent already in children, in which birth weight is negatively associated with higher cardiometabolic risk factors (5-7) and positively associated with risk of obesity (8). Furthermore, physical activity (PA), especially at higher intensities (9-11), is associated with lower cardiometabolic risk factors in the general population of children and adolescents. However, it is unknown if PA modifies the association between birth weight and cardiometabolic risk factors, with two previous studies including only a few cardiometabolic outcomes showing contradictory results (12, 13).

We hypothesized that higher moderate-to-vigorous PA (MVPA) may mitigate the associations between birth weight and cardiometabolic risk factors in children and adolescents. Examining children and adolescents may be of particular interest since interventions early in life may provide an opportunity for early intervention well before cardiovascular diseases manifest. The aim of this study was therefore to examine whether device-measured MVPA modifies the associations between birth weight and several cardiometabolic risk factors in a diverse sample of children and adolescents. By testing the statistical interaction between birth weight and MVPA on these associations we also effectively examined whether MVPA is associated with cardiometabolic health across the birth weight spectrum.

Materials and methods

Study design and participants

We used pooled individual data from studies included in the International Children's Accelerometry Database (ICAD) (14), a sub-cohort of the Norwegian Mother, Father and Child Cohort Study (MoBa) (15), Physical Activity among Norwegian Children Study (PANCS) (16, 17) and Active Smarter Kids (ASK) (18).

Results from three of the studies included in ICAD on the associations between birth weight and insulin and waist circumference, and effect modification of MVPA, have previously been published (13). In the present study, we extend the study with a more than 4-fold increases in the number of participants for insulin and more than 7-fold for waist circumference, and by including additional cardiometabolic variables.

ICAD (14) consists of device-measured PA, anthropometrics and health data collected in children and adolescents from 20 studies worldwide. Detailed description of the aims, design, recruitment of studies, and protocols of the ICAD project have been described in detail elsewhere (14), and the harmonization documents are available at the ICAD website (http://www.mrc-epid.cam.ac.uk/research/studies/icad/data-harmonisation/). For the present analyses we used data from nine ICAD-studies (ICAD 2.0). Three studies are prospective birth-cohort studies (19-22) and six are cross-sectional studies with retrospectively reported birth weight (23-25). In longitudinal studies, data from the first wave of which each person participated is included, unless later waves of data collection comprised a wider array of cardiometabolic risk factors (19, 21, 22, 24). The participants were recruited either from being born at a certain hospital or area in a specific period(19-22), through randomly selected schools(23) or through schools willing to participate within a defined area(24, 25). More information about population and recruitment method in each study is available elsewhere (19-25).

MoBa is an ongoing prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (NIPH) (15). Participants were recruited from all over Norway from 1999-2008. The women consented to participation in 40.6% of the pregnancies. We invited a sub-cohort of 1 603 10-12-year-olds from four areas in Norway, of which 430 children participated and provided sufficient data for the present analyses.

The PANCS 1 study included a national representative sample of Norwegian 9- and 15- year olds (16, 17). In total 2 299 agreed to participate, and the participation rate was 89 % and 74% for 9- and 15- year olds, respectively.

The ASK study is a school-based cluster randomized controlled trial carried out in 2014/15, situated in the western part of Norway (18). Sixty schools were approached and 57 schools (1129 children) agreed to participate (recruitment success of 95% of schools, 94% of children). For the present analyses, we included the baseline data on PA and cardiometabolic risk factors in 857 children.

Each collaborator in the ICAD consulted their research board to make sure sufficient ethical approval had been obtained. Written informed consent was obtained from each child's parent prior to all testing in ICAD, the sub-cohort of MoBa, PANCS and ASK, and the study protocols were approved by the Regional Committee for Medical Research Ethics.

Measurements

Birth weight

Birth weight was either measured at birth (15, 19-22) or retrospective parentally reported (16-18, 23-25).

Cardiometabolic risk factors

Eleven studies provided data on systolic- and diastolic blood pressure (Table 1) (15-18, 20-25). Blood pressure was measured repeatedly in a resting condition using automated blood pressure monitors, and the mean of repeated measures (two or three) was calculated. Eight studies (Table 1) provided data on LDL-cholesterol, HDL-cholesterol and triglycerides (16-18, 21-23, 25). In one study (23) fasting blood samples were drawn from capillary blood. Fasting glucose and insulin levels were available from seven studies (Table 1) (16-18, 21-23, 25). We calculated insulin resistance (Homeostatic model assessment, HOMA-IR) using the updated HOMA2 calculator (26). All blood samples were collected while participants were in a fasting state. All twelve studies included data on waist circumference (15-25). Test-personnel

measured waist circumference midway between the lower rib and the iliac crest (15-17, 19-25), or two cm above the level of the umbilicus (18) at end of gentle expiration.

Clustered risk scores with different combinations of cardiometabolic risk factors are comparable(27), and we therefore used the available variables and calculated a clustered cardiometabolic risk score by summarizing age-group specific standardized values of mean arterial blood pressure (MAP, systolic blood pressure+(diastolic blood pressure*2)/3), triglycerides, LDL/HDL-ratio and HOMA-IR, divided by 4 (number of variables).

Physical activity

PA was measured using uniaxial Actigraph- (model GT1M and 7164)(14, 16, 17) and triaxial Actigraph- (model GT3X+)(15, 18) accelerometers. For data harmonization purposes, all data was reintegrated to uniaxial format and 60 seconds epoch. All studies provided raw Actigraph data files and the data were further reanalyzed in a standardized way to ensure comparability across studies (using Kinesoft version 3.3.20 and version 3.3.80). Non-wear time was defined as ≥60 minutes of consecutive zeros, with an allowance of two minutes of nonzero interruptions. A valid day was defined as at least 480 minutes of measured wear time, and all children providing at least three valid days were included in the analyses. We used two outcome measures of PA - MVPA for main analyses and vigorous PA (VPA) for sensitivity analyses. MVPA was defined as average minutes per day ≥ 2296 counts per minute (cpm), whereas VPA was defined as average minutes per day ≥ 4012 cpm (28). We removed files flagged as spurious in the ICAD-project (14). Overnight activity were removed (14, 16-18), or days with more than 18 hours wear time were set to missing(15).

Covariates and descriptive variables

Potential confounders included in the models were parental education and sex. We further adjusted for waist circumference (model 2) and height (for systolic- and diastolic blood), measured at follow-up, to

examine the direct associations. Age at follow-up were included in the model to improve precision of the outcomes due to the known changes in cardiometabolic risk factors with increasing age in these age-groups (27).

Standardized methods were used to measure height and weight across all studies (15-25). For descriptive purposes, we calculated body mass index (BMI) as weight (in kilograms) divided by height (in meters) squared.

To harmonize the parent's education level, a dichotomous variable was created dividing the maternal and paternal education level into 1: up to and completion of compulsory education and 2: any post-compulsory education. We further combined the parents' education variables into one variable reflecting the highest education level by either the mother or the father.

Statistical analysis

Only participants for whom data for birth weight, PA (≥3 valid days) and at least one cardiometabolic risk factor were available were included in the analyses (=3 534 participants removed). The age-distribution showed two clusters of participants around age 9-10 and 15-16 years. We therefore performed a median split dividing the participants into children (≤11.6 years old) and adolescents (>11.6 years old) for all the analyses. We tested for differences between the age-groups using independent sample t-test, Mann-Whitney two-sample test and chi squared statistics. We used multilevel linear regression, including study as a random factor (12 studies), to examine the associations between birth weight, MVPA and the cardiometabolic outcomes. We adjusted all models for highest parental education, age and sex. When systolic- and diastolic blood pressure were modelled as the outcome we adjusted for childhood height, and excluded age from the model due to risk of collinearity. In model 2 we further adjusted analyses for waist circumference. Furthermore, to examine whether MVPA modified the associations between birth weight and the cardiometabolic outcomes we included the interaction term (birth weight x MVPA) in the

models. A significant interaction indicates an additive interaction given the linearity of the model. We tested all models for the assumptions of linear regression (linearity between independent and dependent variables, normal distribution of residuals and homoscedasticity). For the models including HOMA-IR and triglycerides a slightly skewed distribution of the residuals was shown. However, due to the large sample size and sensitivity analyses with and without log-transformed variables showing similar results, we kept the variables not transformed in the models to ease the interpretation of the effect estimates. Further, we used robust standard errors estimates due to signs of heteroscedasticity in some of the models. A formal interaction test showed no evidence of an interaction with sex on any of the associations. We conducted sensitivity analyses using VPA as effect modifier, and sensitivity analyses where we excluded all participants with birth weight <1.5kg, i.e. participants most likely to be born prematurely (n=66).

In case of a significant interaction ($p<0.10$) we graphically illustrated the predicted values of the outcome variable, based on the final adjusted models with the interaction term, across values of birth weight and the 25^{th}, 50^{th} and 75^{th} percentile of MVPA/VPA. Regardless of an interaction, we also graphically illustrated the predicted values of the clustered cardiometabolic risk score in a similar manner.

Three % (n=116) and 19 % (n=875) of the children and adolescents, respectively, had missing data on one or more of the included covariates. We replaced missing values using multiple imputation (MI) with Fully Conditional Specification (FCS). We imputed 20 datasets. Further details on participants with missing values, the MI-method and results from complete case analyses are provided in Supplementary Information (FileS1).

We performed all analyses using Stata/SE version 14.1. The two-sided statistical level was set to $p<0.05$ for associations and $p<0.10$ for interaction effects.

Results

Descriptive characteristics of study sample are provided in Table 1. The participants wore the accelerometer on average for 4.9 (SD=1.3) and 5.3 (SD=1.4) days, with an average of 792 (SD=69.0) and 814 (SD=89.7) minutes per day, for children and adolescents respectively.

Supplementary Information TableS1 provides characteristics of the different studies.

MVPA was associated with lower cardiometabolic risk factors, except for systolic blood pressure in children and waist circumference in adolescents (Table 2).

Table 1: Descriptive characteristics (mean and SD unless otherwise stated[b]) of study participants and study availability, stratified by age group

	CHILDREN		ADOLESCENTS	
	Studies[a]	Mean (SD)	Studies[a]	Mean (SD)
No. (n(%boys))[b]	2-5, 7, 9-12	4560 (49.9%)	1-4, 6-10, 12	4540 (45.6%)
Age (years) [b]	2-5, 7, 9-12	9.9 (0.8)	1-4, 6-10, 12	15.4(0.5)
BMI (kg/m^2)	2-5, 7, 9-12	17.8 (3.0)	1-4, 6-10, 12	21.0 (3.5)*
>compulsory education,% [bc]	2-5, 7, 9-12	84.1%	1-4, 6-10, 12	76.2%*
Birth weight (kg)	2-5, 7, 9-12	3.51 (0.60)	1-4, 6-10, 12	3.39 (0.57)*
MVPA (min/day)	2-5, 7, 9-12	62.0 (31.8)	1-4, 6-10, 12	44.7 (26.5)*
VPA (min/day)[b]	2-5, 7, 9-12	14.4 (16.7)	1-4, 6-10, 12	10.5 (15.8)*
SBP (mmHg)	2-3, 5, 7, 9-12	102.8 (8.7)	1-3, 6-10, 12	116.5 (12.6) *
DBP (mmHg)	2-3, 5, 7, 9-12	62.3 (8.2)	1-3, 6-10, 12	66.4 (8.9)*
LDL-cholesterol (mmol/l)	2-3, 5,7,9, 11-12	2.48 (0.66)	1-3, 7, 9, 12	2.17 (0.60)*
HDL- cholesterol (mmol/l)	2-3, 5,7, 9,11-12	1.61 (0.36)	1-3, 7, 9, 12	1.35 (0.31)*
Triglycerides (mmol/l) [b]	2-3,5,7, 9, 11-12	0.64 (0.36)	1-3, 7, 9, 12	0.74 (0.4) *
HOMA-IR (score)[b]	2-3, 7, 9, 11-12	0.7 (0.5)	1-3, 7, 9, 12	1.1 (0.7)*
Waist circumference (cm)	2-5, 7, 9-12	62.5 (8.7)	1-4, 6-10, 12	73.2 (8.9)*

DBP- Diastolic blood pressure; HDL- High density lipoprotein; HOMA-IR- Homeostasis Model Assessment (HOMA2); LDL- Low density lipoprotein; MVPA –Moderate to vigorous physical activity; SBP- Systolic blood pressure; VPA- Vigorous physical activity

[a]Studies: 1-ALSPAC, 2-Denmark EYHS, 3-Estionia EYHS, 4-IBDS, 5-Norway EYHS, 6-Pelotas, 7-Portugal EYHS, 8-SPEEDY, 9-KISS, 10-MoBa, 11-ASK, 12-PANCS

[b] Age, VPA, triglycerides and HOMA-IR expressed as median (IQR). Number of participants (%), and % >compulsory education.

[c]Percent (%) of which one or both parents have completed any post-compulsory education.

*p<0.05 for difference between children and adolescents

Lower birth weight was associated with higher systolic- and diastolic blood pressure, an association which became stronger in magnitude after the inclusion of waist circumference in the model (Table 2). Birth weight was not associated with LDL- or HDL-cholesterol, whereas lower birth weight was associated with higher triglyceride levels, HOMA-IR (children only) and clustered cardiometabolic risk score following adjustments for waist circumference (Table 2). A higher birth weight was associated with higher waist circumference. Introducing the interaction term (birth weight x MVPA) into the model suggested an effect modification by MVPA on the association between birth weight and waist circumference in children, and HDL-cholesterol in adolescents (Table 2). Predicted waist circumference increased by higher birth weight in the 25th, 50th and 75th percentile of MVPA, however, the increase is slightly steeper in the 25th percentile compared to the 75th percentile of MVPA (Figure 1A). Figure 1B shows that at the 75th percentile of MVPA the associations between birth weight and HDL-cholesterol was negative, whereas the association was positive at the 25th percentile of MVPA.

Table 2: Association (unstandardized regression coefficients and 95%CI) between birth weight, MVPA and cardiometabolic risk factors in children and adolescents, and interaction between birth weight and MVPA.

	CHILDREN			ADOLESCENTS		
	n	B(95%CI)	p-value	n	B(95%CI)	p-value
SBP (mmHg)	4120			4491		
Model 1[a]						
Birth weight (kg)		-1.10(-1.50, -0.70)			-1.78 (-2.52, -1.04)	
Model 2[b]						
MVPA (min/day)		-0.01 (-0.03,0.00)			-0.02 (-0.03,-0.01)	
Birth weight (kg)		-1.30 (-1.67, -0.94)			-1.98 (-2.66, -1.30)	
Birth weight x MVPA		0.005(-0.007, 0.017)	0.440		-0.005 (-0.032, 0.021)	0.685
DBP (mmHg)	4119			4491		
Model 1[a]						
Birth weight (kg)		-0.66 (-0.80, -0.42)			-0.32 (-0.61, -0.04)	
Model 2[b]						
MVPA (min/day)		-0.01 (-0.03,-0.00)			-0.01 (-0.02,-0.00)	
Birth weight (kg)		-0.74 (-0.99, -0.48)			-0.36 (-0.65, -0.08)	
Birth weight x MVPA		-0.004(-0.011, 0.002)	0.168		-0.002 (-0.023, 0.021)	0.924
LDL–cholesterol (mmol/l)	3225			2868		
Model 1[a]						
Birth weight (kg)		0.03(-0.00, 0.06)			-0.000 (-0.04, 0.04)	
Model 2[b]						
MVPA (min/day)		-0.001 (-0.002,-0.001)			-0.001 (-0.002,-0.000)	
Birth weight (kg)		0.01 (-0.01, 0.03)			-0.01 (-0.05, 0.03)	

Birth weight x MVPA		0.000(-0.001, 0.001)	0.915		-0.000(-0.001,0.000)	0.202
HDL–cholesterol (mmol/l)	3230			2868		
Model 1 [a]						
Birth weight (kg)		-0.02 (-0.05, 0.01)			-0.02 (-0.03, 0.00)	
Model 2 [b]						
MVPA (min/day)		0.001 (0.000,0.002)			0.001 (0.000,0.001)	
Birth weight (kg)		0.001 (-0.028, 0.030)			-0.004 (-0.019, 0.012)	
Birth weight x MVPA		-0.000(-0.001, 0.001)	0.978		-0.001 (-0.001,-0.000)	0.040
Triglycerides (mmol/l)	3207			2866		
Model 1 [a]						
Birth weight (kg)		-0.01 (-0.03, 0.01)			0.003 (-0.007, 0.012)	
Model 2 [b]						
MVPA (min/day)		-0.001(-0.002,-0.000)			-0.001(-0.002, -0.000)	
Birth weight (kg)		-0.03 (-0.05, -0.02)			-0.01 (-0.02, -0.00)	
Birth weight x MVPA		-0.000 (-0.001, 0.001)	0.921		0.000 (-0.000, 0.000)	0.839
HOMA-IR (score)	3109			2859		
Model 1 [a]						
Birth weight (kg)		-0.01 (-0.05, 0.03)			0.01 (-0.03, 0.05)	
Model 2 [b]						
MVPA (min/day)		-0.002(-0.003,-0.001)			-0.002(-0.003,-0.001)	
Birth weight (kg)		-0.07 (-0.11, -0.03)			-0.02 (-0.06, 0.00)	
Birth weight x MVPA		0.000 (-0.000, 0.001)	0.689		-0.000 (-0.001, 0.001)	0.941
Waist Circumference (cm)	4536			4129		
Model 1 [a]						
MVPA (min/day)		-0.03(-0.05,-0.02)			-0.01(-0.03,0.00)	
Birth weight (kg)		1.90 (1.57, 2.23)			1.55 (0.96, 2.15)	
Birth weight x MVPA		-0.010(-0.018, -0.003)	0.005		-0.001 (-0.017, 0.015)	0.896
Clustered risk score	3079			2839		
Model 1 [a]						
Birth weight (kg)		-0.008 (-0.06, 0.04)			-0.003 (-0.04, 0.03)	
Model 2 [b]						
MVPA (min/day)		-0.003(-0.005,-0.002)			-0.003(-0.003,-0.002)	
Birth weight (kg)		-0.08 (-0.12, -0.04)			-0.05 (-0.07, -0.02)	
Birth weight x MVPA		-0.000 (-0.001, 0.001)	0.774		0.000 (-0.001, 0.001)	0.948

DBP- Diastolic blood pressure; HDL- High density lipoprotein; HOMA-IR- Homeostasis Model Assessment (HOMA2); LDL- Low density lipoprotein; MVPA –Moderate to vigorous physical activity; SBP- Systolic blood pressure

Separate models for MVPA and birth weight (model 2). When interaction term (birth weight x MVPA) is examined, both MVPA and birth weight are also included in the model.

[a] Model 1: Adjusted for highest parental education, sex and age. SBP and DBP adjusted for height instead of age.

[b]Model 2: Adjusted for model 1 and waist circumference

[c]Clustered cardiometabolic risk score calculated from summing standardized values for MAP (mean arterial blood pressure), triglycerides, LDL/HDL-ratio and HOMA-IR, divided by 4 (number of variables)

Sensitivity analyses suggested that VPA modified the association between birth weight and diastolic blood pressure in children and between birth weight and LDL-cholesterol and triglycerides in adolescents. These associations are illustrated across the 25th, 50th and 75th percentile of VPA in Figure 2.

Although lower diastolic blood pressure at the 75th percentile compared to the 25th percentile of VPA, the association between birth weight and diastolic blood pressure was somewhat stronger at the 75th percentile (Figure 2A). Figure 2B shows that the association between birth weight and LDL-cholesterol in adolescents appeared to be negative at the 75th percentile, and slightly positive at the 25th percentile of VPA. A somewhat steeper negative association was observed at the 25th percentile of VPA compared to 75th percentile on the association between birth weight and triglycerides in adolescents (Figure 2C).

Figure 3 illustrates the inverse association between birth weight and the clustered cardiometabolic risk score. The magnitude of the associations was similar across levels of MVPA.

Results from sensitivity analyses excluding participants with birth weight <1.5 kg did not differ from the results including the full birth weight spectrum (data not shown).

The complete case analyses (Supplement File1) did not differ from the results using MI on missing values, except for a non-significant interaction of MVPA and birth weight on the association with HDL-cholesterol in adolescents.

Discussion

We observed that MVPA does not modify the association between a lower birth weight and an adverse cardiometabolic clustered risk in children and adolescents, nor consistently modify the associations with single risk factors. MVPA may slightly attenuate the association between higher birth weight and higher waist circumference in children. The observed effect modification of MVPA or VPA on diastolic blood pressure, LDL- cholesterol, HDL- cholesterol and triglycerides are likely clinically insignificant.

Our results are in agreement with others suggesting an association between lower birth weight and higher systolic- and diastolic blood pressure and higher insulin levels in children and adolescents (6, 7, 29-32). In contrast with previous research (6, 30, 32) we did not observe any association between birth weight and measures of insulin resistance in adolescents. Inconsistent results are reported for the

association between birth weight and subsequent triglyceride levels (6, 7, 30, 32, 33). Chiavaroli et al. (34) observed a higher clustered cardiometabolic risk score in both small- and large for gestational age individuals, possibly explained by combining both BMI and cardiometabolic risk factors in the summary score. Most previous studies suggest no association between birth weight and subsequent HDL- and LDL-cholesterol (6, 7, 30, 34, 35), whereas some have suggested that low birth weight are associated with unfavorable cholesterol levels (32, 33). It is well established that the associations between a low birth weight and subsequent cardiometabolic risk are influenced by adjustments for current body size (7, 31, 32). One may argue that the associations between a low birth weight and cardiometabolic risk factors are outweighed by the positive relationship between birth weight and adiposity measures (31, 36). On the other hand, at any given level of waist circumference, a low birth weight is associated with an adverse cardiometabolic risk profile, which is apparent already in childhood, and increase the risk of cardiovascular diseases later in life (3, 4, 37). None of the above-mentioned studies examined whether these associations may differ by levels of PA.

Few previous studies have examined a possible effect modification of PA on the association between low birth weight and measures of insulin resistance or risk of type 2 diabetes, with contradictory results. Findings by Ridgway et al. (13), are similar to ours suggesting that device-measured PA appears not to modify the association between birth weight and HOMA-IR in children and adolescents. In a similar study by Ortega et al. (12), a significant interaction was observed between birth weight and device-measured PA for the association between birth weight and HOMA-IR, suggesting the association was attenuated in the most active adolescents. Laaksonen et al. (38) and Eriksson et al. (39) observed that higher self-reported PA attenuated the odds of type 2 diabetes and metabolic syndrome in the low birth weight group in middle-aged men and elderly people. They observed an interaction on the multiplicative (relative risk) scale which may differ from interaction on the additive (risk difference) scale (40). Our

results extend previous observations by including a substantially larger and more heterogeneous sample likely led to more precise effect estimates.

We observed that MVPA may modify the association between birth weight and HDL-cholesterol in adolescents, whereas the highest intensity is necessary to modify the association with LDL-cholesterol and triglycerides. It appears that a lower birth weight is associated with lower LDL-cholesterol, but also lower HDL-cholesterol in the least active, whereas it is in the opposite direction for the more active adolescents. Furthermore, VPA may alter the association between birth weight and triglycerides in adolescents, in which the negative association is somewhat steeper at the 25th percentile compared with the 75th percentile of VPA. Regardless, the predicted differences in LDL-cholesterol, HDL-cholesterol and triglycerides from low birth weight to high birth weight across the different levels of MVPA or VPA are small and likely not clinically meaningful. These interactions need to be confirmed in future research to investigate whether they are biased by confounding factors (e.g. pubertal status or nutrition), if birth weight influence the response of PA on lipid levels in adolescents and whether these interactions persists into adulthood and may become more clinically important in development of cardiovascular diseases.

Figure 2 indicate that, although diastolic blood pressure is consistently lower in the 75th percentile compared to the 25th percentile of VPA, the association between birth weight and diastolic blood pressure is minimally stronger in the most active. This may indicate different responses of VPA across different birth weight, i.e. children with low birth weight may not respond to VPA to the same extent as children with higher birth weight. This interaction was not observed in adolescents, nor for systolic blood pressure.

Our results further suggest that MVPA may attenuate the association between higher birth weight and abdominal adiposity in children. A difference in MVPA of 40 minutes, moving from the 25th to the 75th percentile of MVPA, only provides a slight mitigation of the association, i.e. the amount of MVPA needed

to fully attenuate this association is likely substantial. Our observations challenge previous observations in smaller and more homogeneous samples, in which no interaction was observed between birth weight and abdominal adiposity (13, 41).

A clustered cardiometabolic risk score is a comprehensive measure for overall cardiometabolic health status and likely more important for future health than single risk factors. MVPA does not modify the association between birth weight and clustered cardiometabolic risk score in this sample. However, it is important to note that the clustered cardiometabolic risk score is consistently lower in more active (75^{th} percentile) compared with less active (25^{th} percentile) across the birth weight spectrum, and thus MVPA should be considered an important public health strategy in children and adolescents.

We consider device-measured PA in a large study sample as an important strength of this study, but this method is also prone to misclassification. Children's PA pattern is sporadic which makes precise measurements difficult; thus, the use of a 60-second epoch length may have led to underestimation of time spent in MVPA (42). In addition, accelerometers underestimates activities with little vertical acceleration of the hip, e.g. bicycling, and water activities due to removal of the monitor. Birth weight is used as a proxy for intrauterine growth and, in some of the included studies, measured using retrospective parental reports. However retrospective parent-reported birth weight show strongly agreement with measured birth weight (43, 44). Optimally we would have adjusted for gestational age in our analyses. Unfortunately, this information was not available. The results from sensitivity analyses where we excluded participants with birth weight <1.5 kg did not differ from the results using the full study sample, however this cannot fully compensate for the lack of data on gestational age. PA and the cardiometabolic risk factors are measured at the same time point, which limits our ability to infer causality. This is of particular concern when waist circumference is modelled as the outcome, as it is likely that a higher waist circumference may lead to reduced PA (45, 46).

Main strengths of this study are the large and diverse sample of children and adolescents with available data on several cardiometabolic risk factors and device-measured PA analyzed in a harmonized manner.

Conclusion

We did not observe strong evidence for a modifying effect of MVPA on the association between birth weight and cardiometabolic risk factors in children and adolescents, although it may to some degree attenuate the association between high birth weight and waist circumference in children. Higher levels of MVPA is consistently associated with a more favorable cardiometabolic risk profile across the birth weight spectrum.

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Conflict of interest

The authors declare no conflict of interest.

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Figures:

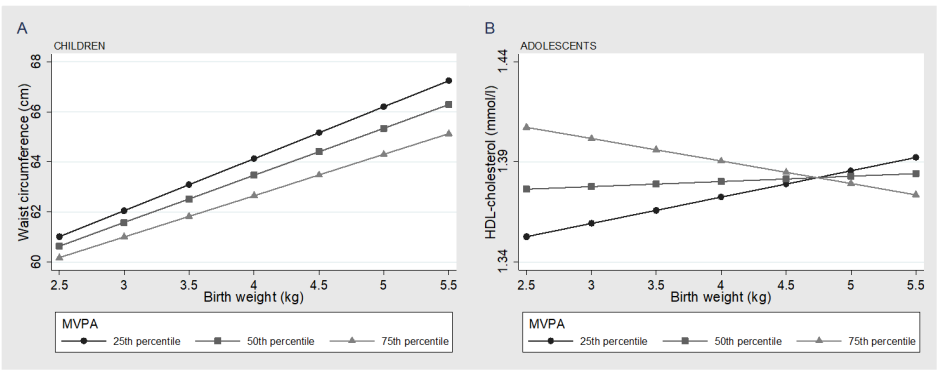


Figure 1: Predicted values of cardiometabolic outcomes (**A**: waist circumference, **B:** HDL-cholesterol) across birth weight and the 25th, 50th and 75th percentile of MVPA in children **(A)** and adolescents **(B)** from regression models with significant interaction between birth weight and MVPA ($p<0.1$).

Adjusted for highest parental education, sex, age and waist circumference (when not the outcome).

HDL- High density lipoprotein; MVPA –Moderate to vigorous physical activity

MVPA children: 25th percentile = 39.6 min/day, 50th percentile = 57.7 min/day, 75th percentile= 80.0 min/day. MVPA adolescents: 25th percentile =25.3 min/day, 50th percentile= 39.8 min/day, 75th percentile= 58.7 min/day.

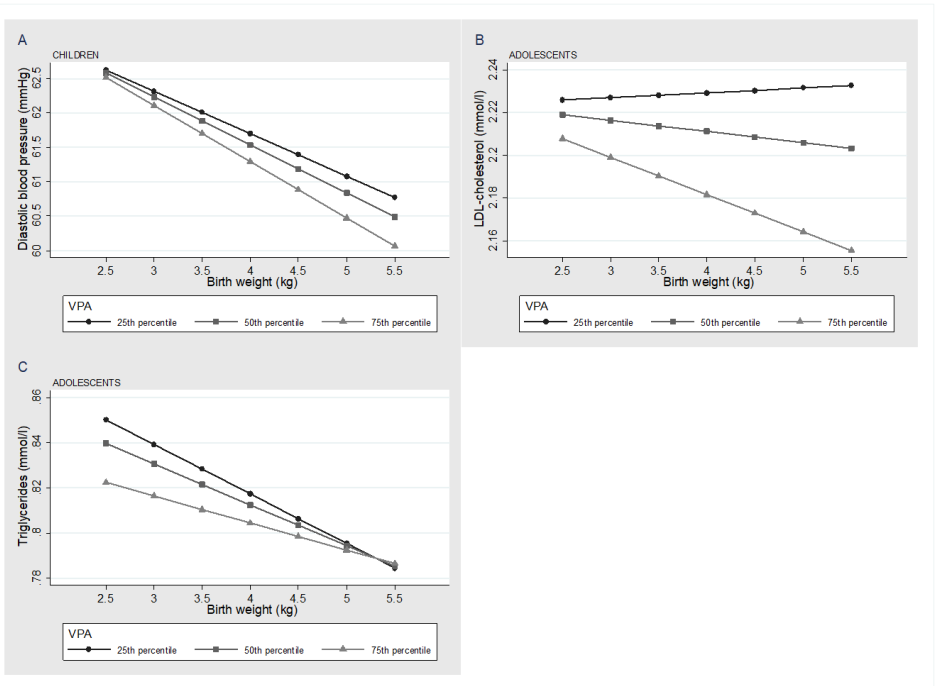


Figure 2: Predicted values of cardiometabolic outcomes (**A**: diastolic blood pressure, **B:** LDL-cholesterol, **C:** triglycerides) across birth weight and the 25th, 50th and 75th percentile of VPA in children **(A)** and adolescents **(B, C)** from regression models with significant interaction between birth weight and VPA ($p<0.1$).

Adjusted for highest parental education, sex, age (height for diastolic blood pressure) and waist circumference (when not the outcome).

HDL- High density lipoprotein; LDL- Low density lipoprotein; MVPA –Moderate to vigorous physical activity; VPA- Vigorous physical activity

VPA children: 25th percentile= 7.7 min/day, 50th percentile=14.4 min/day, 75th percentile=24.5min/day. VPA adolescents: 25th percentile= 4.5 min/day , 50th percentile=10.5 min/day, 75th percentile=20.3 min/day.

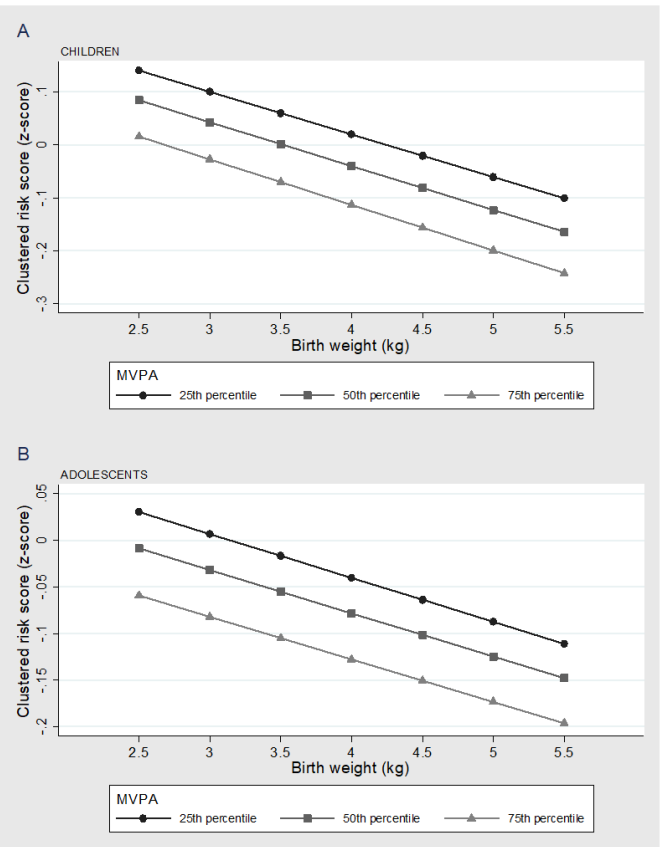


Figure 3: Predicted clustered cardiometabolic risk score across birth weight and 25th, 50th and 75th percentile of MVPA from regression model with interaction term (birth weight x MVPA) in children (**A**) and adolescents (**B**), p-value for interaction between birth weight and MVPA; children p=0.774, adolescents p=0.948).

Adjusted for highest parental education, waist circumference, sex and age.

Clustered cardiometabolic risk score calculated from summing standardized values for MAP (mean arterial blood pressure), triglycerides, LDL/HDL-ratio and HOMA-IR, divided by 4 (number of variables).

MVPA –Moderate to vigorous physical activity

Children MVPA: 25th percentile= 39.6 min/day, 50th percentile= 57.7 min/day, 75th percentile= 80.0 min/day. Adolescents: 25th percentile= 25.3 min/day, 50th percentile= 39.8 min/day, 75th percentile= 58.7 min/day

APPENDIX 1:

Information on imputation method, number of missing values, participants with complete and incomplete data and complete case analyses (Paper II)

We used Fully Conditional Specification (FCS), with ordered logistic regression when imputing values on missing on maternal education, paternal education and breastfeeding category, logistic regression when imputing values on maternal smoking and predictive mean matching (pmm) when imputing values on missing on maternal pre-pregnancy BMI (splines), birth weight (splines or linear), infant weight gain, age at 7 year follow-up and BMI at age 3 years. All variables in the final models were included in the imputation model, in addition to gestational age at delivery, birth length, age at 3 year BMI measurement, BMI at 7 years, length and weight at 1 year, length and weight at 6 months, maternal income and birth region. We conducted the imputation model separately for boys and girls.

There are some differences between participants with missing and participants with complete data (Appendix 1 Table 1) on the outcomes.

We assume that data are missing at random (MAR), given the observed variables that are included in the imputation model.

Appendix 1- Table 1: Descriptive characteristics (mean(sd) for continuous variables unless otherwise stated, and n(%) for categories) of study participants, stratified by sex and participants with complete and incomplete data.

	BOYS		GIRLS	
	Complete data 9 882 (39.8%)	Incomplete data 14 941 (60.2%)	Complete data 9 519 (39.9%)	Incomplete data 14 330 (60.1%)
Maternal pre-pregnancy BMI (kg/m^2)	24.0(4.1)	23.8(4.1)*	24.0(4.2)	23.8(4.0)*
Maternal age[a] (years)	30.6 (4.3)	30.6(4.5)	30.6 (4.3)	30.6(4.5)
Maternal parity[a] (cat)		*		*
Primiparous, n(%)	4 808 (48.6%)	6 527 (43.7%)	4 534 (47.6%)	6 281 (43.8%)
1, n(%)	3 320 (33.6%)	5 472 (36.6%)	3 297 (34.6%)	5 261 (36.7%)
2, n(%)	1 384 (14.0%)	2 316 (15.5%)	1 354 (14.2%)	2 180 (15.2%)
≥3, n(%)	370 (3.7%)	626 (4.2%)	364 (3.5%)	608 (4.2%)
Maternal education[b] (cat)		*		
< High school	349 (4.5%)	727 (5.1%)	340 (3.6%)	363 (5.1%)
High school	2 017 (20.4%)	3 139 (22.1%)	2 016 (21.2%)	2 998 (21.9%)
College/university 1-4 years	4 742 (48.0%)	6 241 (43.9%)	4 483 (47.1%)	5 871 (42.9%)
College/university >4 years	2 774 (28.1%)	4 105 (28.9%)	2 680 (28.1%)	4 116 (30.1%)
Paternal education[b] (cat)		*		*
< High school	763 (7.7 %)	1 118 (8.4%)	776 (8.1%)	1 090 (8.5%)
High school	3 473 (35.1%)	4 470 (33.6%)	3 308 (34.7%)	4 174 (32.7%)
College/university 1-4 years	3 079 (31.2%)	3 932 (29.5%)	2 966 (31.2%)	3 817 (29.9%)
College/university >4 years	2 567 (26.0%)	3 794 (28.5%)	2 469 (25.9%)	3 693 (28.9%)
Maternal smoking		*		*
No	9 139 (92.5%)	9 763 (89.8%)	8 790 (92.3%)	9 299 (90.1%)
Yes	743 (7.5%)	1 106 (10.2%)	729 (7.7%)	1 019 (9.9%)
Child birth weight (g)	3 674 (528)	3 670 (535)	3 551 (511)	3 551 (508)
Child gestational age at birth (weeks)[c]	40 (39-41)	40 (39-41)	40 (39-41)	40 (39-41)
Breastfeeding 0-4 months (cat)		*		
Exclusive	5 949 (60.2%)	6 849 (58.6%)	5 988 (62.9%)	7 062 (63.0%)
Partial	3 829 (38.7%)	4 659 (39.9%)	3 434 (36.1%)	4 001 (35.7%)
None	104 (1.0%)	171 (1.5%)	97 (1.0%)	143 (1.3%)
Child weight 1 year (kg)	10.3 (1.1)	10.3 (1.1)	9.6(1.0)	9.6 (1.0)
Weight gain 0-1 year (z-score)	-0.002 (1.13)	0.005 (1.13)	0.002 (1.12)	0.008 (1.13)
Child BMI 3 years (kg/m^2)	16.2 (1.5)	16.2 (1.5)	16.0 (1.5)	16.0 (1.6)
Child LTPA (frequency/week)	4.3 (2.3)	4.3 (2.3)	3.7 (2.1)	3.6(2.1)
Child BMI 7 years (kg/m^2)	15.79 (1.8)	15.84 (1.8) *	15.86(2.0)	15.81(2.0)

*p<0.05 for difference between complete and incomplete

[a] At time of delivery

[b] Highest completed or ongoing education in pregnancy week 17-20

[c] median (25th-75th percentile)

Appendix 1- Table 2: Included variables with missing values and mean (continuous variables) or proportion (category variables) of complete variables (complete) and the variables with imputed on missing values (MI).

Variable	n missing (%)	Complete	MI
BOYS			
Maternal pre-pregnancy BMI (kg/m^2)	825 (3 %)	23.9	23.9
Maternal age[a] (years)	0 (0%)	-	-
Maternal parity[a] (cat)	0 (%)	-	-
Primiparous, n(%)			
1, n(%)			
2, n(%)			
≥3, n(%)			
Maternal education[b] (cat)	729 (3%)		
< High school, n(%)		4.5 %	4.5%
High school, n(%)		21.4 %	21.4%
College/university 1-4 years, n(%)		45.6%	45.6%
College/university >4 years, n(%)		28.5%	28.5%
Paternal education[b] (cat)	1 627 (7%)		
< High school, n(%)		8.1 %	8.2 %
High school, n(%)		34.2 %	34.4 %
College/university 1-4 years, n(%)		30.2 %	30.2 %
College/university >4 years, n(%)		27.4 %	27.2 %
Maternal smoking in pregnancy (cat)	4 072 (16%)		
No, n(%)		91.1%	91.3%
Yes, n(%)		8.9%	8.7%
Birth weight, z-score	102 (<1%)	0.08	0.08
Breastfeeding 0-4 months (cat)	3 262 (13 %)		
Exclusive, n(%)		59.4%	59.3%
Partial, n(%)		39.4%	39.4%
None, n(%)		1.3%	1.3%
Weight gain 0-1 year (z-score)	4 537 (18%)	0.002	0.003
Child BMI 3 years (kg/m^2)	8 476 (34%)	16.3	16.3
GIRLS			
Maternal pre-pregnancy BMI (kg/m^2)	777 (3%)	23.9	23.9
Maternal age[a] (years)	0 (0%)	-	-
Maternal parity[a] (cat)	0 (0%)	-	-
Primiparous, n(%)			
1, n(%)			
2, n(%)			
≥3, n(%)			
Maternal education[b] (cat)	652 (3%)		
< High school		4.4%	4.5%
High school		21.6%	21.7%

College/university 1-4 years		44.6%	44.6%
College/university >4 years		29.3%	29.2%
Paternal education[b] (cat)	1 556 (7%)		
< High school, n(%)		8.4 %	8.4 %
High school, n(%)		33.6 %	33.7 %
College/university 1-4 years, n(%)		30.4 %	30.4 %
College/university >4 years, n(%)		27.6 %	27.4 %
Maternal smoking in pregnancy (cat)	4 012 (17%)		
No		91.2%	91.4%
Yes		8.8%	8.6%
Birth weight, z-score	114 (<1%)	0.161	0.161
Breastfeeding 0-4 months (cat)	3 124 (13%)		
Exclusive		63.0%	63.0%
Partial		35.9%	35.9%
None		1.2%	1.2%
Weight gain 0-1 year (z-score)	4 276 (18%)	0.005	0.002
Child BMI 3 years (kg/m^2)	8 048 (34%)	16.0	16.0

Appendix 1- Table 3: Association (unstandardized regression coefficients) with 95%CI between early life factors and LTPA in childhood in boys and girls, complete case analyses.

	Boys		Girls	
	n	B(95%CI)	n	B(95%CI)
Maternal pre-pregnancy BMI (kg/m^2)[a]	18 291		17 495	
Spline 1 (B≤21; G≤20)		0.08 (0.03, 0.13)		0.06 (-0.01, 0.13)
Spline 2 (B>21; G>20)		-0.01 (-0.02, -0.005)		0.002 (-0.01, 0.01)
Maternal pre-pregnancy BMI (kg/m^2) -mediators[d]	10 851			
Spline 1 (B≤21)		0.07 (0.01, 0.14)		
Spline 2 (B>21)		-0.01 (-0.03,-0.003)		
Birth weight (z-score)[b]	18 208		17 410	
B: Spline 1 (≤-1)/ G:linear		0.32 (0.14, 0.50)		0.006 (-0.027, 0.040)
B: Spline 2 (>-1)		-0.05 (-0.09, -0.005)		
Infant weight gain (z-score)[c]	13 629		13 045	
Linear		0.06 (0.02, 0.10)		0.002 (-0.035, 0.039)

Abbreviations: B- Boys; BMI-body mass index; G- Girls; LTPA- Leisure Time Physical activity

[a]adjusted for maternal age, parity, maternal education, maternal smoking during pregnancy, and child's age at follow-up

[b]adjusted for maternal pre-pregnancy BMI, maternal age, parity, maternal education, maternal smoking during pregnancy, and child's age at follow-up

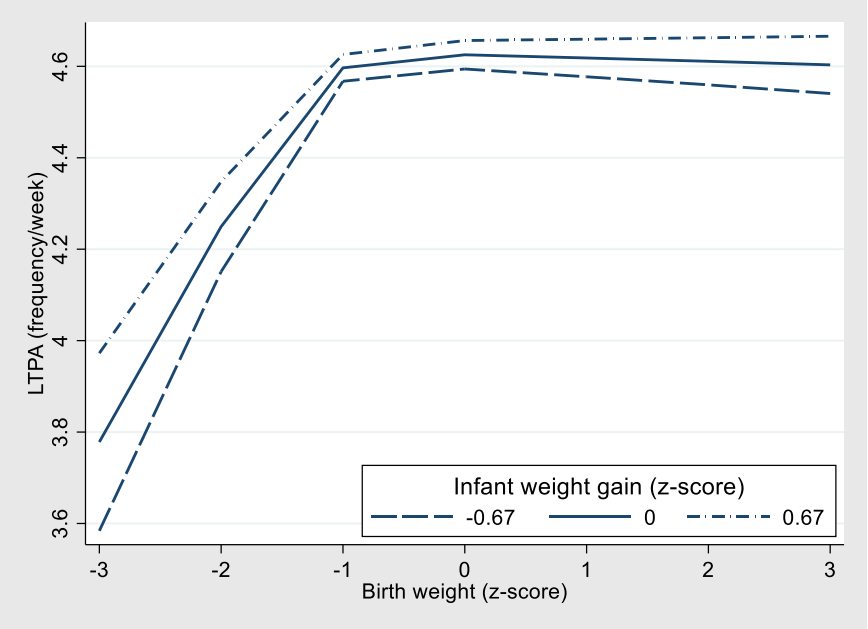
[c]adjusted for birth weight z-score, maternal pre-pregnancy BMI, maternal age, parity, maternal education, maternal smoking during pregnancy, breastfeeding from 0-4 months and child's age at follow-up.

[d]adjusted for [a]- in addition to all possible mediators (birth weight, infant weight gain and BMI at age 3 years).

There was no significant interaction (p=0.152 and 0.396) between birth weight and infant weight gain in complete case analyses, but for comparisons with the dataset with MI we have graphically examined the association between birth weight across infant weight gain (-0.67, 0, 0.67) with and without adjustments for BMI at age 3 years.

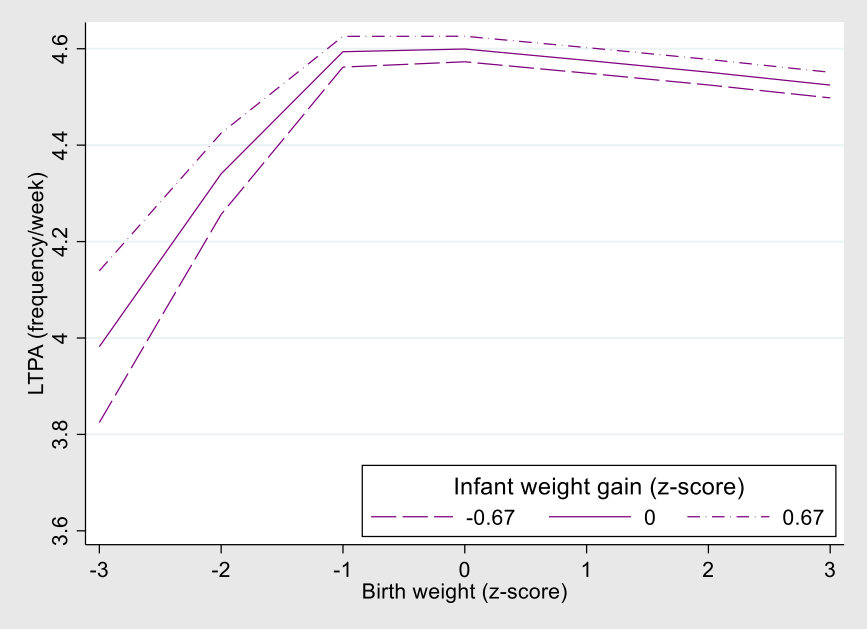
The interaction between birth weight and infant weight gain are graphically illustrated in two figures, without and with adjustments for BMI at age 3 years (Appendix 1- Figure 1 and 2, respectively).

There are some small differences between the figure with (Appendix 1-Figure 2) and the figure without (Appendix 1-Figure 1) adjustments for BMI. It is also important to note that the study sample decreases from 13 629 to 9 882 after adjustments for BMI (due to 34 % missing in this variable – Appendix 1-Table 2).



Appendix 1- Figure 1: Predicted LTPA with 95%CI in childhood across birth weight and infant weight gain (0-1y) z-score from 0-1 year at -0.67, 0 and 0.67. Predicted values from linear mixed model including interaction term birth weight*infant weight gain. Analyses adjusted for birth weight z-score, maternal pre-pregnancy BMI, maternal age, parity, maternal education, paternal education, maternal smoking during pregnancy, breastfeeding from 0-4 months and child's age at follow-up. Complete case analysis

BMI- Body mass index; LTPA- Leisure time physical activity (frequency/week)



Appendix 1- Figure 2: Predicted LTPA with 95%CI in childhood across birth weight and infant weight gain (0-1y) z-score from 0-1 year at -0.67, 0 and 0.67. Predicted values from linear mixed model including interaction term birth weight*infant weight gain. Analyses adjusted for birth weight z-score, maternal pre-pregnancy BMI, maternal age, parity, maternal education, paternal education, maternal smoking during pregnancy, breastfeeding from 0-4 months, child's age at follow-up and BMI at age 3 years. Complete case analysis

BMI- Body mass index; LTPA- Leisure time physical activity (frequency/week)

APPENDIX 2:

Information on imputation method, number of missing values, participants with complete and incomplete data and complete case analyses (Paper III)

We assume that data are missing at random (MAR), given the observed variables that are included in the imputation model.

We used Fully Conditional Specification (FCS), with predictive mean matching (with 5 of the closest observations to draw from) when imputing on missing values on maternal pre-pregnancy weight, birth weight, infant weight gain and interactions terms and ordered logistic regression for parental education. We performed separate imputation models for boys and girls. Number of missing values in each exposure/covariate with missing, and descriptive statistics in the complete and imputed variable are presented in S2 File- Table 2.

All variables in the full models were included in the imputation model, in addition to the auxiliary variables= child's weight at 6 weeks, child's weight at 6 months, child's weight at 15 months, maternal weight by the end of pregnancy, maternal weight 6 months postpartum, test center and childhood waist circumference. Interaction terms (early life risk factor x MVPA/VPA) were included in the imputation model as "just another variable" (JAV). We removed participants with missing on the outcome of interest for each analysis model.

Appendix 2- Table 1: Descriptive characteristics (mean and sd) of study participants, stratified by sex and participants with complete and incomplete data.

	BOYS		GIRLS	
	Complete data (n=192)	Incomplete data (n=50)	Complete data (n=166)	Incomplete data (n=37)
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
MVPA (min/day)	73.0(26.5)	77.6(26.6)	58.5(18.5)	56.6(21.0)
VPA (min/day)	29.4(15.2)	29.9(12.2)	21.3(10.1)	20.8(11.2)
Fat mass (kg)	10.1(4.1)	9.5(4.4)	11.0(3.2)	13.9(7.9)*
Fat free mass (kg)	29.3(3.5)	29.6(3.9)	28.3(4.5)	29.8(5.9)
Percent fat (%)	24.9(6.3)	23.5(5.7)	27.6(4.7)	30.2(8.8)
BMI (kg/m^2)	17.8(2.4)	18.1(2.6)	17.6(2.0)	18.5(3.2)
Maternal pre-pregnancy BMI (kg/m^2)	23.5(3.9)	25.6(5.2)*	23.6(4.0)	24.8(4.0)
Birth weight (z-score)	0.11(1.03)	0.23 (1.09)	0.01(1.05)	0.27(1.16)
Infant weight gain (z-score)	-0.07(1.11)	-0.74(0.90)	-0.07(1.04)	-0.31(0.58)

*p<0.05 for differences between participants with complete- and incomplete data

Appendix 2- Table 2: Covariates and exposures with missing values and descriptive statistics of complete variables (complete) and the variables with imputed on missing values (MI).

Variable	n missing (%)	Complete	MI
Boys			
Parental education (%)	3(1%)		
<High school		2.5%	2.5%
High school		20.9%	20.8%
College/university 1-4years		39.7%	39.7%
College/university >4years		36.8%	36.9%
Maternal pre-pregnancy BMI (kg/m^2) mean(range)	6 (2%)	Mean: 23.9 Range: 17.0-40.23	Mean: 23.9 Range: 17.0-40.23
Birth weight (kg)	1 (<1%)	Mean: 3.7 Range: 1.10-5.45	mean: 3.7 range: 1.10-5.45

Birth weight[a] (z-score)	1 (<1%)	Mean: 0.14 Range: -3.60 - 3.63	mean: 0.14 range: -3.60 - 3.63
Infant weight gain (z-score)	42(17%)	Mean: -0.093 Range: -3.64 - 3.92	Mean: -0.105 Range: -3.64 - 3.92
Maternal BMI x MVPA	6(2%)	Mean: 1764.2 Range: 295.9-4871.5	Mean: 1759.7 Range: 295.9-4871.5
Maternal BMI x VPA	6(2%)	Mean: 698.7 Range: 83.6-2106.4	Mean: 697.5 Range: 83.6-2106.4
Birth weight[a] x MVPA	1(<1%)	Mean: 7.2 Range: -377.0 – 270.6	Mean: 7.2 Range: -377.0 – 270.6
Birth weight[a] x VPA	1(<1%)	Mean: 2.18 Range: -233.9 – 132.5	Mean: 2.21 Range: -233.9 – 132.5
Weight gain x MVPA	42(17%)	Mean: -6.86 Range: -452.0 – 384.4	Mean: -6.82 Range: -452.0 – 384.4
Weight gain x VPA	42(17%)	Mean: -2.91 Range: -204.4 – 130.6	Mean: -2.96 Range: -204.4 – 130.6
Girls			
Parental education *<High school* *High school* *College/university 1-4years* *College/university >4years*	3 (1%)	 2.0% 24.0% 40.0% 34.0%	 2.0% 23.8% 40.0% 34.2%
Maternal pre-pregnancy BMI (kg/m^2)	6(3%)	Mean: 23.8 Range: 14.7-39.6	Mean: 23.8 Range: 14.7-39.6
Birth weight (kg)	0(0%)	-	-
Birth weight[a] (z-score)	0(0%)	-	-
Infant weight gain (z-score)	32(16%)	Mean: -0.081 Range: -3.25 – 3.94	Mean: -0.084 Range: -3.25 – 3.94
Maternal BMI x MVPA	6(3%)	Mean: 1376.3 Range: 382.1-3153.5	Mean: 1372.6 Range: 382.1-3153.5
Maternal BMI x VPA	6(3%)	Mean: 501.2 Range: 80.9-1700.2	Mean: 499.3 Range: 80.9-1700.2
Birth weight[a] x MVPA	0(0%)	-	-
Birth weight[a] x VPA	0(0%)	-	-
Weight gain x MVPA	32(16%)	Mean: -5.72 Range: -172.7- 313.5	Mean: -5.64 Range: -172.7- 313.5
Weight gain x VPA	32 (16%)	Mean -2.02 Range: -66.02- 105.7	Mean: -2.03 Range: -66.02 – 105.7

[a]Birth weight for gestational age (z-score)

Appendix 2 - Table 3: Association (unstandardized regression coefficients with 95%CI) between physical activity (MVPA/VPA) and early life risk factors with body composition and BMI in childhood, and interaction between early life risk factors and MVPA/VPA. Complete case analyses.

	Fat mass (kg)		Fat free mass (kg)		Percent fat (%)		BMI (kg/m^2)	
	Boys	Girls	Boys	Girls	Boys	Girls	Boys	Girls
MVPA (min/day)	-0.03(-0.06,0.00)	-0.03(-0.09,0.02)	-0.01(-0.03,0.02)	-0.01(-0.07,0.04)	-0.04(-0.09,0.00)	-0.03(-010,0.4)	-0.01(-0.03,-0.00)	-0.00(-0.02,0.01)
VPA (min/day)	-0.05(-0.11,0.00)	-0.05(-0.16,0.06)	-0.00(-0.05,0.04)	-0.01(-0.12,0.10)	-0.09 (-0.17, -0.01)	-0.05(-0.19.0.09)	-0.04(-0.06,-0.01)	-0.01(-0.04,0.02)
Maternal pre-pregnancy BMI (kg/m^2)	0.44(0.25,0.62)	0.19(-0.06,0.43)	0.14(0.03,0.25)	0.06(-0.08, 0.20)	0.62(0.32,0.91)	0.25(-0.11,0.60)	0.28(0.22,0.35)	0.09(0.01,0.17)
Maternal pre-pregnancy BMI xMVPA	-0.001(-0.02, 0.00)	-0.001, -0.02,0.01)	-0.005(-0.01,0.00)	-0.003(-0.01, 0.01)	-0.010(-0.03,0.00)	0.005(-0.02,0.03)	-0.001(-0.00, 0.00)	-0.000(-0.00, 0.00)
Maternal pre-pregnancy BMI xVPA	-0.012(-0.03, 0.00)	-0.001(-0.03,0.03)	-0.004(-0.01 ,0.00)	-0.003(-0.02, 0.01)	-0.018(-0.04, 0.01)	0.007(-0.03, 0.05)	-0.005(-0.01, 0.00)	-0.002(-0.01,0.01)
Birth weight for gestational age (z-score)	0.19(-0.53,0.92)	0.23(-0.60,1.06)	0.17(-0.26,0.60)	0.37(-0.10,0.83)	0.22(-0.92,1.37)	0.16(-1.03,1.35)	0.16 (-0.12,0.43)	0.32(0.02,0.63)
Birth weight x MVPA	0.009(-0.01, 0.03)	0.020(-0.03, 0.07)	-0.000(-0.01, 0.01)	0.019(-0.01, 0.05)	0.028(-0.01, 0.06)	0.041(-0.04, 0.12)	0.000(-0.01, 0.01)	0.001(-0.01, 0.02)
Birth weight x VPA	0.007(-0.03,0.04)	-0.002(-0.12, 0.11)	0.003(-0.02, 0.02)	0.043(-0.02, 0.11)	0.031(-0.02, 0.08)	0.021(-0.14,0.19)	0.001(-0.01, 0.01)	-0.004(-0.04, 0.03)
Infant weight gain (z-score)	1.29(0.36,2.21)	0.08(-0.80, 0.96)	0.82(0.30,1.35)	-0.04(-0.62,0.53)	1.87(0.39,3.34)	0.09(-1.37,1.54)	0.75(0.37,1.13)	0.32(-0.04,0.68)
Infant weight gain x MVPA	-0.025(-0.04,-0.00)	-0.005(-0.04,0.03)	-0.002(-0.01, 0.01)	0.000(-0.02, 0.02)	-0.031(-0.06,0.00)	-0.013(-0.07,0.05)	-0.002(-0.01, 0.01)	0.002(-0.01,0.02)
Infant weight gain x VPA	-0.059(-0.10,-0.02)	-0.007(-0.09, 0.08)	-0.004(-0.03, 0.02)	-0.005(-0.06, 0.05)	-0.084(-0.14,0.02)	-0.025(-0.16, 0.11)	-0.007(-0.02, 0.01)	0.007(-0.03, 0.04)

BMI- Body Mass Index; MVPA- Moderate to vigorous physical activity; VPA- Vigorous physical activity,

Number of participants in complete case analyses (boys/girls):

Body composition (fat mass, fat free mass, percent fat) - MVPA: 97/86
Body composition (fat mass, fat free mass, percent fat) - VPA: 97/86
Body composition (fat mass, fat free mass, percent fat) - maternal pre-pregnancy BMI: 94/82
Body composition (fat mass, fat free mass, percent fat) - birth weight: 94/82
Body composition (fat mass, fat free mass, percent fat) - infant weight gain: 82/73
BMI- MVPA/VPA: 239/200
BMI- maternal pre-pregnancy weight: 232/195
BMI- birth weight: 232/195
BMI- infant weight gain: 197/169

APPENDIX 3:

Information on imputation method, number of missing values, participants with complete and incomplete data and complete case analyses (Paper IV)

Amount of missing differed between the studies (% with missing on one or more of the covariates= SPEEDY=5.87%, ALSPAC=37.06%, EYHS-Denmark=5.01%, EYHS Estonia= 0.70%, EYHS-Norway=3.81%, EYHS-Portugal=1.86%, KISS=15.03%, Pelotas=0.23%, IBDS=0.70%, ASK=3.03%, PANCS=0.52%, MoBa=2.09%). The large amount of missing in studies including adolescents (ALSPAC) probably explain much of the large difference in amount of missing between children and adolescents. There are some differences between participants with missing and participants with complete data (S1 File-Table 1) on the outcomes.

We used Fully Conditional Specification (FCS), with logistic regression when imputing values on missing on parental education and predictive mean matching (pmm) when imputing values on missing on waist circumference and height (as well as for the outcome variables). All variables in the final models (including the interaction term) were included in the imputation model, in addition to study and country. We conducted the imputation model separately for children and adolescents. We removed participants with missing on the outcome of interest for each analysis model.

We assume that data are missing at random (MAR), given the observed variables that are included in the imputation model.

Appendix 3- Table1: Descriptive characteristics (mean and sd unless otherwise stated) of study participants, stratified by age group and participants with complete and incomplete data.

	CHILDREN		ADOLESCENTS	
	Complete data (n=4533)	Incomplete data (n=117)	Complete data (n=3769)	Incomplete data (n=879)
	Mean (sd)	Mean (sd)	Mean (sd)	Mean (sd)
Birth weight (kg)	3.51 (0.60)	3.43 (0.59)	3.40 (0.57)	3.37 (0.58)
MVPA (min/day)	62.0 (31.8)	63.5 (32.5)	44.6 (26.8)	45.1 (25.1)
SBP (mmHg)	102.8(8.7)	102.8 (9.3)	115.3(12.5)	121.5 (11.7)*
DBP (mmHg)	62.3 (8.2)	61.7 (7.7)	66.2 (9.0)	67.3 (8.5)*
LDL-cholesterol (mmol/l)	2.5 (0.6)	2.4(0.7)	2.2 (0.6)	2.1 (0.6)*
HDL- cholesterol (mmol/l)	1.6 (0.4)	1.6 (0.3)	1.4(0.3)	1.3 (0.3)*
Triglycerides (mmol/l)	0.64(0.36)	0.65(0.40)	0.74(0.40)	0.74(0.38)
HOMA-IR (score)	0.7 (0.5)	0.7 (0.5)	1.1 (0.7)	1.2 (0.7)*
Waist circumference (cm)	62.6 (8.7)	59.1 (8.2)*	72.9(8.9)	75.7(8.9)*

[b]Triglycerides and insulin expressed as median (25-75 percentile)

DBP- Diastolic blood pressure; HDL- High density lipoprotein; HOMA-IR- Homeostasis Assessment Model (HOMA2); LDL- Low density lipoprotein; MVPA –Moderate to vigorous physical activity; SBP- Systolic blood pressure

*p<0.05 for differences between participants with complete- and incomplete data

Appendix 3-Table 2: Covariates with missing values and descriptive statistics of complete variables (complete) and the variables with imputed on missing values (MI).

Variable	n missing (%)	Complete	MI
Children			
Parental education	87 (2%)	>compulsory education[a]= 84.1%	>compulsory education[a]= 84.2%
Waist circumference (cm)	24 (<1%)	Mean: 62.5 Range: 32.1-121.5	mean: 62.5 range: 32.1-121.5
Height (m)	24 (<1%)	mean: 1.41 range: 1.10-1.74	mean: 1.41 range: 1.10-1.74
Adolescents			

Parental education	563 (12%)	>compulsory education[a]= 76.2%	>compulsory education[a]= 77.5%
Waist circumference	411 (9%)	mean: 73.2 range: 38.0-125.9	mean: 73.5 range: 38.0-125.9
Height	21 (<1%)	mean: 1.67 range: 1.28-1.98	mean: 1.67 range: 1.28-1.98

[a] Percent (%) of which one or both parents have completed any post-compulsory education.

Appendix 3- Table 3: Association (unstandardized regression coefficients and 95%CI) between birth weight and cardiometabolic risk factors, and interaction with MVPA (p-value), complete case analyses

	MODEL 1 [a]		MODEL 2[b]		
		Association		Association	Birth weight x MVPA
	n	B (95% CI)	n	B (95% CI)	p-value
Children					
SBP (mmHg)	4020	-1.15(-1.55, -0.74)	4015	-1.35 (-1.72, -0.98)	0.499
DBP (mmHg)	4019	-0.69 (-0.93, -0.46)	4014	-0.77 (-1.03, -0.51)	0.130
LDL– cholesterol (mmol/l)	3163	0.03(-0.00, 0.07)	3143	0.01 (-0.01, 0.04)	0.975
HDL- cholesterol (mmol/l)	3167	-0.02 (-0.05, 0.01)	3147	0.00 (-0.03, 0.03)	0.967
Triglycerides (mmol/l)	3148	-0.01 (-0.03, 0.01)	3128	-0.03(-0.05, -0.02)	0.786
HOMA-IR (score)	3052	-0.01 (-0.05, 0.03)	3032	-0.07 (-0.11, -0.03)	0.789
Waist circumference (cm)	4449	1.90 (1.57, 2.23)		-	0.003
Clustered risk score[c]	3022	-0.01 (-0.06, 0.04)	3010	-0.08 (-0.13, -0.04)	0.696
Adolescents					
SBP (mmHg)	3919	-1.66 (-2.45, -0.87)	3625	-1.97 (-2.82, -1.13)	0.747
DBP (mmHg)	3919	-0.41 (-0.74, -0.08)	3625	-0.45 (-0.78, -0.12)	0.481
LDL cholesterol (mmol/l)	2507	-0.00 (-0.05, 0.05)	2320	-0.01 (-0.05, 0.04)	0.332
HDL- cholesterol (mmol/l)	2507	-0.02 (-0.04, -0.01)	2320	-0.01 (-0.03, 0.00)	0.147
Triglycerides (mmol/l)	2506	0.00 (-0.01, 0.01)	2319	-0.02(-0.03, -0.01)	0.789
HOMA-IR (score)	2500	0.01 (-0.05, 0.07)	2313	-0.04 (-0.10, 0.01)	0.718
Waist circumference (cm)	3673	1.73 (1.15, 2.30)		-	0.954
Clustered risk score[c]	2486	0.00 (-0.04, 0.04)	2302	-0.05 (-0.08, -0.01)	0.899

DBP- Diastolic blood pressure; HDL- High density lipoprotein; HOMA-IR- Homeostasis Assessment Model (HOMA2); LDL- Low density lipoprotein; MVPA –Moderate to vigorous physical activity; SBP- Systolic blood pressure

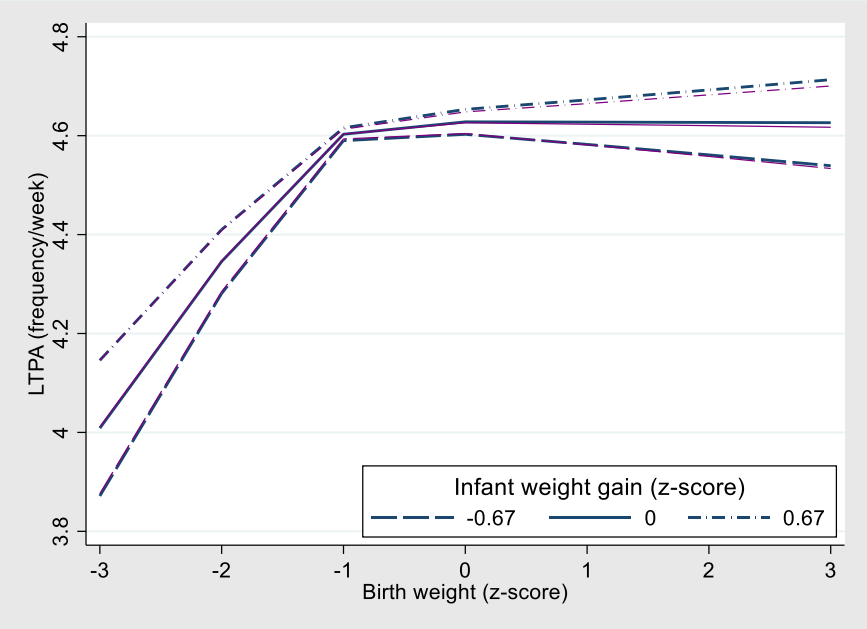
[a] Model 1: Adjusted for highest parental education, sex and age. SBP and DBP adjusted for height instead of age.

[b]Model 2: Adjusted for model 1 and waist circumference

[c]Clustered cardiometabolic risk score calculated from summing standardized values for MAP (mean arterial blood pressure), triglycerides, LDL/HDL-ratio and fasting insulin, divided by 4 (number of variables)

APPENDIX 4:

Figure illustrating the interaction between birth weight and infant weight gain on LTPA in boys, with and without adjustments for BMI at age 3 years (Paper II)



Appendix 4-Figure1: Predicted LTPA with 95%CI in childhood across birth weight and infant weight gain (0-1y) z-score from 0-1 year at -0.67, 0 and 0.67. Predicted values from linear mixed model including interaction term birth weight*infant weight gain. Blue line- analyses adjusted for birth weight z-score, maternal pre-pregnancy BMI, maternal age, parity, maternal education, paternal education, maternal smoking during pregnancy, breastfeeding from 0-4 months and child's age at follow-up. Purple line- additionally adjusted for BMI at age 3 years. Abbreviations: BMI- Body mass index; LTPA- Leisure time physical activity (frequency/week)

APPENDIX 5:

Tables providing information about self-selection and differential loss to follow up in MoBa (Paper II) and the sub-cohort of MoBa (Paper III and Paper IV)

Appendix 5- Table 1: Descriptive characteristics of study participants stratified by loss to follow up and participants included in the analyses, shown as mean (sd) for continuous variables and proportion (%) for categorical variables unless otherwise stated.

Variable	Loss to follow-up (eligible for analyses) n=58 480	Participants in analyses n=48 672
Maternal characteristics		
Maternal pre-pregnancy BMI (kg/m^2)	24.2 (4.4)	23.9 (4.1) *
Maternal pre-pregnancy weight status (cat)		*
Underweight, %	3.5 %	2.8 %
Normal weight, %	63.6 %	67.3 %
Overweight, %	22.2 %	21.5 %
Obese, %	10.7 %	8.4 %
Maternal age[a] (years)	29.7 (4.8)	30.6 (4.4) *
Maternal parity[a] (cat)		*
Primiparous, n(%)	42.7 %	45.5 %
1, %	36.2 %	35.6 %
2, %	16.1 %	14.9 %
≥3, %	4.5 %	4.0 %
Maternal education[b] (cat)		*
< High school, %	9.8 %	4.5 %
High school, %	28.5 %	21.5 %
College/university 1-4 years, %	39.0 %	45.1 %
College/university >4 years, %	22.7 %	28.9 %
Paternal education[b] (cat)		*
< High school, %	12.3 %	8.2 %
High school, %	38.5 %	33.9 %
College/university 1-4 years, %	26.6 %	30.3 %
College/university >4 years, %	22.6 %	27.5 %
Maternal smoking in pregnancy (cat)		*
No, %	84.1 %	91.1 %
Yes, %	15.9 %	8.9 %
Child 0-3 years old characteristics		
Child birth weight (kg)	3.61 (5.4)	3.61 (5.2)
Child gestational age at birth (weeks)[c]	40 (39-41)	40 (39-41)*
Breastfeeding 0-4 months (cat)		*
Exclusive, %	58.0 %	61.1 %
Partial, %	40.4 %	37.7 %
None, %	1.6 %	1.2 %
Child weight 1 year (kg)	10.0 (1.1)	9.9 (1.1) *
Child BMI 3 years (kg/m^2)	16.1 (1.6)	16.1 (1.5)

Note: there could also be participants with missing information within each variable in both groups

*$p<0.05$ for difference between loss to follow-up and included participants

[a] At time of delivery

[b] Highest completed or ongoing education in pregnancy week 17-20

[c] median (25^{th}-75^{th} percentile)

Appendix 5-Table 2: Summary statistics of invited participants to the sub-cohort of MoBa (Paper III and Paper IV), stratified by those who declined and accepted participation (self-selection). Values are median (25^{th}-75^{th} percentile) or proportion of participants (%).

	Declined participation	Participated
Parental education[a]		
<High school	2.8 %	2.3 %
High school	27.0 %	22.1%
College/university 1-4years	36.5 %	39.8%
College/university >4years	33.0 %	35.3%
Child's BMI age 7 years (kg/m^2)	15.4 (14.5-16.7)	15.7 (14.8-16.8)
Child's PA-level 7 years (frequency/week)	3 (2-4)	3 (2-5)
Child's birth weight (kg)	3.63 (3.27-3.99)	3.63 (3.26-4.03)
Maternal pre-pregnancy BMI (kg/m^2)	23.2 (21.1-25.9)	23.0 (20.9-25.5)

[a] the education level of the parent with the highest completed or ongoing education (mother or father)
BMI- Body mass index

APPENDIX 6:

Approval letters from the Regional Committes for Medical Research Ethics and the Norwegian Social Science Data Services

folkehelseinstituttet

Norges idrettshøgskole
Seksjon for idrettsmedisinske fag
Ulf Eklund
PO Boks 4014 Ullevål Stadion
0806 OSLO

Deres ref.:
Vår ref.: 13/2125
Dato: 12.12.2013

Vedtaksbrev for godkjenning av forskningsprosjektet PDB 1464 " Early life determinants of sedentary behaviour and physical activity" og utlevering av forskningsfil fra Mor og barn-undersøkelsen

Vi viser til deres søknad av 10.11.2013 vedrørende utlevering av data fra folkehelseinstituttets register MoBa og MFR.

MoBa ledergruppen har vurdert søknaden og de tillatelser som foreligger, og funnet at forskningsprosjektets formål er i tråd med formålet til Mor og barn-undersøkelsen.

Prosjektet godkjennes under forutsetning av at tillatelse for kobling av data innsamlet i prosjektet «Causal pathways for asthma» ligger inn under REK godkjenningen til prosjektet som har PI Wenche Nystad.

Beskrivelse av godkjente problemstillinger

1) Are infancy and early childhood growth in height and weight associated with childhood sedentary behaviour and physical activity at age 7 to 9 years?

2) Are infancy and early childhood motor development, and temperament associated with childhood sedentary behaviour and physical activity at age 7-9 years?

3) Does physical activity modify or mediate the potential associations between early life determinants (e.g. growth and motor development) and childhood obesity and body composition?

4) Are there any differences in early life determinants for sedentary behaviour and physical activity between contemporary birth cohorts from Norway and Brazil?

Artikkel titler:

1. Maternal and early life determinants of sedentary behaviour and physical activity.

2. Birth weight, infant weight gain and childhood sedentary time and physical activity.

3. Early motor development, temprament and life circumstances and later sedentary behaviour and physical activity

4. Does physical activity mediate or moderate the associations between birth weight and rapid early weigth gain and childhood adiposity?

5. Do the associations between early life factors and childhood sedentary time and physical activity differ between cohorts from developing and developed countries?

Hjemmelsgrunnlag for utlevering:

- MoBa konsesjonen
- REK-godkjenning for kobling av data samlet inn under prosjektet «Causal pathways for asthma» PI Wenche Nystad.

Betaling

I henhold til MoBas prisstrategi vil prosjektet bli fakturert for en doktorgrad – 100 000 NOK.

Tilgang til MoBa datafil versjon VII:
MoBa spørreskjema nr: 1, 2, 3, 4, 5, 6, 7 samt MFR variabler.
Prosjektet skal koble på data fra om fysisk aktivitet, kroppssammensetning og biokjemiske variabler fra prosjektet «Causal pathways for asthma» PI Wenche Nystad.

Utlevering:
Datafilen vil bli utlevert fra datautleveringsenheten i Bergen. De kan kontaktes på e-post: morbarndata@fhi.no.

Dataene som utleveres er avidentifiserte. Dette betyr at direkte identifiserbare kjennetegn som navn og personnummer er fjernet. Variabler som kan være egnet til å identifisere enkeltindivider er fjernet eller kategorisert på en slik at mulighetene for identifisering av enkeltindivider utelukkes. Filen vil med dette fremstå som anonym for mottaker, men Folkehelseinstituttet vil av kvalitetshensyn oppbevare filens koblingsnøkkel så lenge prosjektet pågår. Koblingsnøkkelen slettes ved prosjektets sluttdato.

Sluttdato for prosjektet:

31.12.2017

Vilkår for utlevering:

Vedlagt er datautleveringsavtalen med vilkår for datautleveringen. Vennligst les gjennom avtalen og returner til datatilgang@fhi.no i signert tilstand.

Dette er et enkeltvedtak som kan påklages etter forvaltningsloven § 28. En eventuell klage sendes Folkehelseinstituttet **innen tre uker** etter at brevet er mottatt.

Vennlig hilsen

Charlotte Birke
administrativ leder MoBa

Kristine Vejrup
faglig rådgiver

Norsk samfunnsvitenskapelig datatjeneste AS
NORWEGIAN SOCIAL SCIENCE DATA SERVICES

Harald Hårfagres gate 29
N-5007 Bergen
Norway
Tel: +47-55 58 21 17
Fax: +47-55 58 96 50
nsd@nsd.uib.no
www.nsd.uib.no
Org.nr. 985 321 884

Guro Pauck Øglund
Seksjon for idrettsmedisinske fag Norges idrettshøgskole
Postboks 4014 Ullevål Stadion
0806 OSLO

Vår dato: 28.08.2014 Vår ref: 39462 / 3 / LT Deres dato: Deres ref:

TILBAKEMELDING PÅ MELDING OM BEHANDLING AV PERSONOPPLYSNINGER

Vi viser til melding om behandling av personopplysninger, mottatt 15.08.2014. Meldingen gjelder prosjektet:

39462	*Validitet og reliabilitet av spørreskjema om barns aktivitetsnivå- MoBa*
Behandlingsansvarlig	*Norges idrettshøgskole, ved institusjonens øverste leder*
Daglig ansvarlig	*Guro Pauck Øglund*

Personvernombudet har vurdert prosjektet og finner at behandlingen av personopplysninger er meldepliktig i henhold til personopplysningsloven § 31. Behandlingen tilfredsstiller kravene i personopplysningsloven.

Personvernombudets vurdering forutsetter at prosjektet gjennomføres i tråd med opplysningene gitt i meldeskjemaet, korrespondanse med ombudet, ombudets kommentarer samt personopplysningsloven og helseregisterloven med forskrifter. Behandlingen av personopplysninger kan settes i gang.

Det gjøres oppmerksom på at det skal gis ny melding dersom behandlingen endres i forhold til de opplysninger som ligger til grunn for personvernombudets vurdering. Endringsmeldinger gis via et eget skjema, http://www.nsd.uib.no/personvern/meldeplikt/skjema.html. Det skal også gis melding etter tre år dersom prosjektet fortsatt pågår. Meldinger skal skje skriftlig til ombudet.

Personvernombudet har lagt ut opplysninger om prosjektet i en offentlig database, http://pvo.nsd.no/prosjekt.

Personvernombudet vil ved prosjektets avslutning, 02.03.2015, rette en henvendelse angående status for behandlingen av personopplysninger.

Vennlig hilsen

Katrine Utaaker Segadal

Lis Tenold

Kontaktperson: Lis Tenold tlf: 55 58 33 77
Vedlegg: Prosjektvurdering

Personvernombudet for forskning

Prosjektvurdering - Kommentar

Prosjektnr: 39462

Utvalget informeres skriftlig om prosjektet og samtykker til deltakelse. Personvernombudet finner informasjonsskrivet mottatt 26.08.2014 godt utformet.

Personvernombudet legger til grunn at forsker etterfølger Norges idrettshøgskole sine interne rutiner for datasikkerhet. Dersom personopplysninger skal sendes elektronisk eller lagres på mobile enheter, bør opplysningene krypteres tilstrekkelig.

Forventet prosjektslutt er 02.03.2015. Ifølge prosjektmeldingen skal innsamlede opplysninger da anonymiseres. Anonymisering innebærer å bearbeide datamaterialet slik at ingen enkeltpersoner kan gjenkjennes. Det gjøres ved å:
- slette direkte personopplysninger (som navn/koblingsnøkkel)
- slette/omskrive indirekte personopplysninger (identifiserende sammenstilling av bakgrunnsopplysninger som f.eks. bosted/arbeidssted, alder og kjønn)

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Claus Henning Thorsen	22845515	20.12.2016	2016/2007/REK sør-øst C
			Deres dato:	**Deres referanse:**
			01.11.2016	

Vår referanse må oppgis ved alle henvendelser

Ulf Ekelund
Norges idrettshøyskole
0806 Oslo

2016/2007 Bestæmningsfaktorer før Stillesitting

Forskningsansvarlig: Norges idrettshøgskole
Prosjektleder: Ulf Ekelund

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sør-øst C) i møtet 01.12.2016. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektomtale
Vår övergripande frågeställning är att förstå om mammas livsstil och andra faktorer tidigt i livet påverkar barn och ungas senare omfattning av stillasitting och fysisk aktivitet. Vidare ska vi undersöka om fysisk aktivitet kan modifiera kända samband mellan födelsevikt och snabb, tidig viktuppgång med fetma bland barn och unga. Vi kommer att använda data från Mor och Barnundersökningen (MoBa) en födelsekohort som inkluderar >100,000 mammor och deras barn. Vi kommer att använda data som självrapporterats via frågeformulär av mammorna i kohorten.

Vurdering
Dette er et doktorgradsprosjekt innen idrettsvitenskap, som ved bruk av MoBa-data skal undersøke om mødres livsstil og andre faktorer tidlig i livet påvirker barn og unges forhold til stillesitting og fysisk aktivitet. Betydningen av fysisk aktivitet skal også undersøkes i forhold til fødselsvekt og rask, tidlig vektøkning med fedme blant barn og unge.

Komiteen mener dette i hovedsak er et godt beskrevet prosjekt, og har ingen forskningsetiske innvendinger til designet.

Komiteen finner å kunne godkjenne studien slik som beskrevet i søknaden, og finner at bruken av aktuelle data faller innenfor det brede samtykket som er gitt av deltakerne i MoBa-studien.

Samtykket til MoBa er å betrakte som et bredt samtykke etter helseforskningslovens § 14, noe som gir deltakerne krav på jevnlig informasjon. Komiteen legger derfor til grunn at det informeres om studien på samme måte som for andre prosjekter tilknyttet MoBa

Vedtak
Prosjektet godkjennes, jf. helseforskningslovens §§ 9 og 33.

Tillatelsen er gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknaden og

protokollen, og de bestemmelser som følger av helseforskningsloven med forskrifter.

Tillatelsen gjelder til 31.12.2020. Av dokumentasjons-og oppfølgingshensyn skal opplysningene likevel bevares inntil 31.12.2025. Opplysningene skal lagres avidentifisert, dvs. atskilt i en nøkkel-og en opplysningsfil. Opplysningene skal deretter slettes eller anonymiseres, senest innen et halvt år fra denne dato.

Komiteens avgjørelse var enstemmig.

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

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK sør-øst på eget skjema senest 30.06.2021, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK sør-øst dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Med vennlig hilsen

Britt-Ingjerd Nesheim
professor dr. med.
leder REK sør-øst C

Claus Henning Thorsen
Rådgiver

Kopi til: *Norges idrettshøgskole ved øverste administrative ledelse: postmottak@nih.no*

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst	Claus Henning Thorsen	22845515	18.12.2017	2016/2007/REK sør-øst C
			Deres dato:	**Deres referanse:**
			22.11.2017	

Vår referanse må oppgis ved alle henvendelser

Ulf Ekelund
Seksjon for Idrettsmedisinske fag

2016/2007 Bestæmningsfaktorer før Stillesitting

Forskningsansvarlig: Norges idrettshøgskole
Prosjektleder: Ulf Ekelund

Vi viser til søknad om prosjektendring datert 22.11.2017 for ovennevnte forskningsprosjekt. Søknaden er behandlet av sekretariatet i REK sør-øst på delegert fullmakt fra REK sør-øst C.

Vurdering

De omsøkte endringene er beskrevet i skjema for prosjektendringer, og består av at Guro Pauck Bernhardsen og Silje Malen Andreassen blir nye prosjektmedarbeidere.

Komitéen har ingen forskningsetiske innvendinger til prosjektet slik det nå foreligger.

Vedtak

Komitéen har vurdert endringsmeldingen og godkjenner prosjektet slik det nå foreligger med hjemmel i helseforskningslovens § 11.

Tillatelsen er gitt under forutsetning av at prosjektendringen gjennomføres slik det er beskrevet i prosjektendringsmeldingen og de bestemmelser som følger av helseforskningsloven med forskrifter.

Forskningsprosjektets data skal oppbevares forsvarlig, se personopplysningsforskriften kapittel 2, og Helsedirektoratets veileder for Personvern og informasjonssikkerhet i forskningsprosjekter innenfor helse og omsorgssektoren.

Komiteens vedtak kan påklages til Den nasjonale forskningsetiske komité for medisin og helsefag, jf. helseforskningsloven § 10, 3 ledd og forvaltningsloven § 28. En eventuell klage sendes til REK sør-øst C.

Klagefristen er tre uker fra mottak av dette brevet, jf. forvaltningsloven § 29.

Vi ber om at alle henvendelser sendes inn via vår saksportal: http://helseforskning.etikkom.no eller på e-post til: post@helseforskning.etikkom.no

Vennligst oppgi vårt referansenummer i korrespondansen.

Med vennlig hilsen

Knut W. Ruyter
avdelingsdirektør
REK sør-øst

Claus Henning Thorsen
Rådgiver

Kopi til: *ulf.ekelund@nih.no;postmottak@nih.no*

APPENDIX 7:

Informed consent validation study

NORGES IDRETTSHØGSKOLE

Forespørsel om deltakelse i forskningsprosjektet: Målemetoder for fysisk aktivitet og stillesittende tid

Bakgrunn og hensikt
Dette er en invitasjon til deg om du og ditt barn vil delta i en doktorgradsstudie ved Norges idrettshøgskole (NIH). Hensikten med studien er å undersøke ulike metoder for å måle fysisk aktivitet og stillesittende tid hos barn, dvs. objektivt mål gjennom en aktivitetsmåler og subjektivt mål gjennom spørreskjema som besvares av mor. Å måle fysisk aktivitet og stillesittende tid kan være utfordrende, spesielt hos barn. Det å vite mer om og finne gode målemetoder for fysisk aktivitet og stillesittende tid er viktig i videre forskningsarbeid. Studien vil gi økt kunnskap om et spørreskjema som er benyttet i en stor undersøkelse (den norske Mor og Barn- undersøkelsen) gjennomført av Folkehelseinstituttet hvor over 100 000 barn er inkludert.

Du er valgt ut fordi du er mor til et barn i aldersgruppen 6-8 år, og har blitt rekruttert via barneskole, idrettslag, bekjente til forskningsgruppen, NIH sine hjemmesider og facebook.

Hva innebærer studien?
Deltakelse i studien innebærer et oppmøte på NIH (Sognsveien 220, Oslo) hvor testpersonell måler høyde, vekt, midjemål og kroppssammensetning hos barnet. Målingene på høyde, vekt og midjemål skjer stående ved hjelp av høydemåler, vekt og målebånd. Kroppssammensetning og bentetthet måles med DXA, et spesialkonstruert røntgenapparat med svært lave doser. Barnet må ligge stille på en benk i ca. 10 min. Testene kan ta opptil 30 minutter.

Barnet vil få utdelt en aktivitetsmåler som registrerer fysisk aktivitet og stillesittende tid. Barnet går med måleren fra den utdeles på testdagen og de 7 påfølgende dagene. Måleren er festet til et belte og skal sitte på høyre hofte, og skal kun tas av når barnet legger seg eller bader/dusjer. Etter perioden sendes aktivitetsmåleren tilbake til NIH i en ferdigfrankert konvolutt.

Mor bes besvare spørreskjema om barnets aktivitetsnivå og stillesittende tid ved to anledninger (omtrent to uker, og 4 uker etter barnet har gått med aktivitetsmåler). Spørreskjema sendes ut og besvares via e-post. Første spørreskjema omhandler bakgrunnsinformasjon om mor og barnet (f.eks. barnets søvnvaner), og om barnets aktivitetsnivå og stillesittende tid (tid foran TV, PC o.l.), andre spørreskjema omhandler barnets aktivitetsnivå og stillesittende tid. Det vil ta ca. 5 minutter og 3 minutter å besvare spørreskjemaene.

Mulige fordeler og ulemper
Fordelene med å være med i studien er at barnet vil få et mål på sitt fysiske aktivitetsnivå. Resultatet kan sammenlignes med gjennomsnittet i befolkningen og man kan undersøke om barnet når de norske helsemyndighetenes anbefalinger til fysisk aktivitet. Det er ikke

forventet at barnet vil føle noe ubehag under testene, og noen syns det er spennende og morsomt å være med i et forskningsprosjekt og å gå med aktivitetsmåleren. Ulempene er at det kan ta noe tid å komme seg til og fra NIH og tid på å gjennomføre testene.

Hva skjer med informasjonen om deg?
Det er frivillig å delta i studien. Om du nå sier ja til å delta, kan du senere når som helst og uten å oppgi noen grunn, trekke tilbake ditt samtykke. Informasjonen som registreres om deg og barnet ditt skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste.

Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg.

Prosjektet skal etter planen avsluttes 21.desember 2014. Navnelisten vil da slettes, og datamaterialet anonymiseres.

Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Ved ytterligere spørsmål, eller ønsker du å delta i studien, kontakt Guro Pauck Øglund, Seksjon for idrettsmedisinske fag, tlf: 22 26 22 93/909 72 519, e-post: g.p.oglund@nih.no

Studien er meldt til Personvernombudet for forskning, Norsk samfunnsvitenskapelig datatjeneste AS.

Samtykke til deltakelse i studien

Jeg har mottatt informasjon om studien, og jeg og mitt barn er villige til å delta i studien: «Ulike målemetoder til fysisk aktivitet og stillesittende tid»

Navn mor: _____

Navn barn:_____

Underskrift:

(Signert av mor, dato)

Ønsker du tilbakemelding om ditt barns aktivitetsnivå:

Ja ☐

Nei ☐