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

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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 physical activity (PA) and cardiometabolic risk factors were measured in childhood or adolescence. 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 the development of cardiovascular diseases and obesity later in life [1]. A large number of studies have provided support for the impact of a low birth weight, used as a proxy measure of fetal growth restriction, on subsequent risk of cardiovascular diseases in adulthood [2, 3]. Moreover, a high birth weight is consistently associated with increased risk of obesity later in life [4].

Low physical activity (PA) is another important and widely recognized risk factor for cardiovascular diseases [5]. A recent harmonized meta-analysis showed a nonlinear risk reduction in all-cause mortality across PA at any intensity in middle-aged and older people [6]. The greatest
risk reduction was observed at the lower end of the PA continuum; hence, the proposed public health message is “sit less, move more and more often” [6].

Cardiovascular diseases develop gradually and they rarely manifest in childhood or adolescence; nevertheless, even at young ages early signs of disease are apparent and birth weight is inversely associated with cardiometabolic risk factors [7–9] and positively associated with risk of obesity [10]. Furthermore, PA—especially at higher intensities [11–13]—is consistently 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 [14], with two previous studies in children and adolescents including only a few cardiometabolic outcomes showing contradictory results [15, 16].

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. Furthermore, device-measured PA, more specifically accelerometers, are considered the method of choice when examining associations between intensities of PA and health outcomes in children and adolescents [17, 18]. 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 nine studies included in the International Children’s Accelerometry Database (ICAD) [19], a subcohort of the Norwegian Mother, Father and Child Cohort Study (MoBa) [20], Physical Activity among Norwegian Children Study (PANCS) [21, 22] and Active Smarter Kids (ASK) [23]. Table 1 lists the number of participants and simple descriptive statistics of participants from each study included in the pooled analyses.

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

| Study          | Country, city/area | Year      | n (% boys) | Age, years | BMI, kg/m² | >Compulsory education, (%) |
|----------------|--------------------|-----------|------------|------------|------------|--------------------------|
| ALSPAC         | UK, Avon           | 2006–2008 | 2110 (45.1%) | 15.4 (15.3–15.6) | 21.4 (3.6) | 89.6                     |
| Denmark EYHS   | Denmark, Odense    | 1997–2010 | 1438 (44.0%) | 10.2 (9.6–15.5) | 18.9 (3.3) | 88.7                     |
| Estonia EYHS   | Estonia, Tartu     | 1998–1999 | 568 (44.2%)  | 10.2 (9.5–15.4) | 18.4 (3.0) | 81.2                     |
| IBDS           | US, Iowa           | 2003–2005 | 431 (48.0%)  | 11.0 (10.9–11.3) | 20.4 (4.4) | 86.3                     |
| Norway EYHS    | Norway, Oslo       | 1999–2000 | 236 (50.8%)  | 9.7 (9.4–10.0)  | 16.9 (2.2) | 58.5                     |
| Pelotas        | Brazil, Pelotas    | 2006–2007 | 426 (52.8%)  | 13.3 (13.1–13.6) | 20.3 (3.8) | 23.5                     |
| Portugal EYHS  | Portugal, Madeira  | 1999–2000 | 590 (51.5%)  | 10.0 (9.6–15.4) | 19.4 (3.7) | 6.5                      |
| SPEEDY         | UK, Norfolk        | 2011      | 358 (45.5%)  | 14.3 (14.0–14.5) | 20.8 (3.9) | 68.1                     |
| KISS           | Switzerland        | 2005–2006 | 306 (45.8%)  | 10.4 (7.1–11.2) | 17.3 (2.8) | 92.7                     |
| MoBa           | Norway            | 2013–2015 | 430 (54.4%)  | 11.0 (10.3–11.3) | 17.8 (2.4) | 96.9                     |
| ASK            | Norway            | 2014      | 857 (51.6%)  | 10.2 (10.0–10.5) | 18.1 (3.1) | 97.9                     |
| PANCS          | Norway            | 2005–2006 | 1350 (49.9%) | 9.8 (9.5–15.3)  | 18.6 (3.3) | 94.8                     |

Data are expressed as mean (SD) for BMI, median (25th–75th percentile) for age, number of participants (n), percent boys (%) and percent >compulsory education.

ALSPAC Avon Longitudinal Study of Parents and Children, ASK Active Smarter Kids, BMI body mass index, EYHS European Youth Heart Study, IBDS The Iowa Bone Development Study, KISS The Kinder-Sportstudie, MoBa the Norwegian Mother, Father and Child Cohort Study, PANCS Physical Activity Among Norwegian Children Study, SPEEDY Sport, Physical Activity and Eating Behavior: Environmental Determinants in Young People Study.

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

*Two provinces in Switzerland.

*Four cities in Norway (Oslo, Fredrikstad, Stavanger, and Bergen).

*Sogn and Fjordane county.

*Representative sample from all regions in Norway.
previously been published [16]. In the present study, we extend the study with a more than fourfold increase in the number of participants for insulin and more than sevenfold for waist circumference, and by including additional cardiometabolic variables.

ICAD [19] consists of device-measured PA, anthropometrics, and health data collected in children and adolescents from 20 studies worldwide. A detailed description of the aims, design, recruitment of studies, and protocols of the ICAD project have been described in detail elsewhere [19], 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 [24–27] and six are cross-sectional studies with retrospectively reported birth weight [28–30]. In longitudinal studies, data from the first wave of which each participant is included, unless later waves of data collection comprised a wider array of cardiometabolic risk factors [24, 26, 27, 29]. The participants were recruited either from being born at a certain hospital or area in a specific period [24–27], through randomly selected schools [28] or through schools willing to participate within a defined area [29, 30]. More information about the population and recruitment method in each study is available elsewhere [24–30].

MoBa is an ongoing prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health [20]. Participants were recruited from all over Norway from 1999 to 2008. The women consented to participation in 40.6% of the pregnancies. We invited a subcohort of 1603 10–12-year-old from four areas in Norway, of which 430 children participated and provided sufficient data for the present analyses.

The PANCS 1 study included a nationally representative sample of Norwegian 9- and 15- year-old [21, 22]. In total 2299 agreed to participate, and the participation rate was 89 and 74% for 9- and 15- year-old, respectively.

The ASK study is a school-based cluster randomized controlled trial carried out in 2014/15, situated in the western part of Norway [23]. 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 subcohort 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 [20, 24–27] or retrospective parentally reported [21–23, 28–30].

Cardiometabolic risk factors

Eleven studies provided data on systolic- and diastolic blood pressure (Table 2) [20–23, 25–30]. 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 2) provided data on LDL-cholesterol, HDL-cholesterol, and triglycerides [21–23, 26–28, 30]. In one study, [28] fasting blood samples were drawn from capillary blood. Fasting glucose and insulin levels were available from seven studies (Table 2) [21–23, 26–28, 30]. We calculated insulin resistance (Homeostatic model assessment, HOMA-IR) using the updated HOMA2 calculator [31]. All blood samples were collected while participants were in a fasting state. All twelve studies included data on waist circumference [20–30]. Test-personnel measured waist circumference midway between the lower rib and the iliac crest [20–22, 24–30], or two cm above the level of the umbilicus [23] at the end of a gentle expiration.

Clustered risk scores with different combinations of cardiometabolic risk factors are comparable [32], 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 at the same time-point as the cardiometabolic risk factors using uniaxial Actigraph- (model GT1M and 7164) [19, 21, 22] and triaxial Actigraph- (model GT3X+) [20, 23] accelerometers. The Actigraph accelerometers are previously validated in free-living conditions among children and adolescents, and are significantly and moderately correlated with physical activity energy expenditure derived from double-labeled water [33, 34]. The monitor was attached around the waist (right hip) using an elastic band. The children and adolescents were told to wear the monitor for four to seven consecutive days, removing it only when sleeping or during water-based activities. For data harmonization purposes, all data were reintegrated into uniaxial format and 60 s epoch. All studies provided raw Actigraph data files and
improve the precision of the outcomes due to the known
 associations. Ages at follow-up were included in the model to
 examine the direct association of physical activity in children and... 2055

the data were further reanalyzed in a standardized way to
to ensure comparability across studies (using Kinesoft ver-
sion 3.3.20 and version 3.3.80). Nonwear time was
defined as ≥60 min of consecutive zeros, with an allow-
ance of 2 min of nonzero interruptions. A valid day was
defined as at least 480 min of measured wear time, and all
children providing at least 3 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 min-
utes per day ≥2296 counts per minute (cpm), whereas
VPA was defined as average minutes per day ≥4012 cpm
[35]. We removed files flagged as spurious in the ICAD-
project [19]. The overnight activity was removed [19, 21–23],
or days with more than 18 h wear time were set to missing
[20].

### Covariates and descriptive variables

Potential confounders included in the models were parental
education and sex. We further adjusted for waist cir-
cumference (model 2) and height (for systolic- and diastolic
blood), measured at follow-up, to examine the direct asso-
ciations. Ages at follow-up were included in the model to
improve the precision of the outcomes due to the known

Changes in cardiometabolic risk factors with increasing age
in these age-groups [32].

Standardized methods were used to measure height and
weight across all studies [20–30]. For descriptive purposes,
we calculated body mass index (BMI) as weight (in kilo-
grams) divided by height (in meters) squared.

To harmonize the parent’s education level, a dichotom-ous
variable was created dividing the maternal and
paternal education level into (1): up to and completion of
compulsory education and (2): any post-compulsory edu-
cation. We further combined the parents’ education vari-
ables 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 (=3534 participants
removed). The participant’s age distribution revealed two
clusters around age 9–10 and 15–16 years. To ensure
homogenous groups we therefore performed a median split
dividing the participants into children (≤11.6 years old) and
adolescents (>11.6 years old) for all analyses. We tested for
differences between the age-groups using independent

| Table 2 Descriptive characteristics (mean and SD unless otherwise stated) of study participants and study availability, stratified by age group. |
|---|---|---|---|
| | Children | Adolescents |
| **Studies** | **Mean (SD)** | **Studies** | **Mean (SD)** |
| No. (n (%boys))<sup>b</sup> | 2–5, 7, 9–12 | 4560 (49.9%) | 1–4, 6–10, 12 | 4540 (45.6%) |
| Age (years)<sup>b</sup> | 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<sup>2</sup>)<sup>b</sup> | 2–5, 7, 9–12 | 17.8 (3.0) | 1–4, 6–10, 12 | 21.0 (3.5)* |
| >compulsory education,%<sup>c</sup> | 2–5, 7, 9–12 | 84.1% | 1–4, 6–10, 12 | 76.2%* |
| Birth weight (kg)<sup>b</sup> | 2–5, 7, 9–12 | 3.51 (0.60) | 1–4, 6–10, 12 | 3.39 (0.57)* |
| MVPA (min/day)<sup>b</sup> | 2–5, 7, 9–12 | 62.0 (31.8) | 1–4, 6–10, 12 | 44.7 (26.5)* |
| VPA (min/day)<sup>b</sup> | 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)<sup>b</sup> | 2–3, 5, 7, 9, 11–12 | 2.48 (0.66) | 1–3, 7, 9, 12 | 2.17 (0.60)* |
| HDL- cholesterol (mmol/l)<sup>b</sup> | 2–3, 5, 7, 9, 11–12 | 1.61 (0.36) | 1–3, 7, 9, 12 | 1.35 (0.31)* |
| Triglycerides (mmol/l)<sup>b</sup> | 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)<sup>b</sup> | 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)<sup>b</sup> | 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.

<sup>a</sup>p < 0.05 for difference between children and adolescents.

<sup>b</sup>Studies: 1-ALSPAC, 2-Denmark EYHS, 3-Estonia EYHS, 4-IBDIS, 5-Norway EYHS, 6-Pelotas, 7-Portugal EYHS, 8-Speedy, 9-KISS, 10-MoBa, 11-ASK, 12-PANCS.

<sup>c</sup>Age, VPA, triglycerides and HOMA-IR expressed as median (25th–75th percentile). Number of participants (%), and % >compulsory education.

<sup>d</sup>Percent (%) of which one or both parents have completed any post-compulsory education.
Table 3  Associations (unstandardized regression coefficients and 95%CIs) between both birth weight and MVPA on cardiometabolic risk factors in children and adolescents, and interaction between birth weight and MVPA on the same cardiometabolic outcomes.

| Table 3  | Associations (unstandardized regression coefficients and 95%CIs) between both birth weight and MVPA on cardiometabolic risk factors in children and adolescents, and interaction between birth weight and MVPA on the same cardiometabolic outcomes. |
|----------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|          | Children | Adolescents |          |          |
| n        | B(95%CI) | p value     | n        | B (95%CI) | p value     |
|          |          |            |          |          |            |
| SBP (mmHg) | 4120 | −1.10 (−1.50, −0.70) | 4491 | −1.78 (−2.52, −1.04) |  |
| Model 1a | Birth weight (kg) |          |          |          |          |
|          | −0.01 (−0.03, 0.00) |          |          | −0.02 (−0.03, −0.01) |  |
| Model 2b | MVPA (min/day) | Birth weight (kg) | Birth weight x MVPA | 0.005 (−0.007, 0.017) | 0.440 | −0.005 (−0.032, 0.021) | 0.685 |
| DBP (mmHg) | 4119 | −0.66 (−0.80, −0.42) | 4491 | −0.32 (−0.61, −0.04) |  |
| Model 1a | Birth weight (kg) |          |          |          |          |
|          | −0.01 (−0.03, −0.00) |          |          | −0.01 (−0.02, −0.00) |  |
| Model 2b | MVPA (min/day) | Birth weight (kg) | 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 | 0.03 (−0.00, 0.06) | 2868 | −0.000 (−0.04, 0.04) |  |
| Model 1a | Birth weight (kg) |          |          |          |          |
|          | 0.001 (0.000, 0.002) | 0.001 (0.000, 0.001) | 0.000 (−0.001, 0.001) | 0.915 | −0.000 (−0.001, 0.000) | 0.202 |
| Model 2b | MVPA (min/day) | Birth weight (kg) | Birth weight x MVPA | 0.000 (−0.001, 0.001) | 0.978 | −0.001 (−0.001, −0.000) | 0.040 |
| HDL–cholesterol (mmol/l) | 3230 | −0.02 (−0.05, 0.01) | 2868 | −0.02 (−0.03, 0.00) |  |
| Model 1a | Birth weight (kg) |          |          |          |          |
|          | 0.001 (−0.028, 0.030) | 0.004 (−0.019, 0.012) | −0.001 (−0.001, −0.000) | 0.040 |          |          |
| Model 2b | MVPA (min/day) | Birth weight (kg) | Birth weight x MVPA | −0.000 (−0.001, 0.001) | 0.921 | 0.000 (−0.000, 0.000) | 0.839 |
| Triglycerides (mmol/l) | 3207 | −0.01 (−0.03, 0.01) | 2866 | 0.003 (−0.007, 0.012) |  |
| Model 1a | Birth weight (kg) |          |          |          |          |
|          | −0.01 (−0.05, −0.02) | −0.01 (−0.02, −0.00) | −0.000 (−0.001, 0.001) | 0.921 | 0.000 (−0.000, 0.000) | 0.839 |
| HOMA-IR (score) | 3109 | −0.01 (−0.05, 0.03) | 2859 | 0.01 (−0.03, 0.05) |  |
| Model 1a | Birth weight (kg) |          |          |          |          |
|          | −0.002 (−0.003, −0.001) | −0.002 (−0.003, −0.001) | −0.000 (−0.001, 0.001) | 0.941 |          |          |
| Model 2b | MVPA (min/day) | Birth weight (kg) | Birth weight x MVPA | 0.000 (−0.000, 0.001) | 0.689 | −0.000 (−0.001, 0.001) | 0.941 |
| Waist Circumference (cm) | 4536 | −0.03 (−0.05, −0.02) | 4129 | −0.01 (−0.03, 0.00) |  |
| Model 1a | MVPA (min/day) |          |          |          |          |
|          | −0.00 (−0.00, 0.00) |          |          |          |          |
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.

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.

aModel 1: Adjusted for highest parental education, sex and age. SBP and DBP adjusted for height instead of age.

bModel 2: Adjusted for model 1 and waist circumference.

cClustered 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).
Higher MVPA was associated with lower systolic- and diastolic blood pressure, LDL-cholesterol, triglycerides, HOMA-IR, waist circumference, and clustered cardiometabolic risk score—except for systolic blood pressure in children and waist circumference in adolescents (Table 3). Higher MVPA was further associated with higher HDL-cholesterol (Table 3).

Lower birth weight was associated with higher systolic- and diastolic blood pressure, an association that became stronger in magnitude after the inclusion of waist circumference in the model (Table 3). 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 3). 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 (Table 3).

Higher MVPA was associated with lower systolic- and diastolic blood pressure, LDL-cholesterol, triglycerides, HOMA-IR, waist circumference, and clustered cardiometabolic risk score—except for systolic blood pressure in children and waist circumference in adolescents (Table 3). Higher MVPA was further associated with higher HDL-cholesterol (Table 3).

Fig. 1 Illustration of the interaction between birth weight and MVPA on waist circumference (children) and HDL-cholesterol (adolescents). 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.

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 File 1) did not differ from the results using MI on missing values, except for a nonsignificant 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
The observed effect modification of MVPA or VPA on diastolic blood pressure, LDL-cholesterol, and triglycerides is likely clinically insignificant.

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. [16], 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. A similar study by Ortega et al. [15], 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. [36] and Eriksson et al. [37] 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 [38]. In contrast, Jeanne et al. [39] observed no interaction on the multiplicative scale between birth weight and self-reported MVPA on risk of diabetes or prediabetes in young adulthood. 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. This is in contrast to one study suggesting that an 8-week exercise program may eliminate the difference in LDL-cholesterol between low birth weight and high birth weight in young adulthood, whereas the difference in HDL-cholesterol between the two groups became significantly different first after the exercise.
The observed 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 persist into adulthood and may become more clinically important in the development of cardiovascular diseases.

The observed stronger association between birth weight and diastolic blood pressure in the most active may indicate that children with low birth weight do not respond to VPA to the same extent as children with higher birth weight. This interaction was however not observed in adolescents, nor for systolic blood pressure.

The results from a few previous studies are similar to ours and suggest that self-reported PA attenuates the association between a high birth weight and abdominal adiposity [41] and risk of overweight or obesity [41, 42] in children and adolescents. We observed this interaction in children only, whereas another study observed this interaction in girls only [42]. In contrast, other studies found no interaction between birth weight and PA on the association with abdominal adiposity [16, 42, 43], or other measures of adiposity [43, 44].

A clustered cardiometabolic risk score is likely more important for future health than single risk factors [32]. In contrast to our results, Jeanne et al. [39] observed an interaction between self-reported MVPA and high birth, but not low birth weight, on the association with a cardiovascular disease risk score in young adulthood. Although we did not observe any effect modification of PA, the clustered cardiometabolic risk score is substantially lower in more active compared with less active across the birth weight spectrum, and MVPA should thus 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 [45]; thus, the use of a 60-s epoch length may have led to underestimation of time spent in MVPA [46]. Also, accelerometers underestimate 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 [47, 48].

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 modeled as the outcome, as it is likely that a higher waist circumference may lead to reduced PA [49, 50].

The 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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Compliance with ethical standards

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

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